<table>
<thead>
<tr>
<th>Index of Abstracts by Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Case Series in Upper Airway Resistance Syndrome Masquerading As Periodic Limb Movements of Sleep</td>
</tr>
<tr>
<td>A Cephalometric Study of the Effects of UPPP using Ricketts' method</td>
</tr>
<tr>
<td>A comparative investigation of sleepiness and complex cognitive function in narcolepsy and sleep deprivation.</td>
</tr>
<tr>
<td>A comparative, double-blind study of two non-benzodiazepine hypnotics, zolpidem and zopiclone, in patients with chronic primary insomnia</td>
</tr>
<tr>
<td>A Comparison Between Measurements of Sleep Efficiency and Sleep Latency Measured By Polyomnography and Wrist Actigraphy</td>
</tr>
<tr>
<td>A Comparison Between the Effects of Repeated Practice and Prolonged Wakefulness on Simulated Driving Performance</td>
</tr>
<tr>
<td>A Comparison of Obstructive and Central Respiratory Events using a Respiratory Thermistor, a Pressure Transducer or Both for Scoring.</td>
</tr>
<tr>
<td>A Comparison of the Epworth Sleepiness Scale and the Functional Outcomes of Sleepiness Questionnaire in the Assessment of Excessive Daytime Sleepiness in the Elderly</td>
</tr>
<tr>
<td>A Longer Biological Night in Long Sleepers than in Short Sleepers</td>
</tr>
<tr>
<td>A Man’s Claim to Have Been Raped Unaware While Asleep: Report from a Sleep Specialist to the Criminal Court.</td>
</tr>
<tr>
<td>A NASA Education and Training Module on Alertness Management: A Survey of Implementation and Application</td>
</tr>
<tr>
<td>A New Research Measure for Children’s Sleep</td>
</tr>
<tr>
<td>A Pilot Study of Serologic Markers of Autoimmunity in Patients with Narcolepsy</td>
</tr>
<tr>
<td>A Pilot Study of the Sleep EEG Power Spectral Effects of Behavioral Therapy in Primary Insomniacs</td>
</tr>
<tr>
<td>A prospective study of fatal accidents and sleep disturbances, fatigue, work stress, and work hours</td>
</tr>
<tr>
<td>A Prospective Study on the Treatment of “Complex Insomnia”—Insomnia plus Sleep Disordered Breathing— in a Small Series of Crime Victims with PTSD</td>
</tr>
<tr>
<td>A Protocol for Optimizing and Predicting Nasal-CPAP Efficacy and Compliance</td>
</tr>
<tr>
<td>A prototype of a sensorized and electrically actuated bed for snoring Sleep Apnea relief</td>
</tr>
<tr>
<td>A randomized long-term placebo-controlled multicenter trial of pergolide in the treatment of RLS with central evaluation of polysomnographic data</td>
</tr>
<tr>
<td>A Sleep Therapy Program for Cancer Patients with Insomnia</td>
</tr>
<tr>
<td>A Statistical Model of Cumulative Sleep Debt in Chronic Sleep Restriction</td>
</tr>
<tr>
<td>A structural polymorphism in the tyrosine hydroxylase gene is not associated with Restless legs syndrome</td>
</tr>
<tr>
<td>A test of the reliability and validity of a brief, patient-completed severity questionnaire for the Restless Legs Syndrome: The International RLS Study group rating scale</td>
</tr>
<tr>
<td>A tool to assess sleep apnea knowledge and attitudes among physicians</td>
</tr>
<tr>
<td>A transformation function can equate readings of wrist-worn light measuring devices to those of hand-held light monitors</td>
</tr>
<tr>
<td>A Two-Dimensional Finite Element Model of Collapse in the Male and Female Upper Airway</td>
</tr>
<tr>
<td>Abnormal EEG’s in patients presenting for polysomnography</td>
</tr>
<tr>
<td>Acoustic fMRI during sleep: Negative BOLD response in the visual cortex</td>
</tr>
<tr>
<td>Actigraphic detection of periodic leg movements; a validation study</td>
</tr>
<tr>
<td>Activity of Adenosine Metabolizing Enzymes in Sleep-Related Brain Regions</td>
</tr>
<tr>
<td>Acute Effects of Lighting Changes on Human Performance</td>
</tr>
<tr>
<td>Acute Handling Stress Induces Respiratory Depression in Rats</td>
</tr>
<tr>
<td>Acute Stress Affects Autonomic Tone During Sleep</td>
</tr>
<tr>
<td>Additive Effects of Circadian Rhythms and Sleep on Respiration in the Rat</td>
</tr>
<tr>
<td>Adenosine A1 Receptors Mediate Inhibition of cAMP Formation in the Pontine, REM Sleep-Induction Zone in vitro</td>
</tr>
<tr>
<td>Adenosinolysis in Children: Indications, Practices, and Outcomes Reported by Otolaryngologists</td>
</tr>
<tr>
<td>Adherence to positive pressure therapy in patients with obstructive sleep disordered breathing treated with an oral-nasal mask as salvage therapy</td>
</tr>
<tr>
<td>Adherence with CPAP: Weighing the Pros and the Cons</td>
</tr>
<tr>
<td>Adolescent Sleep and School Start Times</td>
</tr>
<tr>
<td>Adolescent Sleep Spindle Regulation: Circadian and Homeostatic Contributions to Morphology</td>
</tr>
<tr>
<td>Adults’ Beliefs about Sleep: Refinement of the Floyd-Medler Sleep Belief Scale</td>
</tr>
<tr>
<td>Afternoon Siesta Naps in the Elderly: Effects on Sleep, Circadian Rhythms, Alertness and Performance</td>
</tr>
<tr>
<td>Age and Gender Effects in Body Temperature Minimum Estimated in a 90-min Day</td>
</tr>
<tr>
<td>Alertness and Neurobehavioral Performance On Simulated Night Shifts Following Evening Naps</td>
</tr>
<tr>
<td>Alpha-EEG Sleep and Chronic Pain: Challenges to the Alpha-EEG Sleep as a Pain Specific Sleep Anomaly</td>
</tr>
<tr>
<td>Alteration in Central Control of Spontaneous Nocturnal Erections in Psychogenic Erectile Dysfunction</td>
</tr>
<tr>
<td>Alteration of digital pulse amplitude reflects alpha-adrenoceptor mediated constriction of the digital vascular bed</td>
</tr>
<tr>
<td>Alterations in Sleep after Fear Conditioning</td>
</tr>
<tr>
<td>Alterations in the homeostatic mechanisms of sleep in b-amyloid precursor protein transgenic mice</td>
</tr>
<tr>
<td>An absence of adenosine effects in laterodorsal tegmental neurons of A1R knockout mice associated with increased wakefulness</td>
</tr>
<tr>
<td>An Intervention Can Improve Medical Students’ Recognition of Sleep Apnea</td>
</tr>
<tr>
<td>Analysis of Sleep Microstructure Through Cyclic Alternating Pattern in School Age Children</td>
</tr>
<tr>
<td>Analysis of the first night effect on evening and morning waking quantified EEG</td>
</tr>
<tr>
<td>Anti-waking System: Some Arguments in Favour of its Existence</td>
</tr>
</tbody>
</table>
Anticholinesterase Drug Donepezil Increases REM Sleep Duration in Alzheimer’s Disease Patients: Preliminary Data ..........................................................A369
Apolipoprotein E ε4 predisposes to sleep disordered breathing in the normal adult population ......................................................................................A54
Arousal Components Which Differentiate the MWT From the MSLT ..............................................................................................................A106
Arousal Index in 100 Children: Normative Data .................................................................................................................................A217
Arousal response during periodic leg movements: an EEG and ECG study .......................................................................................................A357
Arousal To Acoustic Stimuli In Children With The Obstructive Sleep Apnea Syndrome (OSAS) .................................................................A203
Arterial Stiffness Changes In Association With Obstructive Apeas In Sleep .................................................................................................A308
Assessing the Quality of Sleep of Intensive Care Patients .....................................................................................................................A347
Assessment of a Simulated Driving Task for Sleep Research ..........................................................................................................................A413
Assessment of Patients Preferences Between Two Hypnotics, Zolpidem (10mg) vs. Zaleplon (10mg) .................................................................A332
Assessment of phase shift of melatonin rhythm to a single bright light stimulus is confounded by masking effects of scheduled sleep:wake and/or dim light:dark cycles ................................................................................A85
Assessment Of Sleep Disordered Breathing In Neuromuscular Disease Patients By Heart Rate Variability .................................................................A294
Assessment of Sodium Oxybate for the Long-Term Treatment of Narcolepsy ..............................................................................................A324
Association Between Daily Energy Expenditure and Sleep in Physically Active Adults .....................................................................................A122
Association of Excessive Daytime Sleepiness with Sleep Disordered Breathing: The Influence of Age and BMI ..................................................A91
Associations of Home Atmosphere, School Perceptions, Sleep Disorders, and Selected Health Behaviors with Perceived Alertness in 15-year-olds ..........................................................................................................................A209
Ataxic Respiration and Increased Upper Airway Resistance during Sleep in a Child Following Treatment for Posterior Fossa Medulloblastoma ............................................................A212
Attentional processes in insomnia: The role of monitoring the environment and the body for sleep related cues ............................................A335
Attenuation of the First Night Effect ...............................................................................................................................................................A412
Autonomic Activation Index (AAI) – A new marker of sleep disruption. ........................................................................................................A109
Autonomic Functioning During REM Sleep Differentiates IBS Symptom Subgroups ....................................................................................A38
Average face of the Japanese patients with obstructive sleep apnea ..................................................................................................................A275
Behavioral and Physiological Sleep Characteristics in IBS Symptom Subgroups .............................................................................................A364
Behavioral and Polysomnographic Characterization of Orexin-1 Receptor and Orexin-2 Receptor Double Knockout Mice. ...................................A22
Behavioral Characterization of Orexin-2 Receptor (OX2R) Knockout Mice ..................................................................................................A20
Beliefs and Attitudes About Sleep Before and After Participation in a Group Cognitive-Behavioral Insomnia Treatment Program ..................A60
Benzodiazepine chronic use: possible protective role in dementia ...........................................................................................................A372
Breathing Disorders in Patients with Congestive Heart Failure ..................................................................................................................A291
Breathing Patterns in the Arousal in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome .................................................................A290
Bright Light Treatment for Correction of Shift Work Fatigue ..........................................................................................................................A198
C-fos expression in hypocretinergic neurons during wakefulness and carbachol-induced active sleep .............................................................A155
Caffeine Consumption and Weekly Sleep Patterns in U.S. Seventh, Eighth and Ninth Graders .............................................................................A12
Can Sleep Attacks Occur Without Feeling Sleepy? .................................................................................................................................A428
Cannabinoid Receptor 1 (CB1) Expression Is Modified By Sleep Rebound. ........................................................................................................A252
Carbachol Activates G Proteins in Pontine Reticular Formation of C57BL/6J Mouse .......................................................................................A140
Cataplexy and Cataplexy-like Symptoms in Narcoleptics, non-Narcoleptic Hypersomniacs, and Normal Controls ..............................................A314
Cerebral Oxygenation During Sleep in Chronic Obstructive Pulmonary Disease ..................................................................................................A288
Cerebral Oxygenation Response to Arousal During Sleep in Old & Young Adults ..........................................................................................A115
Changes in autonomic controls and arousability; implications in sudden Infant Death Syndrome (SIDS) ..............................................................A207
Changes in Brain Glucose Uptake Following Acute REM Sleep Deprivation ........................................................................................................A252
Changes in Brain-Derived Neurotrophic Factor (BDNF) mRNA and Protein Levels Following Acute REM Sleep Deprivation. ..................A253
Changes in Dreaming in patients using Continuous Positive Air Pressure(CPAP) for documented Obstructive Sleep Apnea(OSA) .................................................A294
Changes in gene expression during the sleep-wake cycle after lesions of the serotonergic system. .................................................................A151
Changes in Hipocampal Susceptibility to Severe Hypoxia Following Long-Term Exposures to Intermittent or Sustained Hypoxia ...................................A55
Changes in Neuroendocrine Reactivity in Chronically Sleep Restricted Rats .......................................................................................................A73
Changes in neurotransmitter release in motoneuron pools during pontine acetylcholine-induced muscle tone suppression ................................A42
Changes in plasma growth hormone levels following chronic sleep restriction ..........................................................................................A248
Changes in sleep stage distribution during acute CPAP application in obstructive sleep apnea patients ................................................................A304
Characteristics And Scoring Criteria For Leg Movements Recorded During The Suggested Immobilisation Test In Restless Legs Syndrome ..........................A352
Characteristics of the Ideal Hypnotic: A Survey of Primary Care Physicians, Sleep Specialists, and People with Insomnia .......................................A67
Characterizing Sleepwalking Events in a Natural Environment ..................................................................................................................A350
Chemical Odor Intolerance and Sleep Symptoms in a Community Based Sample ..............................................................................................A377
Chocolate Ingestion and REM Sleep Behavior Disorder: A Case Report ........................................................................................................A352
Chronic Administration of Sodium Oxybate Produces Significant and Long-Term Improvements in Narcolepsy Symptoms .......................................A327
Chronic Sleep Restriction: Relation of Sleep Structure to Daytime Sleepiness and Performance .............................................................................A28
Circadian Adjustment to Night Shift Work with a Bright Light Intervention Regimen in the Workplace ...........................................................A88
Circadian and Sleep-Wake Dependant Control of Urine Volume Output on a 28-h Forced Desynchrony .................................................................A90
Circadian and Sleep-Wake Dependent Control of Alertness, Mood and Performance in field studies of blind subjects ........................................A4
Circadian Changes in Hydration in Elders with OSA .................................................................................................................................A235
Circadian Firing Pattern of 95 Patients with Automatic Implantable Cardioverter Defibrillators (AICDs) .............................................................A199
Experiences that Trigger Cataplexy

Variations as a Function of the 24 hr Light-Dark Cycle

AXIX

Immunohistochemical Study Of Serotonergic Neurons In Rats Neonatally Treated With Clomipramine ............................................. A129
Impact of definition of hypopnea on Respiratory Disturbance Index ................................................................................................................. A297
Impact of Gender and Estrogen Replacement Therapy on Sleep Quality and Sleep-related Hormone Secretion in Older Adults ............................................. A232
Impact of sleep length on the 24-h leptin profile .............................................................................................................................................. A74
Impairment of the Sleep Response to Influenza Infection in Mice with a Defective GHRH-receptor ......................................................... A144
In mice restraint stress at light onset produces an increase in REM sleep whereas restraint at dark onset does not .............................................. A192
Incidence of Sleep Disordered Breathing (SDB) in a Population-Based Sample ............................................................................................ A294
Incorporation of Episodic Memories in Dreaming........................................................................................................................................... A179
Increased body-Mass-Index (BMI), appetite and food intake in human narcolepsy, but not in HLA-DR2 positive controls .................... A99
Increased expression of preprohypocretin mRNA in rat hypothalamus after sleep deprivation and sleep rebound .............................................. A419
Increased non-rapid eye movement (NREM) sleep duration and EEG slow wave activity (SWA) in mice after an aggressive social interaction but not after a sexual interaction .................................................................................................................. A141
Increased NREM sleep in Mutant Mice Lacking CREB ................................................................................................................................. A422
Increased Number and Density of Rapid Eye Movements in Individuals of Varying I.Q. Levels Following Acquisition of Two Procedural Tasks .................................................................................................................................................. A163
Increased Upper Airway Collapsibility in Awake Children With Obstructive Sleep Apnea ................................................................. A207
Increasing Sleep Time Effectively Reduces Sleepwalking and Sleep Terrors in Children ................................................................................... A220
Indirect projections from the suprachiasmatic nucleus to wake-related neuronal groups in the forebrain and brainstem in rat. .............................................. A142
Individual Differences in Cognitive Performance Relating to Circadian Typology and Subjective Sleep Quality in the Presence of a Stressor ................................................................................................................................................. A193
Individual Differences in Performance Degradation and Subsequent Recovery in Volunteers Allowed 3 Hours Sleep Time Over 7 Days ............................................................................................................................................... A29
Individual Differences in the Effects of 47-50 hrs Sleep Loss on Mood and Cognition .......................................................................................... A31
Influence of Anticipatory Anxiety on Sleep in Behaviorally “Anxious” and “Non-Anxious” Mice ........................................................................ A53
Initial Findings from a Multi-Site Evaluation of an Unattended Monitoring System for Automatic Detection of Sleep Disordered Breathing Events .......................................................................................................................... A408
Insomnia and its Relationship to Sleepiness in a Community-based Sample .................................................................................................. A348
Insomnia and Oniceric Behavior in Parkinson’s Disease: a case report ......................................................................................................... A371
Insomnia in adults of the rural and isolated African-Brazilian community of Furnas do Dionisio, Brazil ............................................................ A344
Insomnia is Associated with Altered Circadian Interleukin-6 and TNFα Secretion ........................................................................................... A342
Insomniacs with Comorbid Depression Achieved Comparable Improvement in a Cognitive Behavioral Group Treatment Program as Insomniacs without Comorbid Depression ................................................................................................................................. A62
Intermittent Hypoxia Elicits Differential Responses in the CAI and CA3 Regions of the Rat Hippocampus: A Proteomic Analysis ......................................................................................................................................................................... A264
Intracellular calcium is mobilized by adenosine acting via the A1 receptor in the basal forebrain cholinergic neurons, but not in non-cholinergic neurons ......................................................................................................................................... A49
Intrinsic Period Shorter Than 24 Hours in an Adolescent Boy .......................................................................................................................... A5
Iron Deficiency Anemia (IDA) in Infancy Alters the Temporal Organization of Sleep States in Childhood ............................................. A13
Is a History of Hypothyroidism a Risk Factor For Obstructive Sleep Apnea? ............................................................................................ A311
Is Elevation of Serum Vascular Endothelial Growth Factor Concentrations a Reliable Surrogate Biological Marker in Patients With Obstructive Sleep Apnea? .............................................................................................................. A278
Is Fluctuating Cognition in Dementia with Lewy Bodies Attributable to an Underlying Sleep Disorder? ................................................ A374
Is the health related quality of life different between people who have classical narcolepsy and those with narcolepsy without cataplexy? ............................................................................................................................................ A317
Is the MSLT a Valid Measure of sleepiness in All Apnea Patients? ................................................................................................................ A257
Is there a First Night Effect with Ambulatory Polysomnography (PSG)? ........................................................................................................ A403
IV Iron Treatment for the Restless Legs Syndrome (RLS) ....................................................................................................................................... A359
Jerk-Arousals are not Required to Produce Symptoms in PLMD .................................................................................................................. A362
Ketanserin, a 5-HT2 Receptor Antagonist, Reduces Sleep Apeonas in Rats .................................................................................................... A279
Knowledge about Sleep and Driving In Australian Adolescents.............................................................................................................................................. A111
L-364,718, a CCK-A receptor antagonist does not prevent the somnogenic effects of interleukin in rats ........................................................................ A145
Lack of Compensatory Sleep After 7-Day Continuous Cocaine Infusion ...................................................................................................... A73
Lack of Statistical Association between Antidepressant Use and Clinical Restless Legs Syndrome in Patients Referred for Insomnia .................................................................................................................................................. A365
Laser Capture Microdissection of Single Cells for Quantification of 5-HT Receptor Subtypes in XII Motoneurons. .................................................. A147
Lesions of histaminergic neurons do not produce hypersomnolence .................................................................................................................. A51
Linkage Analysis of a Familial Case of Advanced Sleep Phase Syndrome ................................................................................................... A421
Local Field Potential Recordings from Drosophila Mushroom Bodies and their Modulation by Activity State ................................................................ A40
Long term Facilitation During NREM Sleep in Patients with Obstructive Sleep Apnea (OSA) ................................................................................ A69
Long Term Total Sleep Deprivation Results in Altered Cu/Zn-SOD Activity ................................................................................................. A250
Long-lasting Effects of Iron Deficiency Anemia in Infancy on Sleep Autonomic Nervous System Functioning in Childhood .................. A220
Long-term (136 Weeks) Safety and Efficacy of Modafinil for the Treatment of Excessive Daytime Sleepiness Associated With Narcolepsy ............................................................................................................................................. A329
Long-term treatment for Restless Legs Syndrome with pramipexole: augmentation effect findings .............................................................................. A362
Major Exclusion Factors for Elderly Subjects in Primary Insomnia Research Studies ......................................................................................................... A346
<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-Like State in Zebrafish: Effects of Melatonin and Sedatives</td>
<td></td>
</tr>
<tr>
<td>Sleep-Disordered Breathing and Electrocardiographic Indicators of</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td></td>
</tr>
<tr>
<td>Sleep-Dependent and Circadian Influences on Normal Nocturnal Sleep</td>
<td></td>
</tr>
<tr>
<td>Sleep Studies in Pregnancy and Postpartum Depression</td>
<td></td>
</tr>
<tr>
<td>Sleep Spindles During Slow Wave Sleep in Fibromyalgia</td>
<td></td>
</tr>
<tr>
<td>&quot;Sleep Spindles&quot; During REM Sleep - A Quantitative Approach</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality and Blood Pressure Dipping in Obstructive Sleep Apnea</td>
<td></td>
</tr>
<tr>
<td>Sleep problems in dialysis patients with restless legs syndrome</td>
<td></td>
</tr>
<tr>
<td>Sleep Patterns of Patients with Different Types of Gerd</td>
<td></td>
</tr>
<tr>
<td>Sleep patterns in adults of the rural and isolated African-Brazilian</td>
<td></td>
</tr>
<tr>
<td>community of Furnas do Dionisio, Brazil</td>
<td></td>
</tr>
<tr>
<td>Sleep parameters in identical twins discordant for schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Sleep Microarchitecture in Females at Risk for Depression</td>
<td></td>
</tr>
<tr>
<td>Sleep Deprivation Augments Endothelin Plasma Levels</td>
<td></td>
</tr>
<tr>
<td>Sleep Deprivation, EEG, and Functional MRI in Depression: Preliminary</td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders in a Community Sleep Clinic: A cooperative study</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders in a Military Population</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders in Ambulatory Seniors</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders in Children with Mucopolysaccharidosis</td>
<td></td>
</tr>
<tr>
<td>Sleep Disorders in Chronically Sleepy Drivers</td>
<td></td>
</tr>
<tr>
<td>Sleep Disturbances in Lung Transplant Recipients</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances in the elderly: a population study of</td>
<td></td>
</tr>
<tr>
<td>the subjects over 85 years old</td>
<td></td>
</tr>
<tr>
<td>Sleep Duration at Home in a Sample of Commercial Drivers</td>
<td></td>
</tr>
<tr>
<td>Sleep education in high-school students: an Italian experience</td>
<td></td>
</tr>
<tr>
<td>Sleep EEG Changes Following Hemispheric Stroke</td>
<td></td>
</tr>
<tr>
<td>Sleep EEG in de novo patients with Parkinson’s disease: Effects of</td>
<td></td>
</tr>
<tr>
<td>dopamine on the spectral profiles</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency during Chronic Nocturnal Sleep Restriction with and</td>
<td></td>
</tr>
<tr>
<td>without Diurnal Naps</td>
<td></td>
</tr>
<tr>
<td>Sleep Hygiene, Daytime Sleepiness, and Chronotopyology in Young</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>Sleep in Children with Juvenile Rheumatoid Arthritis</td>
<td></td>
</tr>
<tr>
<td>Sleep in Postmenopausal Women A Double Blinded Study, Placebo-Controlled Using Hormone Replacement</td>
<td></td>
</tr>
<tr>
<td>Sleep in randomly selected control subjects with the P10 129 Val/Met polymorphism</td>
<td></td>
</tr>
<tr>
<td>Sleep Induction by Microinjection of Ethanol into the MPA is Prevented by a Benzodiazepine Receptor Antagonist</td>
<td></td>
</tr>
<tr>
<td>Sleep inertia: Subjective, behavioural and electrophysiological</td>
<td></td>
</tr>
<tr>
<td>measurements</td>
<td></td>
</tr>
<tr>
<td>Sleep Microarchitecture in Females at Risk for Depression</td>
<td></td>
</tr>
<tr>
<td>Sleep Onset has a Major Effect on Autonomic Control of Cardiac</td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
</tr>
<tr>
<td>Sleep parameters in identical twins discordant for schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Sleep patterns in adults of the rural and isolated African-Brazilian</td>
<td></td>
</tr>
<tr>
<td>community of Furnas do Dionisio, Brazil</td>
<td></td>
</tr>
<tr>
<td>Sleep Patterns of Patients with Different Types of Gerd</td>
<td></td>
</tr>
<tr>
<td>Sleep Physiology and Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Sleep Predicts Psychological Adjustment and Mortality in Cancer</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Sleep Problems in Children with Epilepsy-Results of Overnight</td>
<td></td>
</tr>
<tr>
<td>Polysomnography</td>
<td></td>
</tr>
<tr>
<td>Sleep problems in dialysis patients with and without restless legs syndrome</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality and Blood Pressure Dipping in Obstructive Sleep Apnea</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality of Patients Enrolled in an Adult Cystic Fibrosis Clinic</td>
<td></td>
</tr>
<tr>
<td>Sleep Rebounds From Total and Paradoxical Sleep Selective Depriation in Rats</td>
<td></td>
</tr>
<tr>
<td>“Sleep Spindles” During REM Sleep - A Quantitative Approach</td>
<td></td>
</tr>
<tr>
<td>Sleep Spindles During Slow Wave Sleep in Fibromyalgia</td>
<td></td>
</tr>
<tr>
<td>Sleep Studies in Pregnancy and Postpartum Depression</td>
<td></td>
</tr>
<tr>
<td>Sleep, Daytime Functioning, and Insomnia in Young Adults</td>
<td></td>
</tr>
<tr>
<td>Sleep, Daytime Sleepiness and Wakefulness in Patients with Retinitis Pigmentosa</td>
<td></td>
</tr>
<tr>
<td>Sleep, Daytime Sleepiness, and Clinical Subtypes of ADHD</td>
<td></td>
</tr>
<tr>
<td>Sleep, well-being and health-related behaviour in early adolescence:</td>
<td></td>
</tr>
<tr>
<td>Preliminary data on an Italian sample</td>
<td></td>
</tr>
<tr>
<td>Sleep-Dependent and Circadian Influences on Normal Nocturnal Sleep</td>
<td></td>
</tr>
<tr>
<td>Sleep-Disordered Breathing and Electrocardiographic Indicators of</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td></td>
</tr>
<tr>
<td>in the Wisconsin Sleep Cohort Study.</td>
<td></td>
</tr>
<tr>
<td>Sleep-Like State in Zebras: Effects of Melatonin and Sedatives</td>
<td></td>
</tr>
<tr>
<td>Sleep-related markers of idiopathic and PTSD nightmare sufferers:</td>
<td></td>
</tr>
<tr>
<td>nighttime awakenings vs. leg movements in sleep</td>
<td></td>
</tr>
</tbody>
</table>

AXXVII

Author Index

Abel T .................. A167, A422
Aboubaik G A69
Acebo C A5, A88, A190, A222, A413
Achermann P A29, A53, A112, A370, A373
Ackerson LC A76
Adler CH A368
Adler Y A111, A219, A257
Adrien J A146
Aeschbach D A6
Agid Y A372
Ahrens SR A426
Aikawa R A330
Akaishi NM A216
Akanmu M A132
Akersted T A191
Akersted TG A123, A188
Akhbar SD A67
Alkensor D A274
Alam MN A150
Alam N A9
Alam T A58
Almededde M A428
Albers HE A227
Albertario E A31
Albertario CL A31
Albin CR A13, A220
Allain H A29, A336
Allan L A404
Allen NJ A114
Allen A A58
Alley LG A383
Almeida FR A280, A281
Almeida FS A295, A300, A301
Almeida TF A378
Alboecky S A311
Aloe F A292, A428
Aloia MS A55
Al-Shajari N A307
Alt JA A144
Alvarez JC A172
Alves AC A343, A344
Alves RC A291
Amato RJ A383
Amirati N A99
Amlaner CJ A202
Anand S A392
Ancoli-Israel S A10, A164, A223, A228, A255, A268,
A286, A376, A391, A380
Andersen L A239
Anderson J A429
Andrades T A265, A300, A309
Angeli S A58
Ansari FP A227
Anson K A328
ApesianoGux X A284
Apte-Deshpande A A132, A138
Arand DL A106
Arendt J A4
Ari J A312
Armitage R A46, A46, A47, A119, A147
Armour BS A383
Arnold-Briant V A424
Arnett JT A55, A190, A413
Arner H A233
Arnold J A229
Arnulf I A172, A372
Arrigoni E A43, A49, A153
Arunabah A A303
Atallah NA A214
Atkinson D A271
Attarian HP A279
Atwell KKA A305
Atwood CW A288, A296
Atzram M A68
Aubrey JB A240
Auer DP A158
Avidan A A110, A414
Avish K A5
Avix A A252
Hinklebrad KR ......................................................... A195
Hill J ................................................................. A173
Hill SL ................................................................. A156
Hiltunen H .......................................................... A171, A291
Hilmanen H .......................................................... A291, A348, A419
Hidpale DC ............................................................ A237, A238, A419
Hirata M ................................................................. A266, A290
Hikata K ................................................................. A530
Hirsch LG ............................................................... A356
Hirschwick M ......................................................... A46, A47, A119, A147
Hirvonen K ............................................................ A171, A291, A399
Hiss K ................................................................. A302
Hof AH ................................................................. A251
Hoban TR ............................................................... A222, A394
Hobson JA .............................................................. A179, A178, A337, A338
Hock B ................................................................. A102
Hock L ................................................................. A303
Hoege B ................................................................. A373
Hofmann R ............................................................. A65, A117
Hoffmann E ............................................................ A232
Högl B ................................................................. A370, A371
Hollbrook CR ........................................................ A126, A211
Holltfield M ............................................................ A170, A348
Holmblad U ........................................................... A188
Holmes AL .............................................................. A201
Homma R ............................................................... A250
Hommia Y .............................................................. A251
Honda K ............................................................... A222, A23, A132
Hong S ................................................................. A317
Hong M ................................................................. A333
Hoo PK ................................................................. A428
Hood BD ................................................................. A19
Hooks K ................................................................. A11
Hop TV ................................................................. A94
Horajcada C ........................................................... A16
Horlucka M ............................................................. A50
Horne A ................................................................. A123, A380
Horne RL ............................................................... A68, A70, A71, A85
Horny A ................................................................. A341
Horton HT ............................................................... A224
HortonTh ............................................................... A192
Hos N ................................................................. A186
Hossain J .............................................................. A186
Hossain N ............................................................. A281, A353
Houck P ................................................................. A1
Houlette G ............................................................. A121
Housham DM .......................................................... A350, A355
Howard RS ............................................................ A293, A294
Hsieh M ................................................................. A433
Hsieh S ................................................................. A217
Hu Y ................................................................. A397
Huang Y ............................................................... A225
HUBBARD R .......................................................... A8
Huber R ............................................................... A112
Huber R ............................................................... A171, A172
Huff PM ................................................................. A118
Hughes RJ ............................................................. A122, A200
Hultron-Resendiz S ................................................ A146, A152, A230
Hulft JT ................................................................. A8, A89
Hummer R ............................................................ A17, A18
Hundemer H .......................................................... A17, A18
Hunsley MS ........................................................... A420
Hurni C ................................................................. A166
Husain AM ............................................................ A84
Husain M .............................................................. A47
Hutchins G ............................................................ A11
Huupponen E .......................................................... A166
Hyde PR ................................................................. A417
Ianci G ................................................................. A48
Iannone K ............................................................. A49
Iamano H ............................................................... A292
Imeri L ................................................................. A59
Inoue S ................................................................. A132
Ionescu D .............................................................. A23, A348
Ishiguro H .............................................................. A330
Ishik U ................................................................. A208
Ito H ................................................................. A229
Israel DN ............................................................... A376
Itasaka Y ............................................................... A414, A432
Ivers H ................................................................. A337
<table>
<thead>
<tr>
<th>Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfson A</td>
<td>A425</td>
</tr>
<tr>
<td>Wolintz A</td>
<td>A232</td>
</tr>
<tr>
<td>Wright Jr. KP</td>
<td>A3, A4, A89, A90, A200</td>
</tr>
<tr>
<td>Wronkiewicz C</td>
<td>A173</td>
</tr>
<tr>
<td>Wu C</td>
<td>A433</td>
</tr>
<tr>
<td>Wu MF</td>
<td>A20</td>
</tr>
<tr>
<td>Wurts SW</td>
<td>A23, A138, A154</td>
</tr>
<tr>
<td>Xi X</td>
<td>A296</td>
</tr>
<tr>
<td>Xiaobin X</td>
<td>A69</td>
</tr>
<tr>
<td>Xie JX</td>
<td>A257</td>
</tr>
<tr>
<td>Xie X</td>
<td>A418</td>
</tr>
<tr>
<td>Xiong Y</td>
<td>A21</td>
</tr>
<tr>
<td>Xu M</td>
<td>A129</td>
</tr>
<tr>
<td>Yamagishi K</td>
<td>A292</td>
</tr>
<tr>
<td>Yamashiro Y</td>
<td>A275</td>
</tr>
<tr>
<td>Yamuy J</td>
<td>A155</td>
</tr>
<tr>
<td>Yanagisawa M</td>
<td>A20, A21, A22, A24, A26, A27, A156</td>
</tr>
<tr>
<td>Yanai K</td>
<td>A23</td>
</tr>
<tr>
<td>Yang C</td>
<td>A433</td>
</tr>
<tr>
<td>Yano T</td>
<td>A330</td>
</tr>
<tr>
<td>Yarnell T</td>
<td>A306</td>
</tr>
<tr>
<td>Yassouridis A</td>
<td>A364, A373</td>
</tr>
<tr>
<td>Yesavage J</td>
<td>A346, A349</td>
</tr>
<tr>
<td>Yim RE</td>
<td>A375</td>
</tr>
<tr>
<td>Yoshida Y</td>
<td>A22, A96</td>
</tr>
<tr>
<td>You G</td>
<td>A331</td>
</tr>
<tr>
<td>Young T</td>
<td>A54, A230, A270, A300, A302, A422</td>
</tr>
<tr>
<td>Youngstedt SD</td>
<td>A122</td>
</tr>
<tr>
<td>Yousef EA</td>
<td>A356</td>
</tr>
<tr>
<td>Yu JC</td>
<td>A393</td>
</tr>
<tr>
<td>Yuen KM</td>
<td>A199, A284, A311</td>
</tr>
<tr>
<td>Zadra A</td>
<td>A351</td>
</tr>
<tr>
<td>Zampon A</td>
<td>A205</td>
</tr>
<tr>
<td>Zammit GK</td>
<td>A67</td>
</tr>
<tr>
<td>Zanotta</td>
<td>A259</td>
</tr>
<tr>
<td>Zanetone</td>
<td>A117, A328</td>
</tr>
<tr>
<td>Zaurov M</td>
<td>A174</td>
</tr>
<tr>
<td>Zee P</td>
<td>A86, A110, A198, A393, A421</td>
</tr>
<tr>
<td>Zeltz JM</td>
<td>A76, A197</td>
</tr>
<tr>
<td>Zemaitie D</td>
<td>A81</td>
</tr>
<tr>
<td>Zhan GX</td>
<td>A147</td>
</tr>
<tr>
<td>Zhang H</td>
<td>A92, A280, A284</td>
</tr>
<tr>
<td>Zhang K</td>
<td>A331</td>
</tr>
<tr>
<td>Zhang L</td>
<td>A421</td>
</tr>
<tr>
<td>Zhdanova IV</td>
<td>A39</td>
</tr>
<tr>
<td>Zhu S</td>
<td>A331</td>
</tr>
<tr>
<td>Ziegler MG</td>
<td>A223</td>
</tr>
<tr>
<td>Zizi F</td>
<td>A231, A232, A430</td>
</tr>
<tr>
<td>Zornetzer S</td>
<td>A185</td>
</tr>
<tr>
<td>Zoumakis M</td>
<td>A342</td>
</tr>
<tr>
<td>Zozula R</td>
<td>A9, A110</td>
</tr>
<tr>
<td>Zucconi M</td>
<td>A19, A219, A362, A372</td>
</tr>
<tr>
<td>Zukerman E</td>
<td>A367</td>
</tr>
</tbody>
</table>
Oral Presentations

001.E

Sleep-Dependent and Circadian Influences on Normal Nocturnal Sleep

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Introduction: Sleep propensity is influenced by both circadian and sleep-dependent factors, and may be further modified by age. In forced desynchrony, older men have reduced ability to maintain sleep after the circadian core body temperature minimum (CBTmin) compared to young men. It is uncertain whether the same relationship applies to sleep on a normal schedule. Our goals were: 1) To examine sleep efficiency (SE) in relation to CBTmin and sleep onset time (SOT) during normal nocturnal sleep; and 2) To examine age-related differences in these relationships.

Methods: Subjects included 36 older (18F, 18M; mean age 80.5 years) and 36 young adults (18F, 18M; mean age 24.5 years) who participated in various sleep and circadian rhythm studies. Subjects had no significant sleep, medical, or psychiatric disorders. They all had one night of baseline EEG sleep and CBT measurement at habitual sleep-wake times. CBTmin for each subject was estimated using linear mixed effects (LME) models. Sleep was visually scored in 60-second epochs. SE, the dependent variable, was analyzed in one-hour bins relative to SOT, and in one-hour bins relative to CBTmin. Statistical analysis consisted of two LME models for SE, using SOT or CBTmin as the referent. Models estimated age group effects and linear and quadratic time trends. Each model also examined the significance of the other referent (either CBTmin or SOT) as a covariate.

Results: Age groups differed significantly in overall sleep efficiency (92% versus 74%; t=8.14, p<0.0001), and wake-up time (0718 versus 0638; t=3.33, p=0.001), but not in time of CBTmin or interval between CBTmin and SOT. Results of LME models were as follows: 1) SE relative to SOT (Figure 1): The older group had progressively worse SE over time relative to the young group, indicated by a significant age group difference in the quadratic trend (Z=2.02, p=0.04). In addition, CBTmin was a significant covariate for the quadratic trend (Z=2.06, p=0.04), indicating that SE declined more slowly in those with later CBTmin. 2) SE relative to CBTmin (Figure 2): The older age group had significantly worse SE overall (Z=2.86, p=0.004), but the groups did not have different time courses relative to CBTmin, indicated by linear or quadratic trends. SOT was a significant covariate; maximal SE occurred earlier in subjects with an earlier SOT.

Conclusions: Even during nocturnal sleep at habitual sleep times, SE is significantly influenced by time into the sleep episode, circadian phase, and their interaction. Older adults have worse SE than young adults, particularly during the later hours of the morning. This effect is related to sleep-dependent, rather than circadian influences; the time course of SE in older and younger subjects differs as a function of time from SOT, but not as a function of time from CBTmin. Scheduling sleep at optimal circadian times and increasing homeostatic sleep drive may maximize SE in older adults.

Research supported by AG15138, AG00972, RR00056, MH30915, MH24652, AG13396, AG15136

002.E

Phase Advance of Habitual Sleep Timing and Circadian Temperature Rhythm in Middle-Aged Subjects

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Introduction: Compared to the young, elderly subjects show an earlier habitual sleep timing which is associated with a phase advance of the output of the circadian timing system (1-2). In the middle years of life (20-60y), increasing age is already related to earlier habitual wake time, earlier bedtime and higher morningness-eveningness scores (3). To our knowledge, no study compared characteristics of circadian temperature rhythm between young (20-39y) and middle-aged subjects (40-60y). Our aim was to evaluate whether age-related differences in circadian temperature rhythm are associated with changes in habitual sleep habits in the middle years of life.

Methods: Twenty-four healthy subjects were studied. They were separated into two groups according to their age: 11 Young (20-39 years, 5 women, 6 men; mean age: 31.0 ± 4.5 y) and 13 Middle-aged (40-59 years, 7 women, 6 men; mean age: 49.2 ± 6.4 y). Subjects completed a sleep diary for 14 days. Habitual bedtime, wake time, night time in bed and subjective sleep quality were calculated from the sleep diary. Subjects came to the laboratory for consecutive 4 nights and 2 days. Immediately following their habitual wake time of the third night, they entered a mini-constant routine of 25 hours during which rectal temperature was recorded every minute. During the mini-constant routine, subjects were kept awake in bed in constant behavioral and environmental conditions. Estimates of temperature circadian phase were derived from cosinor analysis with a 24h period applied to each subject’s temperature rhythm. Habitual phase angle was defined as the time interval between clock time occurrence of the fitted minimum and habitual wake time.
Results: Compared to the young subjects, bedtime and wake time were significantly earlier by approximately one hour in the middle-aged subjects (see Table). No significant difference was found between the groups in habitual night time in bed or in subjective sleep quality. The Figure illustrates habitual bedtime/wake time (rectangles) and 30-minute means of body temperature for the two groups. The fitted minimum of the circadian temperature rhythm was significantly earlier by approximately 1.45 hour in the middle-aged compared to the young (see Table). There was no significant difference among the groups on amplitude of the circadian temperature rhythm or on habitual phase-angle. After we controlled for the effect of group, phase was significantly associated with habitual bedtime and wake time. The phase of the circadian temperature rhythm explained 24% of the variance for habitual bedtime and 34% of the variance for habitual wake time.

Table 1

<table>
<thead>
<tr>
<th>Habitual Sleep timing parameters</th>
<th>Y (n=11)</th>
<th>M (n=13)</th>
<th>P</th>
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<tr>
<td>Wake time</td>
<td>7:51 ± 0.46</td>
<td>6:47 ± 0.56</td>
<td>0.01</td>
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<tr>
<td>Bedtime</td>
<td>23:41 ± 0.48</td>
<td>22:42 ± 0.56</td>
<td>0.01</td>
</tr>
<tr>
<td>Night time bed (min)</td>
<td>451.7 ± 44.2</td>
<td>457.5 ± 38.3</td>
<td>n.s</td>
</tr>
<tr>
<td>Subjective sleep quality</td>
<td>77.2 ± 9.8</td>
<td>77.4 ± 8.2</td>
<td>n.s</td>
</tr>
<tr>
<td>Time of the nadir</td>
<td>6:33 ± 1:14</td>
<td>4:46 ± 1:59</td>
<td>0.02</td>
</tr>
<tr>
<td>Amplitude</td>
<td>0.25 ± 0.07</td>
<td>0.28 ± 0.12</td>
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<tr>
<td>Phase-angle</td>
<td>1:18 ± 1:24</td>
<td>2:01 ± 1:22</td>
<td>n.s</td>
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Correlation with phase after controlling for the effects of age

<table>
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<th>Habitual Sleep timing parameters</th>
<th>Beta</th>
<th>R²</th>
<th>P</th>
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<tr>
<td>Wake time</td>
<td>.611</td>
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<td>0.001</td>
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<tr>
<td>Bedtime</td>
<td>.520</td>
<td>.249</td>
<td>0.007</td>
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Conclusions: To our knowledge, this is the first demonstration that people in their forties and fifties not only show earlier sleep timing but also a phase advance of temperature circadian rhythm compared to young subjects. These age-related differences are of the same magnitude as those reported in healthy elderly subjects (2-3). Other age-related circadian differences such as a reduction in circadian temperature amplitude and smaller habitual phase-angle between temperature nadir and habitual wake time may arise later in life. These results suggest that age-related changes in the timing of the output of the circadian timing system appear as early as the middle years of life.

References:

Sleep Ability and Sleep Need in Aging: Insights From a 90-Minute Day Study

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Introduction: Older adults have reduced ability to sleep, but whether they have reduced need to sleep is less clear. One operational way to define sleep need is to measure subjective state and performance related to sleep drive or sleep loss. The goal of this study was to compare sleep ability, subjective state, and performance in older adult (OA) and young adult (YA) groups using a 90-minute day paradigm.

Methods: Subjects included 18 young (10M, 8F, 23.2±2.7 years) and 10 older (5M, 5F, 77±6 years) adults with no significant medical, psychiatric, or sleep disorders. One baseline day and night on the subjects’ habitual schedule was followed by 60 hours of a 90-minute sleep-wake cycle (40 cycles). All sleep episodes were recorded, and scored in 20-second epochs. Core body temperature (CBT) was measured continuously. Each 90-minute cycle began with 30-minutes of enforced bedtime in darkness. During 60-minute wake periods, subjects completed visual analog ratings of subjective state; during alternate cycles, they completed either a four-choice reaction time or a response inhibition task (inhibiting button presses on 25% of trials with an auditory cue). The number of correct inhibitions was the dependent measure. Five-minute average CBT data were expressed as deviation from the subject’s 60-hour mean; other data were expressed in original units, and referenced to CBT phase. Linear mixed effects were used to model linear, 24, 12, and 6-hour components in the data, as well as age group and group*time interactions. Rhythm parameter estimates in each group were also contrasted with 95% confidence intervals (C.I.) based on bootstrapping.

Results: OA and YA did not differ in CBT amplitude or phase. OA had lower sleep time (difference in means 5.28 minutes, C.I. 3.85-6.71) and lower amplitude of the circadian sleep rhythm (difference in means 4.0 minutes, C.I. 1.40-5.89) (Figure 1). Despite getting less sleep, OA had a lower mean level (difference in means 7.56, C.I. 0-14.36) and lower amplitude (difference in means 13.51, C.I. 3.10-17.85) of the circadian rhythm in self-rated sleepiness. On most performance measures, OA performed more slowly than YA, and the two groups showed similar rhythmic and linear trends. However, YA had increased commission errors on the inhibition task over time, whereas OA showed improvement (group*time interaction F=9.42, p=0.002) (Figure 2)
Conclusions: Older adults had less sleep and a blunted circadian rhythm of sleep compared to young adults. However, the older adults did not show greater subjective or performance impairments in a circadian or cumulative sense. On the inhibition task, the elderly showed improvement when the young adults showed worsening. As judged by subjective state and performance in this paradigm, healthy older adults not only get less sleep, they may need less sleep. The observed changes may relate to reduced homeostatic sleep drive in the elderly. This study also confirms that older adults can generate robust endogenous circadian rhythms (CBT), but that rhythms further downstream from the pacemaker (sleep, performance) show reduced circadian variation.

Research supported by AG15138, AG00972, RR00056, MH30915

004.E

Relationship Between Cognitive Performance and Core Body Temperature During a 28-hr Forced Desynchrony Protocol

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Introduction: It has long been recognized that there exists a positive relationship between core body temperature and performance levels (1). In general, during total sleep deprivation body temperature and performance levels exhibit a circadian pattern with high levels during the habitual waking day and low levels during habitual sleep time at night. Whether this relationship between body temperature and performance simply reflects the regulation of both body temperature and performance by the circadian pacemaker and sleep homeostasis or whether performance is to some degree also regulated by core body temperature level is unclear given previous research designs. To address the latter, we used a 28-hr forced desynchrony protocol to investigate whether higher temperature levels were associated with higher performance levels while controlling for circadian phase and time awake.

Methods: Fourteen healthy subjects, 3 females and 11 males (mean±SD age 31.6 ± 6.4; range 20-41), were studied as part of a 55-day inpatient protocol on circadian entrainment. Following the entrainment protocol (2), subjects were scheduled to a 28-hr day (18.66 hr awake and 9.33 hr asleep) for 12 consecutive days. Subjects performed a battery of tests every 2 hours during wakefulness. Performance on a digit symbol substitution test was analyzed. Performance data were averaged into 60 degree (4 hr) bins for the circadian component and 2 hr bins for the time awake component. Body temperature data, recorded every minute, were averaged into 1 hr bins, associated with the performance battery, during scheduled wake episodes. The temperature minimum was assigned to 0 degrees and averaged into 15 degree (1 hr) bins for the circadian component. Performance data were transformed into deviation from the mean. Performance scores were categorized as being associated with the highest or lowest temperature value for each separate circadian and time awake bin. If more than 2 performance tests or temperature values occurred at the same bin, only the scores associated with the lowest and highest temperature level were used in the analyses. Significance was analyzed with repeated measure ANOVA techniques.

Results: Results for the cognitive performance test (see Figures) and core body temperature (data not shown) showed significant main effects of circadian phase and hours awake (P<0.0001). Performance levels were lowest near to but shortly after the core body temperature minimum and decreased throughout the waking day regardless of temperature level. However, subjects performed better when temperature levels were high at the same circadian and hours awake bin (P<0.0001).

Figure 1

Figure 2
Conclusions: The results of this study suggest that core body temperature level independent of circadian phase and time awake can influence cognitive performance levels and provides further support for the hypothesis that body temperature is an underlying mechanism regulating performance. However, whether this result applies to other types of neurobehavioural function remains to be determined.

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005.E

Circadian and Sleep-Wake Dependent Control of Alertness, Mood and Performance in Field Studies of Blind Subjects

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Introduction: Laboratory-based ‘forced desynchrony’ protocols have demonstrated that the circadian system and sleep homeostatic processes interact to determine alertness, mood and neurobehavioural performance (1). We have investigated whether these processes contribute to the decrements in alertness and mood reported by blind individuals with free-running circadian rhythms while living in society and attempting to maintain a 24-h sleep-wake schedule.

Methods: Seventeen free-running blind subjects (15 males, 2 females; aged 32-68 yrs) were studied (2). Regression analysis of cosinor-derived acrophase (peak) times for urinary 6-sulphatoxymelatonin (aMT6s) was used to determine the free-running period of the subjects’ rhythms (τ=24h+slope; range=23.92-24.79 h). Over at least four weeks, subjects completed daily sleep and nap diaries. Mood and performance were assessed from four 9-point mood scales (alert-sleepy, cheerful-miserable) completed daily and performance (reaction time for all responses) data were collected in 16 and 15 subjects, respectively. Each observation was assigned a circadian phase (0°-aMT6s acrophase) and time elapsed since night-time sleep or time elapsed since waking from the last sleep (3h intervals) were assessed by ANOVA.

Results: There was a significant effect of circadian phase on alertness and cheerfulness (p<0.01), with minimal alertness and cheerfulness coincident with aMT6s acrophase time (0 degrees) (Figure A). Both time elapsed since night-time sleep and time elapsed since the last sleep had a significant relationship with alertness (p<0.001), with maximal alertness at 3-6 hours after waking. Alertness remained at a plateau until 15-18 hours after waking following which a marked reduction in alertness occurred (Figure B). A sleep inertia effect was also observed, with reduced alertness 0-3 hours after waking (Figure B). Cheerfulness also showed a significant effect with time since last sleep (p<0.05) with an increase in cheerfulness with hours awake. No other mood parameter showed significant effects. Performance (reaction time for all responses) showed similar changes to alertness with respect to time elapsed since both night-time and last sleep (p<0.001) with slowest reaction times 0-3 and 15-18 hours after waking.

Conclusions: This study demonstrates circadian- and wake-dependent changes in alertness, mood and performance in free-running blind people studied in an uncontrolled field environment. This finding implies that desynchrony between the sleep-wake cycle and endogenous circadian rhythms contribute to the decrements in alertness and waking performance reported by blind individuals.

References:

The authors would like to thank Prof. Simon Folkard and Dr. Peter Totterdell for development of the performance test. This work was supported by South Thames Regional Health Authority, Servier and The Wellcome Trust (grants 048197/Z/96/Z and 060018B/99/Z).

006.E

Practice Effects Observed Over a Month-long 28-hour Forced Desynchrony Protocol in a Cognitive Throughput Task are well Described by a Saturating Exponential Function

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Introduction: Previous research examining cognitive performance during forced desynchrony (FD) experiments have controlled for individual differences in performance ability by transforming raw performance scores into deviations from mean performance across the FD1. However, this method does not account for practice effects that may be present. Practice effects are commonly recognized as an initial high rate of performance improvement while the test is being learned, followed by continued improvement with additional exposure to the test. Here we assess whether practice effects may be present in FD performance data, and, if so, whether the deviation from a saturating exponential curve fitted to the data would provide a better description of performance across the FD than deviation from the mean.

Methods: Eleven healthy male subjects (18-30 yrs), were studied for approximately one month in the laboratory. After 2 baseline days and a 40-hour constant routine (CR), subjects participated in a FD in which they were scheduled to a 28-h day; 8.67 h of scheduled wakefulness in dim light (10-20 lux) and 9.33 h of scheduled sleep in darkness. Cogni-
tive performance was assessed throughout the study approximately every hour during wakefulness using a 4-minute addition task (ADD). The ADD was scored as the number of sums completed, irrespective of errors. Satirating exponential functions of the form $A + Be^{-(time/C)}$ were fit to the ADD scores from the entire experiment except for hours 16-40 of wakefulness on the CR. In this function, $A$ represents the practice effect asymptote, $A + B$ represents performance level at the start of the experiment, and $C$ represents the time constant of the practice effect.

**Results:** Overall performance on the ADD improved across the entire month-long experiment for all but one subject. Therefore, the mean FD value (figure, dashed lines) tended to overestimate typical performance levels during the beginning of the FD and underestimate typical levels at the end of the FD. The saturating exponential functions (solid lines) provided good fits to the data of all the subjects, regardless of whether their scores improved in a saturating (top panel) or in a linear (bottom panel) manner. There were large inter-individual differences in the rate of improvement across the study (median time constant = 22.62 days, IQR = 7.5 to 34.1 days), with some subjects nearing their asymptotes quite rapidly, and others continuing to show marked improvement after an entire month of hourly testing.

**Conclusions:** The results of this study suggest that practice effects can continue to occur in simple cognitive tests for as long as a month. However, the rate and manner of improvement varies widely across individuals. We found that saturating exponential function provides a more accurate approximation of performance changes across time than a simple mean. However, it remains to be determined whether the use of deviation from a fitted saturating exponential rather than deviation from the mean to transform cognitive performance data significantly alters the conclusions derived from performance data gathered in prior forced desynchrony studies.

**References:**

Research supported by NIA grant PO1-AG09975; NIH GCRC grant MO1-RR02635; NASA-NSBRI cooperative agreements NCC9-58 and NCC2-1167; AFOSR grants F49620-95-1-0388 and F49620-01-1-0004; ARO grant DAAD19-99-1-0241.

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007.E

**Intrinsic Period Shorter Than 24 Hours in an Adolescent Boy**

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**Introduction:** Methods of assessing circadian period in humans using forced desynchrony (FD) in dim light show period lengths close to 24 hours (1); whereas techniques in which lighting was controlled by participants resulted in periods measured closer to 25 hours. With FD, reports of period less than 24 have been infrequent; two young adults have been reported (1,2). We have postulated that the sleep phase delay during adolescent development may be associated with longer intrinsic period, and we have assessed period in adolescents using a 28-hr FD, finding slightly longer period than in adults. The present case is the first adolescent we have assessed in whom period is shorter than 24 hr.

**Methods:** The participant kept a self-selected schedule for one week followed by melatonin onset phase determination, 10 cycles of a 24-h sleep-wake schedule at home (lights off 2200; lights on 0800), and a 20-day in-lab session where lighting was held at <20 lux. A 36h constant routine followed one adaptation night, after which a recovery night and 12 cycles of 28h FD ensued. FD included an 11h40m sleep opportunity and 16h20m wake episode each cycle. Saliva was collected during waking episodes for subsequent melatonin assay. Rectal temperature was collected during constant routines at the beginning and end of FD.

**Results:** The adolescent was a 14.9-year-old male, Tanner stage 5. He and his parents reported no family history of sleep or psychiatric disorders in his first-degree relatives, no chronic medical conditions, and no current illness or drug use. A urine toxicology test was negative. His morningness/eveningness score on the 1989 Smith et al. Scale was 45, demonstrating strong morning phase preference. Actigraphy during self-selected sleep showed an average bedtime of 2156 and rise time of 0608. Melatonin onset phase at the initial assessment was 2022; after the scheduled nights, melatonin onset phase was 2013. The figure depicts phase of melatonin onsets, melatonin offsets, and core temperature minimum from cycles spanning constant routine assessments and forced desynchrony. Linear regression across phase markers was used to estimate intrinsic period: melatonin onset estimate = 23.70 hr; melatonin offset = 23.71 hr; temperature minimum = 23.75 hr.

**Conclusions:** These data provide a coherent set of evidence for an unusually short intrinsic period in this adolescent male. Of interest is the boy’s considerable morning phase preference. In addition, a subsequent test of evening melatonin suppression to light showed minimal response
A Longer Biological Night in Long Sleepers than in Short Sleepers

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Introduction: Habitual sleep duration varies greatly among individuals. Whether there is a physiological system that mediates short sleep in some individuals and long sleep in others is unknown. Previous studies found no difference in the kinetics of the homeostatic process between habitual short sleepers and long sleepers. In the present study, we tried to find out whether individual differences in sleep duration are associated with systematic differences in the temporal program of the circadian pacemaker. We hypothesized that the duration of the nocturnal interval of circadian rhythms (i.e., the ‘biological night’) is longer in long sleepers than in short sleepers.

Methods: Young (20-34 years) healthy short sleepers (8 males, 6 females; sleep duration <6 h) and long sleepers (5 males, 5 females; >9 h) who were recruited on the basis of questionnaires, 2-4 week sleep logs and wrist motor activity recordings underwent a '~40-h constant routine protocol during which they stayed awake in bed in dim light (<10 lux), without having access to clocks. Blood samples were collected half-hourly for 24 h (14:00-14:00) and plasma melatonin concentrations were measured. Rectal temperature was measured continuously. Subjective sleepiness ratings were obtained half-hourly on 100-mm visual analog scales. We compared between the two groups the duration of the nocturnal intervals of high melatonin levels (interval between first and last detectable plasma concentration), low body temperature (interval between the two midrange crossing points of smoothed temperature data), and increasing sleepiness (interval between last local minimum and maximum of smoothed sleepiness data).

Results: The nocturnal interval of high plasma melatonin levels was longer (p<0.05, one-tailed t-test) in long sleepers (10.5±0.2 (SEM) h) than in short sleepers (9.6±0.3 h). The interval duration did not correlate (r=0.20, n.s., N=22) with melatonin amplitude (maximum of smoothed plasma levels), nor did the amplitude differ significantly between the two groups. The nocturnal interval of low body temperature was longer (p<0.05) in long sleepers (11.7±0.7 h) than in short sleepers (10.1±0.4 h). The nocturnal interval of increasing sleepiness (see Figure) was also longer (p<0.05) in long sleepers (11.4±1.2 h) than in short sleepers (8.5±0.6 h). The maximum in sleepiness showed a close relationship to habitual wake-up time, which occurred ~2.5 h later in long sleepers than in short sleepers.

Conclusions: The biological night that is programmed by the circadian pacemaker is longer in long sleepers than in short sleepers. We suggest that the persistence of a circadian pacemaker’s individual program, as was evident under constant conditions, underlies the commonly experienced difficulty of changing habitual sleep duration willfully.

References:

Research supported by fellowships from the National Institutes of Health, the Swiss National Science Foundation and the Boral Foundation (to D.A.).
Research supported by Cyberonics and NINDS KO2 NS02099

medically refractory seizures underwent baseline polysomnograms (PSGs). Three months after VNS was activated, treatment PSGs were performed. Stimulus intensities ranged from 0.75-2.75 mA. Sleep and respiratory analyses were done by a registered polysomnographer (MM) blinded to the VNS signal. In our laboratory, an obstructive apnea is defined by a decrease in airflow of 80% or more from baseline for 10 or more seconds, with preservation of any effort. A hypopnea is defined by any decrease in airflow or effort for 10 or more seconds that is accompanied by an EEG arousal or a 4% or more desaturation from baseline oxygen saturation. Overall AHIs and separate AHIs were calculated for VNS activation and non-activation.

Results: Baseline PSGs: One of 16 patients had AHIs >5 (6.8). Treatment PSGs: Five patients of the 16 had treatment AHIs >5 and are depicted in Table 1. Two of the five patients had a treatment AHI above 10. Both had preexisting obstructive sleep apnea (OSA), one was untreated (#1) and one had received tonsillectomy (#2). The other three patients had a treatment AHI in the 5-10 range. The activation AHI was higher than the non-activation AHI indicating that events were more frequent during stimulation than without stimulation (t = 3.93; p = 0.017; paired two-tailed t-test). Eleven of the 16 patients had an AHI < 5, including one patient with preexisting OSA on CPAP therapy during the study. Follow-up studies: Patient #1, who had a treatment AHI of 11.3, received a CPAP trial. All respiratory events were associated with VNS stimulation at low CPAP levels and were resolved at a higher CPAP level (9 cm water). The results of esophageal pressure monitoring in the patient with a baseline AHI of 6.8 indicated that crescendos in esophageal pressure occurred during VNS activation, suggesting an obstructive pattern.

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stimulus Intensity</th>
<th>Base AHI</th>
<th>Treat. AHI</th>
<th>Activation AHI</th>
<th>Non-Activation AHI</th>
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<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>4.0</td>
<td>11.3</td>
<td>26.2</td>
<td>6.9</td>
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<tr>
<td>2</td>
<td>1.25</td>
<td>2.0</td>
<td>10.1</td>
<td>11.9</td>
<td>7.9</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>1.4</td>
<td>5.9</td>
<td>10.7</td>
<td>5.2</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>0.9</td>
<td>9.9</td>
<td>20.2</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>4.9</td>
<td>8.2</td>
<td>16.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Stimulation on/off time for this patient was 30 seconds every 3 minutes and was 30 seconds every 5 minutes in all other patients

Conclusions: Our results indicate that VNS affects respiration during sleep and should be used with care, particularly in patients with preexisting OSA. VNS activation was associated with respiratory events, although the overall AHI remained <5 in the majority of patients and was only modestly elevated (<10) in three others without preexisting OSA. CPAP resolved VNS-related respiratory events. So far, our results support an obstructive pattern. Experimental studies will be necessary to further define the effects of VNS on breathing.

References:

010J

The Effect of Surgically Induced Weight Loss on Sleep-Disordered Breathing and Pharyngeal Anatomy

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(1) Brigham and Women’s Hospital, Boston, MA, (2) Harvard Medical School, Boston, MA

Introduction: Obesity is the most important risk factor for the development of Obstructive Sleep Apnea. While previous studies have documented improvement in sleep disordered breathing following substantial weight loss, the impact of weight loss on pharyngeal anatomy as evaluated by three-dimensional reconstruction of the upper airway has not been assessed. We hypothesized that surgically induced weight loss would lead to a increase in the pharyngeal lumen, decreased fat in the upper airway, and less lung-volume dependence of pharyngeal airway size.

Methods: We studied 8 morbidly obese subjects (BMI > 45 kg/m2 ) before and after (7 to date) substantial weight loss following gastroplasty. All subjects underwent standard polysomnography. Measurement of pharyngeal anatomy was performed using spiral computed tomography (CT) and computer-aided three dimensional reconstruction software (3-D Slicer, BWH Surgical Planning Laboratory). CT scans were acquired during a single breath-hold at 3 lung volumes—FRC, TLC and RV. Analysis of images included both measurements at the level of the smallest airway lumen as well as the entire pharyngeal airway between the hard palate and the top of the hyoid bone.

Results: Table 1 shows that associated with significant weight loss, sleep-disordered breathing improved in all subjects. Evaluation of pharyngeal anatomy revealed an increase in the size of the minimal cross-sectional area of the pharyngeal area, an increase in pharyngeal airway volume, and a decrease in the volume of the pharyngeal fat pads. The lung-volume dependence of the pharyngeal airway (the amount of airway collapse at RV when compared to TLC) markedly decreased (figure 1). In addition, both before (r = 0.66 p = 0.01) and after weight loss (r = 0.71 p = 0.07) lung volume dependence of pharyngeal volume correlated with RDI.

Conclusions: Our results indicate that surgically induced weight loss improves sleep-disordered breathing, increases pharyngeal lumen, decreases fat in the pharyngeal fat pads and decreases lung-volume dependence of the pharyngeal area.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>PRE-OP</th>
<th>POST-OP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEIGHT (lbs)</td>
<td>351 +/- 21.9</td>
<td>240 +/- 2.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>48.6 +/- 4.0</td>
<td>43.8 +/- 2.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>54 +/- 28</td>
<td>25 +/- 14</td>
<td>0.03</td>
</tr>
<tr>
<td>Minimal Airway Area (mm2)</td>
<td>30.7 +/- 0.06</td>
<td>47.5 +/- 8.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Airway Volume (mm3)</td>
<td>9005 +/- 168</td>
<td>12454 +/- 1515</td>
<td>0.10</td>
</tr>
<tr>
<td>Pharyngeal Fat Pad Volume (mm3)</td>
<td>2491 +/- 991</td>
<td>2453 +/- 874</td>
<td>0.02</td>
</tr>
</tbody>
</table>

References:
(1) Jakab M, 2001

Figure 1
Conclusions: Weight loss is associated with an improvement in sleep disordered breathing as well as improved pharyngeal airway anatomy. As we have previously shown a decrease in pharyngeal dilator muscle activity with weight loss, this strongly suggests that anatomical changes are the primary effect of weight loss, yielding decreased resistance and less requirement for neuromuscular compensation.

References:

Research supported by NHLBI HL48531/HL60292/HL1024601, NSF Pickwick Fellowship

011.J

The Influence of Pressure versus Flow on Genioglossal Activation During Passive Mechanical Ventilation

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Introduction: Pharyngeal dilator muscles are important in the maintenance of pharyngeal patency and in the pathogenesis of obstructive sleep apnea. Both local and central mechanisms are likely important in the control of phasic pharyngeal dilator muscle activity. However, the relative influence of negative intrapharyngeal pressure, flow, resistance and carbon dioxide on genioglossal muscle activation within a breath has not been carefully assessed.

Methods: Using a previously reported iron lung model to diminish the influence of central respiratory pattern generators, we studied 18 subjects who were normal based on history and physical exam. In each subject, we measured intramuscular genioglossus electromyogram (GGEMG, as a percent of maximum activation), epiglottic (Pepi) and choanal pressure (using nasally placed Millar pressure catheters), mask pressure, and flow (pneumotachometer). In order to dissociate pressure and flow stimuli, a low density gas mixture (Heliox, 80% helium and 20% oxygen) was used. Each subject was studied during seven conditions including spontaneous breathing (air and Heliox), and passive ventilation (at two CO2 levels, each with both air and Heliox). We assessed both within breath and between breath relationships.

Results: During spontaneous breathing, Heliox was associated with a fall in genioglossal phasic activation compared with air breathing (4.74±1.32 to 3.96±0.99 %maximum units, p<0.08), in association with a reduced negative pressure stimulus. In addition, during spontaneous breathing, the within breath GG/flow slope tended to change (7.39±2.1 vs 5.53±1.35 %max/l/sec, p=0.06 air vs heliox), while the GG/Pepi slope was quite stable (-1.63±0.48 vs –1.03±0.71 %max/cmH2O, p=0.5). During passive ventilation, there was no substantial change in the within breath GG/Pepi relationship, despite alterations in pressure, gas density, carbon dioxide, and resistance (repeated measures ANOVA, p=0.74). The GG/flow relationship varied substantially. Forward stepwise regression analysis within subjects suggests that epiglottic pressure is the most important variable in predicting phasic genioglossal activation within a breath across all conditions. Using group mean averages, an extremely robust relationship was observed between GGEMG and Pepi (R2=0.98, see Figure), with less robust relationship for flow/GG (R2=0.45) and resistance/GG (R2=0.68).

Figure 1

Conclusions: These data suggest that intrapharyngeal pressure is the most important determinant of genioglossal activation both within a breath and between breaths. Flow, resistance, and carbon dioxide level appear to be less important

Research supported by NHLBI HL48531/HL60292, Medical Research Council of Canada, American Heart Association (New England Chapter)

012.J

A Two-Dimensional Finite Element Model of Collapse in the Male and Female Upper Airway

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Introduction: Although male gender is an important risk factor for obstructive sleep apnea syndrome, the mechanisms by which gender increases the risk of upper airway collapse during sleep are unclear. Using magnetic resonance imaging (MRI), we have previously observed gender differences in pharyngeal anatomy in normal subjects. Men have a longer pharyngeal airway (hard palate to epiglottis) and increased soft palate cross sectional area, independent of body size. We now sought, using a computational airway model, to determine the influence of these variables on pharyngeal collapsibility.

Methods: We used the finite element method (ADINA software), which is a widely accepted numerical procedure for obtaining solutions in engineering analyses, to develop a 2D model. The anatomical structures were generated based on MRI measurements from 10 normal subjects (5 men, 5 women) which were signal averaged to produce a representative male and a representative female airway. We estimated the elastic modulus (measure of tissue deformation) of the tongue and uvula under paralyzed (passive) and sleeping conditions using the published P pclose values (Isonen 1997 & Schwartz 1988, respectively). Assuming the pharynx to be two dimensional in the middle sagittal plane, we simulated the effects of tongue and uvula movements anteroposteriorly during the development of negative pharyngeal pressure.

Results: Under simulated paralyzed conditions, the upper airway of men was more collapsible than that of women (P close = -5 cmH2O men vs -7 cmH2O in women) based on purely anatomical factors. Under sleeping conditions, the same behavior was demonstrated (P close =13 cmH2O in men vs -18 cmH2O in women, see Figure). We also observed that pharyngeal airway length in isolation had a substantial influence on P close. With a 30% reduction in pharyngeal airway length, the P close fell from –13 cmH2O to –19 cmH2O. The figure demonstrates the male and female airway in the “sleeping” condition both prior to and after the development of –13cmH2O pressure in the airway. As can be seen, the male airway collapsed completely at this pressure while the female air-
way was reduced by 65% but remained patent.

Figure 1

Conclusions: This model confirms the importance of gender differences in pharyngeal anatomy and the isolated influence of pharyngeal airway length on upper airway collapsibility. Purely anatomical factors explain substantial differences in upper airway biomechanics between men and women.

Research supported by NIH NHLBI HL60292/HL48531, American Heart Association (New England), Medical Research Council Canada, Sleep Medical Education Res. Fdn.

013.J

Predicting Therapeutic Protrusive Distance for a Mandibular Advancing Device

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Introduction: Mandibular advancement devices (MAD) have been shown to be effective treating 45-70% of patients with obstructive sleep apnea (OSA). MAD’s allow progressive protrusion under clinical supervision. The purpose of this study was to prospectively identify favourable candidates for MAD therapy and to accurately estimate the optimal protrusive distance. We have developed a remotely controlled mandibular positioner (RCMP) to advance the mandible during polysomnographic monitoring to predetermine therapeutic protrusive distance.

Methods: Forty-four patients were recruited sequentially from all patients referred for suspected OSA at the Alberta Lung Association Sleep Centre. Patients with home diagnostic studies confirming OSA who had suitable dentitions underwent baseline clinical evaluation. An overnight RCMP PSG study was performed on all subjects. The mandible was advanced in 1mm increments following visualization of pharyngeal anatomy and the isolated influence of pharyngeal airway closed @ -13 cmH2O. The RCMP predicted 16 successes, 12 partial successes and 10 failures. Overall success rate of 14/38 (37%). The MAD was a success at target in 10/16 (63%) of predicted successes. Average Baseline ESS was 8.7 Average ESS at one month post titration was 5.9. Average baseline Calgary SAQULI was 4.3 and 5.3 at one month post titration.

Table 1

<table>
<thead>
<tr>
<th>RDI Prediction</th>
<th>Initial</th>
<th>Target</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success X=16</td>
<td>20.5</td>
<td>12.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Partial X=12</td>
<td>37.4</td>
<td>29.0</td>
<td>30.0</td>
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<tr>
<td>Failure X=10</td>
<td>21.5</td>
<td>21.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Total X=38</td>
<td>26.9</td>
<td></td>
<td>18.1</td>
</tr>
</tbody>
</table>

Mean RDI of Prediction Groups

Conclusions: The RCMP was predictive of MAD failure and of success. The negative predictive capability of the RCMP test could be of clinical value in presenting treatment options. Such information may enhance acceptance of CPAP therapy. Patients with a successful RCMP test could benefit by the reduction of time to effective treatment and treatment cost. Target distance was a reliable therapeutic advancement. Target advancement could increase MAD compliance, decrease titration time and decrease the need for extensive adjustment capabilities of an appliance.

Research supported by Alberta Heritage Foundation for Medical Research

014.J

CPAP Compliance: An Assessment and Education Intervention Study

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Introduction: Nasal continuous positive airway pressure (CPAP) therapy is the non-surgical treatment of choice for obstructive sleep apnea (OSA), although failure to comply with treatment has been reported as high as 25%-50%(1). Few studies have examined cognitive/behavioral factors associated with CPAP compliance(2). This study was designed to: 1) assess possible barriers to compliance in patients recently diagnosed with OSA using a “stages of change” model(3); 2) provide educational interventions for patients early in the treatment process; and 3) objectively assess the efficacy of patient-directed educational interventions.

Methods: Twenty-nine patients (23M, 6F) with polysomnographically diagnosed OSA were recruited for the study. All patients underwent CPAP/Bilevel titration in the sleep laboratory and were prescribed the Sullivan V Elite, VPAP II or VPAP II ST (ResMed Corp., Sydney, Australia). These devices provided compliance data on the “number of hours at effective pressure” and “missed nights”. All patients received homecare visits at Weeks #1, 2 and 4 to ensure proper usage of the equipment. Patients were randomized to either a “usual care” (N=12) or “educational intervention” group (N=17). Those assigned to the “educational intervention” group received written or videotape materials that were deemed appropriate to their present “stage of change” (“Precontemplation”, “Contemplation”, “Preparation”, “Action”, or “Maintenance”). Subjective assessment of daytime functioning was obtained at baseline (Week...
Results: The mean age of the overall sample was 49.6±11.5 years. At baseline, mean AHI was 64.2±33.9 events/hr; mean initial CPAP level was 8.9±2.4 cm H2O. No significant differences were observed between the groups on baseline sleep and demographic characteristics. To date, 12/29 patients have completed the full 6-month protocol. At baseline, 59% of patients were in “Action”; 24% were in “Contemplation”; 17% were in “Preparation”. Despite incomplete data at this time, a number of interesting trends were observed. In particular, a small difference between the usual care and educational intervention group was observed in mean CPAP hours at Week #2 (4.0±2.3 hrs vs. 4.4±2.4 hrs.) and was almost doubled by Week #24 (3.3±2.3 hrs vs. 6.0±2.1 hrs.). A similar trend towards improved compliance was noted for the number of missed nights at Week #24 (20.6±18.0 vs. 3.7±5.1). Subjective measures of improvement (ESS and FOSQ scores) did not reveal any trends between groups at either Week #6 or #24. Both groups showed significant improvement on ESS mean scores from baseline (13.5 usual care vs. 11.1 educational intervention group) to Week #6 (7.7 vs. 7.5).

Conclusions: Despite the small sample size, several noteworthy trends were observed. First, the educational intervention group was found to have increased compliance as measured by both CPAP hours and number of missed nights. Additionally, a positive treatment effect on ESS scores was observed in both groups.

References:

(2) Stepnowsky CJ, Ancoli-Israel S. CPAP adherence is associated with the decisional balance index. Sleep 2000; 23:A287.

We acknowledge the assistance of ResMed Corp., A&J Care, Inc. (Glendale, NY), PromptCare (Clark, NJ), Community Care Services (Somerset, NJ), and Young’s Medical (Somerville, NJ) in data collection. Research supported by K07 HL03635 to RR.

015.J

CPAP Adherence: Predictors from Social-Cognitive Theory

Stepnowsky, Jr. CJ Marler MR, Ancoli-Israel S
Department of Psychiatry, University of California, San Diego and Veterans Affairs San Diego Healthcare System

Introduction: Low patient adherence limits the effectiveness of nasal CPAP therapy, the treatment-of-choice for obstructive sleep apnea. Previous studies examining the predictors of adherence to CPAP have limited the variables studied to patient, disease status, and treatment variables, with no reliable predictors found. This prospective study investigated the relationship between Social Cognitive Theory (SCT) (Bandura, 1986) variables and objectively measured CPAP adherence over a one month time period.

Methods: Fifty-one consecutively presenting patients (49 men) to the Pulmonary Clinic at the Veterans Affairs San Diego Healthcare System participated. All participants were diagnosed with sleep apnea and were prescribed the Respironics Aria LX CPAP machine (Respironics, Inc., Pittsburgh, PA), which came outfitted with an internal clock counter that recorded usage information. Adherence was defined as the number of hours of CPAP use per night and was measured at one-month. All participants were first-time users of CPAP and none had previous surgical or other treatment for sleep apnea. Measures included scales developed specifically to measure SCT variables: self-efficacy, outcome expectations, social support, and knowledge. Each has been shown to have acceptable internal consistency (.90, .85, .92 and .66, respectively). Scales were administered at one-week post CPAP-fitting. Hierarchical regression analysis was performed between the number of hours of CPAP usage per night and the four SCT variables. CPAP pressure was chosen as the covariate because it has been shown that CPAP pressure is in large part a function of body mass index (BMI) and AHI.

Results: The mean age of the sample was 54.1 ± 12.3 years (range 30-76). The mean BMI was 36.4 ± 9.0 (range 21-61). The mean AHI of the sample was 40.1 ± 25.3 (range 2.1-120). The mean initial CPAP pressure was 9.1 ± 2.0 cm H2O (range 6-15). Mean nightly usage for the sample was 3.4 ± 2.5 (range 0-10.8) hours per night. The mean CPAP usage period for the entire group was 31.7 ± 8 days (range 20-67). The results of the regression analyses are shown in the table. At step 1 R² = .046, adjusted R² = .025 (p = .148). At step 2 R² = .280, adjusted R² = .193 (p = .016). The change in R² between the two steps was .234 (p = .019), meaning that SCT measured one-week post CPAP-fitting accounted for a statistically significant amount of variance in objective CPAP adherence measured at one month.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>T</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP Pressure</td>
<td>0.22</td>
<td>1.47</td>
<td>0.148</td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPAP Pressure</td>
<td>0.22</td>
<td>1.52</td>
<td>0.136</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>0.26</td>
<td>1.46</td>
<td>0.152</td>
</tr>
<tr>
<td>Outcome Expectations</td>
<td>0.09</td>
<td>0.51</td>
<td>0.661</td>
</tr>
<tr>
<td>Social Support</td>
<td>0.08</td>
<td>0.56</td>
<td>0.580</td>
</tr>
<tr>
<td>Knowledge</td>
<td>0.16</td>
<td>1.00</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Conclusions: Twenty-three percent of the variance in CPAP adherence can be predicted by knowing the scores on the four Social-Cognitive Theory variables measured one week after starting CPAP, over and beyond that accounted for by CPAP pressure (and thereby BMI and AHI). These results are encouraging because they provide us with a new direction of research in order to better understand the factors associated with CPAP adherence. The advantage to studying variables such as these from Social-Cognitive Theory is that they are modifiable and amenable to intervention.

References:


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016.J


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Introduction: Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS)
is often associated with excessive daytime sleepiness. Modafinil is a central nonamphetamine awakening substance with vigilance promoting properties, however its use in OSAHS is not well defined yet. The aim of this randomized, double-blind, placebo-controlled study was to investigate the efficacy and safety of modafinil on daytime sleepiness, memory, night sleep and respiration in patients with OSAHS. Fifty patients with OSAHS 34 males and 16 females aged 35 to 58 years were studied. Thirty of them were under CPAP treatment but they had residual daytime sleepiness (group I, 20 had OSAHS but they refused therapy with CPAP (group II).

Methods: Patients were given daily modafinil or placebo in a crossover design for 12 weeks. Daily measurements of arterial blood pressure and a 12-week sleep-wake diary kept by the patients. Sleep laboratory evaluation took place before starting modafinil or placebo and 84 days after. It included, full night polysomnography followed by a Multiple Sleep Latency Test (MSLT) and a verbal memory test (Mini Mental State:MMSE). All patients completed the Epworth Sleepiness Scale (ESS).

Results: Modafinil was well tolerated, and no patient stopped the treatment during the study. A significant (p<0.0001) reduction of daytime sleepiness and sleep as well as an overall improvement in the verbal memory test was seen in the modafinil treatment vs placebo in both groups. Drug tolerance was good, night sleep and respiration were not modified.

Conclusions: Our results suggest that modafinil is a safe mode of treatment since reduces daytime sleepiness, improves objective and subjective daytime vigilance, and memory without modifying night sleep and respiratory events, and may be an adjunctive therapy in patients with OSAHS and residual daytime sleepiness.

References:

017.G

Adolescent Sleep and School Start Times

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(1) University of Kentucky, (2) Fayette County Schools

Introduction: There is considerable evidence that a majority of adolescents do not get enough sleep to function well during the day (1,2). Both social and biological pressures appear to cause a shift in sleep patterns during the transition to adolescence, with the result that adolescents stay up progressively later as they progress through high school (3). Since high schools almost always start earlier than elementary and middle schools, this virtually guarantees that adolescents will suffer from chronic sleep deprivation during the school week. While concern is growing among the sleep community about the possible detrimental effect of early school start times for adolescents, school scheduling is incredibly complex. For example, parents of younger children complain about their children waiting for buses in the dark and others argue that starting high school later will simply result in adolescents staying up even later, with no net gain in sleep. To assess the actual effect of delayed high school start times, we administered a survey of the sleep habits of the children and adolescents from an entire school district before and after a change in school start times.

Methods: In April of Year 1 (1998), a total of 13,150 students from grades 6-12 and parents of children from grades K-5 filled out questionnaires concerning students’ sleep habits and various aspects of their daytime functioning. In April of Year 2 (1999), 14,659 students or parents filled out the same questionnaire. School start times during Year 1 were 7:30, 8:00, and 9:00 AM for high, middle and elementary schools, respectively. In Year 2, elementary schools started one hour earlier and the high and middle schools started one hour later. The data reported here focus on the sleep habits of middle and high school students before and after the change in school start times.

Results: Students in Grades 6-12 averaged from 15 to 50 additional minutes of sleep per weeknight in Year 2 compared with Year 1. When considering only those students who provided data both years, there were significant overall gains in weekday sleep from Year 1 to Year 2 (F=167.8, p<.001), with 31% of middle school students and 47% of high school students sleeping at least 30 minutes more per weeknight. The percentage of adolescents who got at least 8 hours of sleep per weeknight increased from 69.6% to 78.9% in middle schools and from 19.6% to 42.2% in high schools. The percentage of adolescents who got at least 9 hours of sleep increased from 28.4% to 41.5% in middle schools and from 2.8% to 8% in high schools. The amount of additional sleep on Friday nights (a crude proxy for sleep deprivation) decreased significantly among middle school students from 1.2 hours to 1.0 hours (F=22.8, p<.001) and among high school students from 2.1 hours to 1.2 hours (F=310.2, p<.001).

Figure 1
Conclusions: Moving the school start time one hour later for adolescents resulted in meaningful increases in sleep time, an increase in the percentage of students who got an adequate amount of sleep, and a decrease in catch-up sleep on weekends. Nevertheless, a majority of these adolescents are still probably not getting enough sleep to function optimally in school.

References:
(3) Carskadon M: When worlds collide: Adolescent need for sleep ver-

Research supported by Research supported by NIH grant 5 K07 HL03637-03

Caffeine Consumption and Weekly Sleep Patterns in U.S. Seventh, Eighth and Ninth Graders

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Ohio State University

Introduction: Coffee has long been considered a substance for adults, but no limitations have been placed on the consumption of caffeinated soft drinks by teenagers. Soda dispensing machines have become increasingly common in U.S. middle and high schools, and no public policy regarding caffeine consumption by youngsters has been formulated.

Methods: Seventh, eighth and ninth-grade students of a public school in Columbus, Ohio were surveyed in 1998 and 1999 by one of us (D.B.) while he was himself a 9th and 10th grader. Students completed an investigator-developed questionnaire in science class each morning for while he was himself a 9th and 10th grader. Students completed an investigator-developed questionnaire in science class each morning for 14-23 days. Total daily caffeine intake was calculated from the caffeine investigators and followed a weekly cycle, peaking on Saturday & reaching a mini-

Results: The participation rate was 35.6%. The 191 respondents (125 girls, 66 boys) ranged between 12-15 years of age. Questionnaires were completed for an average of 21.5 days. Caffeine was consumed on over 70% of all days that were surveyed. The respondents consumed a mean of 1.1 caffeine-containing items per day, representing 60.1 mg of caffeine. The largest intake was 379.4 mg/day by a 13.3 year-old, male eighth grader. An ANOVA revealed that caffeine use was greater in boys than girls, and followed a weekly cycle, peaking on Saturday & reaching a minimum on Wednesday. Higher caffeine consumption was associated with shorter sleep times, greater WASO (wake time after sleep onset) and increased nap time. WASO increased on days when more caffeine was consumed. Older teenagers went to sleep later, as did boys. The latest bedtimes occurred on Saturdays, and the earliest were on Tuesdays. Boys got up later and both boys & girls got up later on weekend mornings. Mean sleep durations ranged from 6.1 to 9.8 hrs/day (mean 8.3 hrs/day). Sleep duration was shorter in boys, shorter with greater use of caffeine and shorter when nap times were shorter. Sleep durations also varied by day of week (longest on Sundays, shortest on Mondays).

Conclusions: The observations on weekly sleep confirm earlier findings (Mantz et al, 2000), whereas those on caffeine are new. Teenagers are moderate consumers of caffeine, mostly in soft drinks of an ordinary (not high-caffeine) type. Boys are heavier users of caffeine, as previously reported (Lee et al., 1999). The data do not establish whether caffeine causes disturbed sleep or is a response to it. In either case, they strongly suggest that caffeinated beverages were employed by teenagers for their pharmacological effect and not simply for their flavor or ability to quench thirst. The increasing availability of soft-drink dispensing machines in schools is apparently welcomed by students and is profitable to school boards, but our findings suggest that it may be interfering with the nightly sleep of teenagers. Studies of caffeine use and sleep should be conducted elsewhere to either confirm or refute these findings.

References:

Feasibility of Using Unattended Polysomnography in Children—Preliminary Report of the Tucson Children Assessment of Sleep Apnea Study (TuCASA)

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Introduction: Obstructive sleep apnea (OSA) and, more broadly sleep disordered breathing (SDB) in childhood, may produce adverse neurobehavioral and cardiopulmonary consequences [1]. However, the prevalence of OSA/SDB in children is difficult to determine because there are no normative data based on large epidemiologic studies employing polysomnography (PSG). The TuCASA study, which began recruiting in November 1999, is utilizing unattended home PSG to objectively determine the prevalence of OSA/SDB in children, and to determine its relationship to symptoms, performance on neurobehavioral measures and physiologic/anatomic risk factors. This is a preliminary report of the feasibility of using home PSG to assess the presence of OSA/SDB in the initial cohort of children enrolled in the TuCASA study.

Methods: Parents of all children in 4 Tucson elementary schools were asked to complete a survey inquiring about symptoms attributable to OSA/SDB. Additionally, parents were asked whether they would be interested in having their child undergo a PSG. Children of those who consented had a PSG performed in their home using the Compumedics P Series System (Abbotsville, Australia). It consists of a patient interface box (PIB, containing amplifiers and filters) which is connected to a data recorder (containing a PCMCIA flashcard, rechargeable battery and oximeter). Electrodes and sensors are attached to the recorder through the PIB. This system has been successfully used to perform unattended PSG in 6,440 adults as part of the Sleep Heart Health Study (SHHS)[2]. The TuCASA recording montage consisted of EEG (C3A2, C4A1), right and left EOG, chin EMG, thoracic and abdominal excursions (inductive
plethysmography), nasal/oral airflow by thermistry, nasal pressure, a single lead ECG, body position (Hg gauge sensor), sound and a light sensor. Sensors were placed and the equipment calibrated during an evening home visit and removed the next day. Subsequently, a technician scored the data using Compumedics software on an epoch by epoch basis. An acceptable study contained at least 4 hours of scorable EEG, oximetry and respiratory data (airflow, thoracic or abdominal signals). Attempts were made to restudy those participants in whom an acceptable study was not obtained. Overall study grades were assigned using criteria adapted from SHHS [2].

**Results:** As of 10/31/00, 105 children (boys: 64 and girls: 41; age 6-8 years: 46 and age 9-11 years: 49) have undergone PSG. 95 studies (90%) met minimal acceptable criteria on the first attempt, 8 studies (8%) on a second attempt and 1 study (1%) on a third attempt. In only 1 participant (a 6 year old girl) was there a failure to eventually obtain a successful study. Causes for study failure were equipment malfunction (3), inadequate oximetry (5) and < 4 hours of scorable data (2). Study failures occurred more frequently in younger children. Overall study grades for the 104 acceptable studies were Excellent 58%, Good 39% and Fair 3%. For individual channels, > 6 hours of artifact free signal were seen in 96% of EEG, 94% of EOG, 84% of chin EMG, 52% of thermistor airflow, 48% of nasal pressure airflow, 94% of chest movement, 95% of abdominal movement, 91% of oximetry and 97% of position sensor. Acquisition of nasal pressure signals was poor in younger children. The overall respiratory disturbance index recorded in the cohort ranged from 0.6 to 72.4 events/hour/total sleep time (median=6.5).

**Conclusions:** This preliminary analysis of the TuCASA study indicates that it is feasible to perform unattended PSG in children ranging from 6-11 years of age with a high rate of success. Study failures occurred slightly more often in younger children and in most cases were related to equipment malfunction or failure to obtain an adequate oximetry recording. Nasal pressure recordings were poor in younger children and probably should not be used as the only measure of airflow in this setting.

**References:**

**Research supported by HL 62373**

**020.G**

**Iron Deficiency Anemia (IDA) in Infancy Alters the Temporal Organization of Sleep States in Childhood**

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**Introduction:** Abnormalities in sleep/wake and activity rhythms have been reported in IDA rodents. When IDA occurs in rat pups, changes in these rhythms are not reverted with iron therapy (1). Although these long-lasting changes have not yet be explained, they may relate to altered CNS trans-mission and/or myelination. Thus far, modifications in IDA animals have been identified in several neurotransmitter systems (eg, dopamine, serotonin, catecholamine and GABA), and in myelin formation and maintenance (1). Since the organization of sleep is a complex phenomenon that depends on many CNS processes, and iron is required by several CNS functions, there are many ways that IDA might disrupt sleep. Moreover, since IDA in human infants generally occurs during the latter part of the brain’s growth spurt, the normal development of sleep patterns could be affected. We predicted that IDA in infancy will be associated with altered sleep organization in childhood.

**Methods:** All-night polysomnographic recordings were done in a group of healthy 3- to 4-year-old chilean children who were treated for IDA (n=24) or were nonanemic (controls, n=26) in infancy. The following variables were simultaneously recorded: EEG, EOG, EMG, cardiac, respiratory and motor activities, and oximetry. All data was automatically converted from analog-to-digital signals, collected on an internal high capacity hard drive, and then transferred to a CD-R drive for off-line analyses. Sleep was scored according to Rechtschaffen and Kales criteria; NREM stages III and IV were grouped as SWS. For each child the duration of each SWS and REM sleep episode was determined, and then analyzed according to the successive thirds of the night.

**Results:** Between groups, REM and SWS episodes were differently distributed throughout the night (Table 1). The pattern in duration of REM sleep episodes was different between groups: in controls, there was a net increase of the duration of REM episodes with advancing thirds, while in former IDA children the duration was similar in all thirds. Differences between groups attained significance for the first and last third. In addition, former IDA children showed short latency and a consistent tendency for long duration of the first REM episode. Although SWS episodes duration followed the same trend throughout the night in both groups — a significant reduction between the first and the next thirds—, differences between groups were apparent during the first third.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>FORMER IDA</th>
<th>CONTROLS</th>
<th>P&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>REM latency (min)</td>
<td>115.5</td>
<td>150.5</td>
<td>.02</td>
</tr>
<tr>
<td>First REM episode duration (min)</td>
<td>15.7</td>
<td>10.8</td>
<td>.06</td>
</tr>
<tr>
<td>REM episodes duration throughout the night</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st third (min)</td>
<td>12.6</td>
<td>5.6</td>
<td>.02</td>
</tr>
<tr>
<td>2nd third (min)</td>
<td>16.6</td>
<td>13.6</td>
<td>NS</td>
</tr>
<tr>
<td>3rd third (min)</td>
<td>13.1</td>
<td>20.1</td>
<td>.001</td>
</tr>
<tr>
<td>SWS episodes duration throughout the night</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st third (min)</td>
<td>26.9</td>
<td>38.3</td>
<td>.01</td>
</tr>
<tr>
<td>2nd third (min)</td>
<td>17.0</td>
<td>15.6</td>
<td>NS</td>
</tr>
<tr>
<td>3rd third (min)</td>
<td>16.0</td>
<td>14.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusions:** The characteristics of REM sleep organization especially during the first part of the night are reminiscent of REM sleep patterns often observed in depressive patients and could be related to the depressive symptomatology observed in former IDA in early adolescence (3). Altered temporal organization of sleep patterns in healthy former IDA children suggest that iron is an essential micronutrient for the normal progression of sleep patterns. It is conceivable that alterations in sleep organization relate to behavioral changes that characterize former IDA children during wakefulness (1).

**References:**

**Research supported by Grants from NICHD (HD33487) and Fondecyt (CONICYT, Chile 1000657)**
Periodic Limb Movement Disorder and Ferritin Level in Children

Simakajornboon N,1,2 Mack C,2 Sharon D,2 Jackson T,1 Vlasic V,1 Beckerman RC,1,2
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Introduction: Restless leg syndrome and periodic limb movement disorder (PLMD) in adult and elderly are correlated with low ferritin which reflects low tissue iron concentration (1). This disorder has been described in children with some different clinical presentation (2). The association between ferritin level and PLMD in pediatric population is currently unknown.

Methods: Children who have been diagnosed with PLMD for the last two years at Tulane Sleep Center were retrospectively analyzed. All of these children underwent a formal overnight polysomnographic evaluation in the sleep laboratory with monitoring of the following parameters; body position, EOG, 3 channel EEG, chin EMG, EMG of the anterior tibialis, pulse oximetry, thoracic and abdominal inductance plethysmography, oronasal airflow, end-tidal pCO2, transcutaneous pO2 and pCO2. Periodic limb movements in sleep (PLMS) were scored consistent with ASDA Atlas Task Force criteria (3). PLMS were identified on EMG of the anterior tibialis as a sequence of four or more leg movements, each 0.5 to 5 seconds in duration, and separated by at least 5 but not more than 90 seconds. Initial ferritin level and complete blood count were performed in every case; iron level and follow up ferritin level were done formed in every case; iron level and follow up ferritin level were done in some children with PLMD. Patients were excluded from the analysis if they were on any iron supplementation within 2 months before sleep study, or other medication that may alter PLMD for example opiate, dopaminergic agonists, clonazepam etc.

Results: A total of eight patients met the criteria for entry into the analysis. These patients ranged from 1 to 13 years (Mean=6.25 years). Most of patients presented with sleep disturbance; six of the eight patients (75%) had sleep onset problems, four of the eight patients (50%) had sleep maintenance problems, seven of the eight patients (87.5%) were restless sleeper. PLMD affected daytime function with six of eight patients (75%) had either excessive daytime sleepiness or hyperactivity. Three of the patients (37.5%) were diagnosed with attention deficit hyperactivity disorders and two of the patients (25%) were previously diagnosed with sleep onset association disorder. All patients had a moderate periodic leg movements with PLMS index ranged from 15 to 27.9 per hour (Mean=19.2, SD.=7.0). Seven of the eight patients (87.5%) had ferritin level below 50 ng/ml (Mean=23.7, SD=10.4) and four of them had ferritin level below 25 ng/ml. Complete blood count revealed no difference in hemoglobin or hematocrit compared to age-matched normative data. Six of the eight patients were treated with iron sulfate and four of six treated patients (66.7%) revealed a clinical improvement. The remaining two patients required additional treatment with dopaminergic agonist.

Conclusions: PLMD in children is associated with low ferritin level and iron therapy improves clinical symptoms in some children.

References:
(2) Picchietti DL., Walters AS. Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 1999;22(3):297-300.

Research supported by Constance S. Kaufman Fund

The Relationship Between Sleep Disorders and Attention Deficit Hyperactivity Disorder (ADHD): Objective Findings

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Introduction: Children with sleep disorders often display daytime symptoms of both inattention and hyperactivity. Previous studies have found an elevated incidence of sleep-related symptoms, including snoring and complaints of restless legs, in ADHD patients. Furthermore, there is some evidence for an increased incidence of periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) in children with ADHD. However, currently there are no scale polysomnographic studies investigating the incidence of sleep disorders in these children. The objective of this study was to investigate the incidence of sleep disorders, diagnosed via polysomnography, in children diagnosed with ADHD. The data presented here represent our preliminary results from an ongoing study of sleep in ADHD children.

Methods: 19 children (16 males, 3 females) with a confirmed diagnosis of ADHD were studied. The mean age was 10.3 (range = 6-14) years. All children were referred from a developmental pediatrician specializing in ADHD and were not selected on the basis of sleep complaints or symptoms of sleep disorders. Patients did not have a history of other neurological or psychiatric disorders. 17 of the 19 subjects were on stimulant treatment for their ADHD although all subjects refrained from stimulant use for 48-hours prior to their overnight study. All subjects underwent a complete diagnostic polysomnographic study (16 channels) including a standard 4-channel EEG montage, and assessment of respiratory and leg EMG parameters. Airflow was assessed via the combination of a nasal pressure transducer and oral thermocouple. Descriptive statistics along with percentages of patients meeting AASM diagnostic criteria for OSAS and PLMD are presented below.

Results: Patients had a mean total sleep time of 433.9 ± 13.2 with an average sleep efficiency of 88.5% ± 2.0. The mean sleep-onset latency was 35.8 ± 8.1 minutes. The mean RDI for the group was 3.8 ± 1.4. The mean PLM Index was 5.8 ± 1.2. 15.8% (3 of 19) of the subjects met the diagnostic criteria for OSAS (RDI > 5) with RDI values ranging from 10.7 to 22.2. 42.1% (8 of 19) of the children met the diagnostic criteria for PLMD (PLM Index > 5) with index values ranging from 5.2 to 19.1. Two of the eight PLMD positive patients also report symptoms consistent with RLS. In total, 57.9% (11 of 19) of subjects had a positive diagnosis for one or more sleep disorders.

Conclusions: The children studied clearly have elevated incidence of sleep disorders compared to reported prevalence in the general population (1-3% for OSAS, 5-15% for PLMD). Clearly this is of concern since several case studies have shown that treatment of sleep disorders in children with ADHD can lead to dramatic improvement in daytime behavior and discontinuation of stimulant medication. Further research is necessary in order to provide better diagnostic criteria for ADHD as well to clarify the role sleep plays in the etiology of the disorder.

This research was supported by a grant by the Oklahoma Center for the Advancement of Science and Technology (OCAST) and an equipment donation by Grass Instruments, Inc.
Sleep, Daytime Sleepiness, and Clinical Subtypes of ADHD

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Introduction: The present study compares children with attention deficit/hyperactivity disorder (ADHD) with children from the general population on the following factors: nocturnal breathing, daytime sleepiness, and behavior. Studies using parental report measures have found an increase in sleep complaints among children with ADHD, including habitual snoring and excessive daytime sleepiness\(^1\). ADHD can be differentiated by groups of symptoms that define its presentation. Two clinical subtypes include predominantly inattentive type (ADHD-I) and predominantly hyperactive/impulsive type (ADHD-HI). There is a need to investigate differences in daytime sleepiness and symptoms of sleep-related breathing disorders between children with different clinical subtypes of ADHD.

Methods: Data were collected on 65 children ages 6 to 16 years (mean = 10.14, SD = 2.82) diagnosed with ADHD-HI (n = 16) or ADHD-I (n = 19). Thirty children from the general population served as controls. Ninety-six percent were Caucasian and 4\% were African-American. The ADHD group did not differ significantly from the control group on age, race, and gender. Children with ADHD were recruited from two sources: The University of Southern Mississippi School Psychology Service Center and a local pediatrician’s office. Diagnosis was based on DSM-IV criteria, intelligence testing, achievement testing, home and school rating scales, and a computerized performance test. Children with learning disorders were excluded. Children and parents that were participating in a research project concerning the relationship between working memory and ADHD were asked to complete a general information form and the Pediatric Sleep Questionnaire (PSQ). The PSQ is a 22-item parental-report questionnaire that contains questions related to snoring, witnessed apneas, daytime sleepiness, inattention, hyperactivity, and other symptoms. Items on the PSQ can be divided into three subscales: breathing, sleepiness, and behavior. Response rate was 63%.

Results

Table 1

<table>
<thead>
<tr>
<th>Breathing Items</th>
<th>ADHD</th>
<th>ADHD-I</th>
<th>ADHD-HI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habitual snoring</td>
<td>5(16.7)</td>
<td>2(12.5)</td>
<td>3(21.4)</td>
<td>3(10.3)</td>
</tr>
<tr>
<td>Always snores</td>
<td>4(12.5)</td>
<td>2(12.5)</td>
<td>2(12.5)</td>
<td>1(3.3)</td>
</tr>
<tr>
<td>Snores loudly</td>
<td>3(9.4)</td>
<td>2(11.8)</td>
<td>1(6.7)</td>
<td>7(24.1)</td>
</tr>
<tr>
<td>Heavy breathing</td>
<td>7(21.2)</td>
<td>4(23.5)</td>
<td>3(18.8)</td>
<td>11(37.9)</td>
</tr>
<tr>
<td>Trouble breathing</td>
<td>1(3.1)</td>
<td>1(6.3)</td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Stops breathing</td>
<td>1(2.9)</td>
<td>0(0)</td>
<td>1(6.3)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Mouth breathing</td>
<td>4(12.9)</td>
<td>3(15.8)</td>
<td>1(8.3)</td>
<td>5(16.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10(37.0)</td>
<td>6(37.5)</td>
<td>4(36.4)</td>
<td>8(28.6)</td>
</tr>
<tr>
<td>A.m. headaches</td>
<td>6(17.1)</td>
<td>4(21.1)</td>
<td>2(12.5)</td>
<td>2(6.7)</td>
</tr>
</tbody>
</table>

Sleeplessness Items

<table>
<thead>
<tr>
<th>Daytime sleepiness</th>
<th>ADHD</th>
<th>ADHD-I</th>
<th>ADHD-HI</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>14(45.5)</td>
<td>10(52.6)</td>
<td>5(35.7)</td>
<td>2(6.9)</td>
<td></td>
</tr>
<tr>
<td>12(34.4)</td>
<td>10(52.6)</td>
<td>2(12.5)</td>
<td>1(3.3)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) ch-square p<.05
\(^b\) ADHD-I sleepier than ADHD-HI and Control group
\(^c\) ADHD-HI sleepier than Control group

Percent of subjects was determined by the number of positive answers divided by the number of positive and negative answers and multiplied by 100 (don’t knows and missing values were excluded).

Results: As expected, the behavior subscale scores were significantly higher among the ADHD-I children (mean = 81.30) and ADHD-HI children (mean = 81.30) than among the children in the Control group (mean = 26.1), \(F(2,59)=34.04\) (p<.001). The ADHD children did not have significantly higher scores on the breathing subscale (p=.755) nor was significance found for any of the specific items that comprised this scale (see Table 1). Group differences were found on both items of the sleepiness subscale (see Table 1). The sleepiness of the Inattentive group was greater than that of the Hyperactive/Impulsive group and both these groups were rated sleepier than the Control group (Table 1).

Conclusions: These results did not confirm that children with ADHD are more likely to habitually snore than non-ADHD children. As compared to children in the general population, children with ADHD are sleepier during the daytime, with sleepiness being greater for the inattentive subtype. These findings confirm the need to differentiate between subtypes when studying the sleep of children with ADHD.

References


Sleep in Children with Juvenile Rheumatoid Arthritis

Labysek E, Stein L, Bloom B, Owens J, Lunsford V
(1) University of North Carolina, (2) Brown University

Introduction: Sleep disturbances, daytime sleepiness and fatigue have been widely documented in adults diagnosed with rheumatoid arthritis; however, little has been done to evaluate sleep in children diagnosed with Juvenile Rheumatoid Arthritis (JRA). The present study examines sleep patterns in children with JRA and age/sex-matched controls.

Methods: Participants included 28 children ages 6-12. Fourteen children (3 boys, 11 girls) diagnosed with polyarticular JRA (>5 joints affected) were recruited from the pediatric rheumatology clinic, and 14 age/sex matched healthy control children were recruited locally. Exclusion criteria included psychiatric illness, history of a major sleep disorder, or chronic illness from a non-arthritis condition. Children kept a self-selected sleep schedule for 8 days while wearing a wrist actigraph (Mini-Motionlogger AMI, Ardsley, NY), and completed a daily sleep diary and pain scale1 at bedtime and risetime. Actigraph data were analyzed in association with the diary to estimate sleep/wake using Action-W software and algorithm2 (AMI). Six variables were averaged for school nights: sleep onset (first min. of at least 3 consecutive min. of sleep after bedtime), sleep offset (last min. of at least 5 consecutive min. of sleep before risetime), sleep period time (SPT = sleep onset to sleep offset), minutes scored as wake and minutes scored as sleep during SPT, and sleep% (min. in SPT/min. of sleep). Independent t-tests were computed to examine group differences, and partial correlations were done to evaluate the relationship of pain to sleep.

Results: Values for sleep behavior derived from wrist actigraphy are listed in Table 1. In JRA children, morning pain was positively correlated with SPT (r=.29; p = 0.038); no significant correlations were noted between evening pain and identified sleep variables. Reports of pain in control children were negligible; therefore correlations were not computed.
### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>JRA (n=14)</th>
<th>Control (n=14)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>Mean ± SE</td>
<td>p value</td>
</tr>
<tr>
<td>Sleep Onset</td>
<td>21:31 ± 5.2 m</td>
<td>21:29 ± 4.3 m</td>
<td>.831</td>
</tr>
<tr>
<td>(hr:min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Offset</td>
<td>06:19 ± 5.8 m</td>
<td>06:34 ± 2.7 m</td>
<td>.297</td>
</tr>
<tr>
<td>(hr:min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Period Time</td>
<td>529.6 ± 6.1</td>
<td>545.4 ± 5.1</td>
<td>.228</td>
</tr>
<tr>
<td>(min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake</td>
<td>57.0 ± 3.8</td>
<td>47.1 ± 3.5</td>
<td>.448</td>
</tr>
<tr>
<td>(min.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>472.6 ± 7.5</td>
<td>498.4 ± 5.0</td>
<td>.083</td>
</tr>
<tr>
<td>%</td>
<td>89.1 ± 0.8</td>
<td>91.5 ± 0.6</td>
<td>.270</td>
</tr>
<tr>
<td>Morning Pain</td>
<td>13.0 ± 2.3</td>
<td>2.9 ± 0.8</td>
<td>.014</td>
</tr>
<tr>
<td>(scale 0-100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evening Pain</td>
<td>12.5 ± 2.7</td>
<td>2.1 ± 0.5</td>
<td>.032</td>
</tr>
<tr>
<td>(scale 0-100)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions

Sample size was small; however, trends in the data suggest that JRA children are more variable and spend less time asleep at night during SPT than healthy controls. Furthermore, longer SPT is associated with increased morning pain. Future analyses will focus on longitudinal evaluations of sleep in JRA children during periods of disease exacerbation and remission and will include actigraphy and polysomnographic measurements.

### References

3. Schroeder CM, Nguyen-Michel V, Thibault A, Krieger J. Sleep Disorders Unit - University Hospital - Strasbourg - France

### Results

For the total sample, significant differences were found between the RLS group and the control group concerning BMI (28.4 ± 6.0 vs. 33.9 ± 12.6, p<0.0001) and serum ferritin levels (154.1 ng/ml ± 141.7 vs. 201.1 ng/ml ± 131.9, p<0.005), indicating a lower BMI and lower serum ferritin levels in the RLS group, whereas there were no significant differences in age, serum iron and serum transferrin levels. After matching for age, sex and BMI and excluding serum ferritin values exceeding 300 ng/ml, no significant difference could be found between the RLS group and controls, as shown in the table below. The differences found in the total sample between patients and controls seem to be mainly due to a) the larger percentage of women in the unmatched RLS group compared to the control group (38% vs. 22%) and b) to a higher percentage of control patients with a dysmetabolic disorder associated with especially high levels of serum ferritin.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>RLS n=52</th>
<th>Controls n=52</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.9 ± 10.7</td>
<td>53.7 ± 10.9</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.0 ± 5.4</td>
<td>29.4 ± 5.1</td>
<td>ns</td>
</tr>
<tr>
<td>Iron (umol/l)</td>
<td>16.7 ± 6.9</td>
<td>18.4 ± 6.9</td>
<td>ns</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>144.3 ± 79.2</td>
<td>162.8 ± 67.0</td>
<td>ns</td>
</tr>
<tr>
<td>Transferrin (g/l)</td>
<td>2.4 ± 0.5</td>
<td>2.4 ± 0.4</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Conclusions

No differences could be found in serum iron status in patients with RLS compared to controls after matching for age, sex and BMI.

### References

challenge at two different times (2300 and 1100), at least 7 days apart. After an insertion of an antecubital iv line for blood drawing, patients were asked to lay down in bed for 90 min. An oral administration of 200 mg L-dopa/50 mg carbidopa was provided at 2300 on one occasion, and at 1100 on the other. Blood was drawn 20 and 5 minutes before administration of the drug, as well as at 15, 30, 45, 60, 75, 90, 105 and 120 minutes after, and analyzed for plasma values of GH and prolactine (PRL). Statistical analysis was performed by means of non-parametric tests (Wilcoxon test) both on the time series of (baseline corrected) hormonal plasma values as well as on the area under the response curve (AUC).

Results: No statistically significant differences were observed between 2300 and 1100 plasma values of GH and PRL. Following nighttime administration of L-DOPA, a reduction in the AUC of the PRL response (p=0.01) and a trend toward an increased response of GH following were found. Comparison of the hormonal responses across time showed increased nighttime responses of GH 75 (p< 0.05) and 90 min. (p< 0.1) after the administration of L-DOPA, but no differences on PRL responses.

Conclusions: The results suggest mainly an enhanced stimulation of GH along with an inhibition in the AUC of PRL following nighttime administration of L-DOPA, supporting an increased sensitivity at night of dopamine receptors in I-RLS patients. We hypothesize that these changes in dopamine receptor sensitivity reflect circadian variations in dopaminergic function, with hypofunction at night. The result support the view that the function of the dopamine system may vary significantly with the circadian cycle, producing different functional outcomes at different times. However, in the absence of data on a control population, it remains to be seen whether the finding merely represents normal physiological circadian changes. More patients, along with a control group are planned to be included in the future.

References:

Conclusions: In this first study on the long-term (1year) safety of pergolide in the treatment of RLS, there was no significant difference compared to placebo when looking at the overall number of patients with AEs. Compared to the AE-profile of pergolide in PD, nausea was more frequent in this study, but frequent AEs like dyskinesia, hallucinations, and confusion did not occur at all, others like dizziness and somnolence were less frequent. Overall pergolide therapy in RLS was safe and well tolerated.

Research supported by Eli Lilly Indianapolis
Pramipexole in the Management of Restless Legs Syndrome: An Extended Study

Silber MH, Girish M, Izurieta R
Sleep Disorders Center, Mayo Clinic, Rochester, MN

Introduction: Pramipexole, a dopamine agonist predominantly binding to the D3 receptor, is effective in the treatment of restless legs syndrome (RLS)[1]. Experience suggests that fewer side effects are experienced with pramipexole compared to pergolide. A follow up study (7 patients for a mean of 7.8 months) showed continued effectiveness, no augmentation, only mild side effects and a mean daily dose of 0.5 mg [2]. Our study aims were to assess dosage, effectiveness, side effects, and augmentation in consecutive patients prescribed pramipexole and followed in our Sleep Center.

Methods: We identified all patients fulfilling the International Restless Legs Study Group criteria for RLS treated with pramipexole between January 1, 1998 and December 31, 1999. Charts were reviewed, data abstracted and analyzed.

Results: 75 patients were identified; adequate information was available for 61 (81%) (37 female; 24 male). All but 3 patients had failed previous medication, usually levodopa or pergolide. Eleven patients (18%) discontinued pramipexole after a mean of 3.8 months (only 1 > 6 months) because of side effects in 8, lack of effect in 1, and both in 2. The remaining 50 patients were followed for a mean of 13.1 months (range 1-29 months). All patients were commenced on 0.125 or 0.25 mg in a single evening dose. The mean final daily dose was 0.66 mg (range 0.125-3.0 mg). The dose was higher than 0.75 mg in 14 patients (28%). There was no correlation between duration of use and final dose (r=0.17). The drug was completely effective in 41 patients (67%), partially effective in 16 (26%) and ineffective in 4 (7%). Daytime augmentation occurred in 11 patients (18%) at a mean daily dose of 0.61 mg and a mean duration on the drug of 8.5 months (range 2-16 months). 64% of these patients had experienced augmentation with pergolide or levodopa. Augmentation was generally treatable with extra doses of pramipexole earlier in the day. Side effects, most mild and transient, were described by 24 patients (39%). These included insomnia (13%), nausea or dyspepsia (11%), postural dizziness (10%), excessive daytime sleepiness (5%) and nasal stuffiness (5%).

Conclusions: Pramipexole was well tolerated by most of our patients over a mean of 13.1 months. Most patients’ symptoms were well controlled on a dose of no more than 0.75 mg daily, but 28% required increasing doses to sustain therapeutic effect. Daytime augmentation occurred in 18% (compared to 27% described with pergolide3), but was mild and easily controlled with earlier doses of the drug. Side effects were generally fewer than described with pergolide3, and only resulted in pramipexole being discontinued in 16%. Nausea was not a major problem and sleepiness only occurred in 5%. All but 3 of this group of patients had failed at least one previous medication, and thus one could speculate that even more promising results might be achievable with patients commenced de novo on pramipexole.

References:
**Effectiveness of the D2-Agonist Cabergoline as Single-Drug Therapy for Restless Legs Syndrome: Clinical and Actigraphic Evaluation**

**Zucconi M, Oldani A, Castronovo VE, Ferini-Strambi L**
Sleep Disorders Center, IRCCS H San Raffaele, Milan, Italy

**Introduction:** Dopaminergic drugs are recently considered as a possible first-choice treatment for Restless Legs Syndrome (RLS) both for its efficacy at low dosage and for the lower augmentation phenomena respect to l-dopa. However the relatively short half-life of the main dopaminergic drugs used in RLS may be a factor that plays a role in the rebound or augmentation effect of long-term treatment of RLS (1). Cabergoline (half-life>65hrs, D1/D2 dopamine agonist) showed efficacy as add-on treatment in severe RLS patients unresponsive to l-dopa (2). Aim of our study was to evaluate the effectiveness and the tolerance of cabergoline in de-novo RLS patients, as first-choice drug treatment. The study was a single blind open-label study, where patients were evaluated by the International Rating Scale for RLS (RLSRS) and by nocturnal monitoring by means of actigraph worn at the ankle (3).

**Methods:** 12 patients (mean age 58.4 yrs), with idiopathic or symptomatic RLS for a mean of 37.3 yrs (range 30-44yrs) and never treated with dopaminergic agents were selected to enter the study after a full-night PSG to document the presence of PLMS. After a first evaluation with RLSRS (baseline) and one-week of Placebo administration (with actigraphy monitoring and RLSRS administered on day seven, T0), cabergoline (0.5-2 mg 2 hours before bedtime) was started. The efficacy of treatment was measured by means of RLSRS and actigraphy after 1 week (T1) and after three months (T2).

**Results:** Nocturnal PSG confirmed RLS and showed a pathologic number of PLMS in all the patients. According to the baseline RLSRS the syndrome resulted severe in 11 patients (score between 21-30) and very severe in one patient (score 35). The RLSRS score was not significantly different between baseline and Placebo (mean ± SD, 26.6 ± 4.9 vs 25.7 ± 6.2 , p=0.6), but it decreased after cabergoline both at T1 and T2 (T1 13.8±5.6, T2 9.5±3.1, p=0.01 and p=0.001, respectively versus Baseline, and p=0.01 and p=0.005, respectively versus T0). The mean activity value of actigraphic recording decreased from 17.6±9.3 (T0) to 14.4±9.1 (T1) and 12.2±4.4 (T2) with a trend towards significance (p=0.08) for the difference between T0 and T2. Two patients stopped the treatment after the T1 observation due to marked nausea (one) and inefficacy (one). The global impression scale for the observer indicated a significant improvement in RLS in 11 out of 12 patients.

**Conclusions:** Cabergoline administered in a single evening dose (mean of 1.5 mg), showed a significant clinical improvement of symptoms both in acute and short-term treatment of patients with severe RLS. In some patients the motor activity during the night decreased while in some others did not; these may be due to the instrument that detects PLMS only when associated with arousals (3). Cabergoline may be indicated as a first-choice dopaminergic agents for RLS treatment both for its effectiveness and for low side effects.

**References:**

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**Efficacy of Different Opioids in the Treatment of Restless Legs Syndrome (RLS): A Naturalistic Study**

**Becker PM**
(1) Sleep Medicine Institute, Presbyterian Hospital of Dallas, (2) Department of Psychiatry, UT Southwestern Medical Center at Dallas

**Introduction:** In evidence-based medicine, comparison of treatments provides valuable information to clinical decision making. Placebo-controlled studies have shown that the opioids oxycodone and propoxyphene can reduce the severity of RLS symptoms over extended use without serious side effects or loss of efficacy. There is no literature comparing the efficacy of opioids in RLS. The sudden unavailability of levorphanol tartrate (Levo-Dromoran) provided a naturalistic opportunity to measure the efficacy of different opioids in 18 patients with severe RLS.

**Methods:** Levorphanol (half-life: 8-15 hours) is twice as potent as morphine, rapidly absorbed, and well tolerated. The author was prescribing levorphanol to 18 severe RLS patients, many of whom tolerated dopaminergic agents poorly, for a median of 5.1 years at a stable mean dose of 3.05 (0.43) mg per day. In May 1999, the manufacture of levorphanol tartrate was interrupted. The author recognized the unavailability as an opportunity to measure the efficacy of levorphanol, propoxyphene, hydrocodone and hydromorphone in severe RLS. Not all patients received each therapy. To measure efficacy, the International Restless Legs Syndrome Scale (IRLSS) (see abstract in this volume) was utilized. As the IRLSS was not available at original visit, the author extracted baseline scores from initial notes. Efficacy measurements were completed by the patient and then reviewed by the author. Measurement occurred at the maximum dosage for five (5) days or longer of the study agent. For levorphanol, ten (10) patients completed measurement when they returned to its use in November, 1999, while eight were assessed from review of earlier records (no significant difference; p=0.74). Four patients had not previously received dopamine agonists and pramipexole was their end-point therapy. Statistical analysis among groups was with the Wilcoxon Rank Sum test (significance: p<0.05).

**Results:** Of the 18 patients on levorphanol, seven (7) were initially treated with propoxyphene, eight (8) initiated hydrocodone, and three (3) began on hydromorphone. Six (6) patients who took propoxyphene were switched to hydrocodone and one went directly to hydromorphone. Fourteen (14) patients took hydromorphone of which only one stayed on it. Nine (9) patients went on to hydromorphone and four (4) took pramipexole. When levorphanol again became available, ten (10) returned to it, four (4) continued on pramipexole, three (3) remained on hydromorphone, and one (1) stayed on hydromorphone. The table below shows the results for each agent by number treated, mean daily dosage, IRLSS scores, and statistical comparison of efficacy.

**Table 1**

<table>
<thead>
<tr>
<th>Efficacy of Different Opioids for 18 Severe RLS Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td># Pts.</td>
</tr>
<tr>
<td>Av. Dose/d</td>
</tr>
<tr>
<td>IRLSS Score</td>
</tr>
<tr>
<td>SD</td>
</tr>
</tbody>
</table>

**Notes:**
- Base proxyphene -- na
- Levorphanol -- 0.001
- Levetaramine -- 0.001
- Propoxyphene -- 0.001
- Pramipexole -- 0.001
- Hydromorphone -- 0.001

---

Conclusions: Higher potency opioids are more effective treatments for severe RLS than lower potency agents. The least potent agent, propoxyphene (Darvon and others), was only partially beneficial at a mean dosage of 185 mg/day and no severe patient reported adequate RLS control. Hydrocodone (Vicodin and others) offered some benefit at a moderate dosage, but only one of fourteen patients continued it. Higher dosages of evening hydrocodone increased side effects. Hydromorphone (Dilaudid) is nearly as effective as levorphanol, although its half-life (3-6 hours) resulted in more frequent dosing and occasional awakenings that required mid-sleep doses. Levorphanol appears to be a highly efficacious therapy for those severe RLS patients who cannot tolerate dopamine agonists.

References:

Poster Symposia

032.A

Hypocretin-1 (orexin-A) Produced Changes in Glutamate and GABA Release: An in vivo Microdialysis Study.

John J, Wu MF, Kodama T, Siegel JM
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Introduction: Most human narcolepsy is caused by a loss of hypocretin (Hcrt) neurons (Thannickal et al. 2000). Recently, we found that systemic administration of Hcrt-1 could reverse various symptoms in canine narcolepsy (John et al. 2000). The mechanism through which systemic Hcrt exerts its effects is not known. Application of Hcrt to the hypothalamic cells in vitro has been shown to alter amino acid release (van den Pol et al.1998). The central nucleus of the amygdala contains a high density of Hcrt receptors and projects to Hcrt neurons in the lateral hypothalamus. In contrast, the cerebellum has very low levels of Hcrt containing fibers and receptors. This study investigated the effect of systemic administration of Hcrt-1 on the release of amino acids using in vivo microdialysis of the amygdala and cerebellum.

Methods: This study was conducted on seven adult male Sprague-Dawley rats (275-350g). Under pentobarbital sodium anesthesia (45-50mg/kg), rats were implanted with guide cannuale in the central nucleus of amygdala (A 6.5, L 4.2, H 2) and cerebellum (preculminate fissure-4) (A -1.3, L 1.5, H 6.7; Paxinos & Watson, 1989). Screw electrodes were implanted onto the skull for electroencephalogram (EEG) monitoring. The study was done in anesthetized rats. The microdialysis probes (A-I- Model; Eicom Corp., Japan) with 1-mm long membrane were inserted into the cannulae and perfused (4 ml/min) with artificial cerebrospinal fluid for two hours prior to the experiment. Hypocretin-1 (Hcrt-1; orexin-A, Phoenix Pharmaceuticals, CA) dissolved in normal saline, was administered (3 mg/kg) through the tail vein, using a glass syringe coated with BSA. In control studies, saline was administered in the same manner. Perfusate was collected from both the targets for 30 min before and 90 min after the Hcrt-1/saline injection, at 10 min intervals using an automated and refrigerated fraction collector (Eicom Corp., Japan). The concentration of glutamate and GABA in the perfusate was detected by a HPLC (EDT-300; Eicom Corp., Japan) with fluorescent detection (Soma S-3350: excitation/emission =340/440nm).

Results: Intravenous administration of Hcrt-1 produced a significant change in the amino acid level in the central nucleus of amygdala (n=9). A significant increase (60%) in glutamate was found within 10 min after Hcrt-1 administration (P<0.001). The increase in glutamate level lasted more than 70 min after drug administration. There was a significant decrease in GABA level over a period of 60 minutes after intravenous injection, and thereafter a recovery trend towards the basal level. There was no significant change in the glutamate (n=7) or GABA (n=5) level in the cerebellum after systemic administration of Hcrt-1. Intravenous administration of saline instead of Hcrt-1 did not change the amino acid level in the amygdala and cerebellum.

Conclusions: Systemic administration of Hcrt-1 changes amino acid levels in the brain. Differential release of glutamate and GABA in the amygdala as compared to the cerebellum suggests that the amino acid modulation elicited by systemic administration of Hcrt is dependent on Hcrt innervation. Some Hcrt induced changes in neural activity may be mediated by modulation of amino acid release.

References:

Research supported by NS 14610 and the VA.

033.A

Behavioral Characterization of Orexin-2 Receptor (OX2R) Knockout Mice

Tokita S,1 Chemelli RM,2 Willie JT,1 Yanagisawa M1
(1) Department of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas, Howard Hughes Medical Institute, (2) Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Howard Hughes Medical Institute

Introduction: Orexin knockout (orexin-/-) mice exhibit a phenotype remarkably similar to human narcolepsy1. Mutations in the orexin-2 receptor (OX2R) gene cause autosomal recessive canine narcolepsy2, suggesting that disruption of orexin-2 receptor-mediated neurotransmission is important in narcolepsy. Orexin-2 receptor knockout (OX2R/-/-) mice exhibit sleep disturbances similar to those of orexin-/- mice, with decreased wakefulness, increased non-REM sleep, and rapid state cycling3. However, orexin-/- mice have more severe REM sleep disturbance and direct transitions from wakefulness to REM are rare in OX2R/-/- mice1,3. Here, we report the behavioral characterization of OX2R/-/- mice compared with orexin-/- mice.

Methods: Characterization of dark phase behavior in 14- to 15-week-old male mice was performed using infrared videophotography as previously described1. Preliminary studies demonstrated the onset of behavioral arrest in OX2R/-/- mice is often characterized by a gradual onset from quiet wakefulness, in contrast to orexin/-/- mice where an abrupt cessation of purposeful motor activity occurs. We therefore adopted less stringent criteria for behavioral arrest onset (OX2R Criteria) but maintained strict requirements for sustained postural change and abrupt exit found in our previously published criteria (OXL Criteria). Coded videotapes of OX2R/-/- and wildtype littermates were scored according to both behav-
ioral criteria by two independent observers blinded to genotype. No behavioral arrests were identified in wildtype mice confirming the specificity of both behavioral scoring paradigms.

Results: Behavioral arrests in OX2R-/- mice are less severe than in orexin-in/- mice with a reduced mean number of episodes, 6±2 vs. 17±2 arrests/mouse/4h, and a significantly reduced mean episode duration 37±4 vs. 67±4 seconds. Only 11% of behavioral arrests in OX2R-/- mice satisfy the more rigorous OXL criteria. While gait disturbance precedes about 25% of all orexin-/- arrests this was not observed during any OX2R-/- arrests. Similarly, rocking/tottering occurred during about 75% of all arrests in orexin-/- mice but was never observed in OX2R-/- mice. Pre- and post-episode behavior in OX2R-/- mice is predominantly quiet awake behaviors while excited motor activity is often associated with orexin-/- behavioral arrests.

Table 1

<table>
<thead>
<tr>
<th>OXL vs. OX2R Behavioral Arrests</th>
</tr>
</thead>
<tbody>
<tr>
<td>OX Knockout</td>
</tr>
<tr>
<td>Feeding</td>
</tr>
<tr>
<td>Drinking</td>
</tr>
<tr>
<td>Ambulating</td>
</tr>
<tr>
<td>Grooming</td>
</tr>
<tr>
<td>Burrowing</td>
</tr>
<tr>
<td>Climbing</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Conclusions: Behavioral arrests in OX2R-/- mice are characterized by a gradual onset from quiet wakefulness that occurs less frequently and is of shorter duration than arrests in orexin-in/- mice. Gait disturbance in orexin-in/- mice may likely be a behavioral manifestation of partial catalepsy, while rocking/tottering appears to be the mouse equivalent of periodic leg movements in human narcoleptics. The absence of these behavioral epiphenomena in OX2R-/- mice suggest less disruption of REM atonia mechanisms and the need for disruption of both OX1R- and OX2R-mediated signaling to reproduce the severe REM-associated behavioral arrests of orexin-in/- mice. Polysomnographic studies of orexin-in/- and OX2R-/- behavioral arrests may lead to better understanding of narcoleptic neurophysiopathology.

References:

034.A

Metabolic Characterization of Orexin Knockout Mice

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Introduction: Localization of orexin-expressing neurons exclusively within the lateral hypothalamus and its historic importance as a “feeding center” has led many investigators to focus on orexins’ probable role in energy homeostasis. Indeed, we have previously reported that fasting up-regulates orexin expression1, that intracerebroventricular injection of orexin peptides dose-dependently increases food intake1, and that there are dense reciprocal innervations between orexin neurons and leptin-responsive neurons of the arcuate nucleus2. Other laboratories have demonstrated that orexin neurons respond positively to hypoglycemia and negatively to leptin, and that exogenous orexin administration can increase metabolic rate. The orexin neuropeptide system also plays a role in vigilance state regulation since orexin knockout (orexin +/-) mice mimic human narcolepsy3. Here we report the growth, feeding and metabolic phenotypes of orexin +/- mice.

Methods: Age-matched F2 or F3 littermates were used for all studies. Characterization of growth, food intake, diet-induced obesity, and food shift paradigms were performed using standard methods. Twenty-four hour indirect calorimetry was performed with age-matched littermates housed in “live-in” metabolic chambers after acclimation for 4 days.

Results: From 3 to 26 weeks of age, orexin +/- mice maintain body weights that are statistically indistinguishable from wildtype littermates. However, when maintained on high fat (10% or 45%) or highly palatable diets they are prone to diet-induced obesity (Figure 1). Nevertheless, male and female orexin +/- mice consume about 15% less food than age-matched wildtype littermates (Figure 2). When forced to consume their entire daily food intake during 4 hours of the light phase (food shift), orexin +/- mice lose less weight than wildtype littermates, but also fail to adapt and regain weight as well as wildtypes. Preliminary indirect calorimetry studies demonstrate no difference in light phase oxygen consumption, but a significantly decreased dark phase oxygen consumption in orexin +/- mice compared to wildtype controls.

Figure 1
Conclusions: Orexin-/- mice consume less food than wildtype littermates yet maintain normal body weights and lose less weight when fasted. Basal metabolic rate appears unaffected in orexin-/- mice since oxygen consumption is unchanged during the inactive light phase. Reduced dark phase oxygen consumption may explain the hypophagia relative to body weight and resistance to fasting-induced weight loss in orexin-/- mice. Further study is needed to determine whether these differences are independent phenomena or simply a consequence of narcoleptic attacks and hypersomnolence in these mice. Nevertheless, the finding of significant phenotypes both in vigilance and metabolic states in orexin-/- mice suggests that the orexin system may play a role in the coordinated regulation of sleep-wakefulness and energy homeostasis.

References:

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035.A

Behavioral and Polysomnographic Characterization of Orexin-1 Receptor and Orexin-2 Receptor Double Knockout Mice.

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Introduction: Orexin knockout (orexin-/-) mice have frequent episodes of behavioral arrest1, while orexin-1 receptor knockout (OX1R-/-) mice do not have behavioral arrests2, and orexin-2 receptor knockout (OX2R-/-) mice have attacks that are much less severe. Direct transitions from wakefulness to REM sleep, frequently observed in orexin-/- mice, are rarely observed in OX1R-/- and OX2R-/- mice. In addition, disturbance of vigilance state parameters and fragmentation of sleep-state cycling is less severe in OX1R-/- and OX2R-/- mice compared to orexin-/- mice2,3. Here we report the complete behavioral and polysomnographic analysis of OX1R-/- OX2R-/- mice.

Methods: Characterization of dark phase behavior in 14- to 15-week-old male mice was performed using infrared videophotography as previously described1. These mice were then chronically implanted with EEG/EMG electrodes and their sleep-wakefulness patterns studied as previously described1.

Results: Frequent episodes of behavioral arrest indistinguishable from those described for orexin-/- mice1 were identified in all OX1R-/- OX2R-/- mice. The mean number of behavioral arrests (25.1±8.7 vs. 17±4 episodes/mouse/4 h) and the mean duration of these attacks (55±8 vs. 66±4 seconds) were very similar between the OX1R-/- OX2R-/- and orexin-/- mice, respectively. Other behavioral epiphenomena seen in orexin-/- mice, including gait disturbance preceding and rocking/tottering during behavioral arrests, are also frequently observed in the OX1R-/- OX2R-/- mice. Direct transitions from wakefulness to REM sleep are frequently observed in OX1R-/- OX2R-/- mice and are associated with episodes of behavioral arrest. In addition, OX1R-/- OX2R-/- mice have disruption of dark phase vigilance parameters and marked fragmentation of sleep-state cycling very similar to orexin-/- mice.

Conclusions: Based on behavioral and polysomnographic evidence, the severe narcoleptic phenotype of orexin-/- mice is completely reproduced in OX1R-/- OX2R-/- mice. Interestingly, while direct transitions from wakefulness to REM, as well as gait disturbance preceding and rocking activity during behavioral arrest episodes, are frequently observed in orexin-/- and OX1R-/- OX2R-/- mice, these phenotypes are not found in either OX1R-/- or OX2R-/- mice. These results suggest that disruption of both the OX1R and OX2R receptor pathways are necessary and sufficient to reproduce all of the narcoleptic findings in orexin-/- mice. Furthermore, this implies that the OX1R receptor pathway is important in REM gating and REM atonia mechanisms in the absence of the OX2R signaling.

References:

036.A

Measurement of CSF Hypocretin-1 Levels in Rats by Repeated Cisternal Taps

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Introduction: Recent studies suggest that low cerebrospinal fluid (CSF) hypocretin-1 levels (1) are likely to reflect an absence of hypocretin transcripts in the brains of sporadic cases of human narcolepsy (2). Thus, measurement of CSF hypocretin levels may prove useful in diagnosing hypocretin-deficient narcolepsy (see Nishino et al, Ripley et al, this issue). However, functional roles of CSF hypocretin are not well known. Immunohistochemical staining of hypocretin neurons has demonstrated that hypocretin fibers appear to protrude into the third ventricle. This suggests that hypocretin is released directly into the CSF, and may therefore play a role in “volume transmission”. In the current study, we exam-
Methods: Adult male Wister rats (318-520g) (n = 20) maintained under 12 hr light/dark cycles (lights on 09:30 hr) were used for repeated CSF collection. Rats were anesthetized with Isoflurane and set in a prone position. A 1 ml syringe with 27 G needle was introduced into the cisternal magna just beneath the dura. The CSF collection (50 - 200 µl) procedure took less that 5 min per rat. 1) Physiological fluctuation: We divided rats into group 1 (n = 7) and group 2 (n = 8). CSF collection times for group 1 were at 0, 4, 8, 12, 16, 20 hr circadian time (CT) and for group 2 were at 2, 6, 10, 14, 18, 22 hr CT. 2) Food deprivation: One day before food deprivation, CSF was collected from 18 rats and cisternal taps were repeated 24 and 72 hours after commencement of food deprivation (CT 8 hr). Hypocretin-1 was measured with commercially available 125I RIA kits (hcrt-1: Phoenix Pharmaceuticals).

Results: 1) Physiological fluctuation: We carried out 198 taps in 20 animals over a 2 month period (6 to 12 times in each animal). CSF samples contaminated by blood (1.5 % of total number of taps) were not used for analysis. Hypocretin-1 levels significantly fluctuated across time (P<0.01, Kruskal-Wallis test). At CT 0 hr, levels were high (1403.0±46.4 pg/ml) and subsequently decreased over the duration of the lights-on period, reaching a low point (1000.7 ± 62.4 pg/ml) at CT 8 hr. After lights off, the level immediately increased and remained elevated (1354 to 1524 pg/ml) throughout the duration of the dark phase (14 to 22 hr CT). The high levels at CT 0 hr (1403.0±67.8 pg/ml) and low levels at CT 8 hr (846.7±43.6 pg/ml) were further confirmed in a separate session by paired comparison in 17 rats, 13 of which were also used in the first session (P=0.0004, Wilcoxon signed-rank test). 2) Food deprivation: CSF hypocretin-1 levels showed a significant increase 72 hours after food deprivation (from 1010.9±50.1 to 1354.2±81.9 pg/ml) (P<0.01, Friedman test followed by Sheffe’s multiple-comparison test), but not after 24 hours.

Conclusions: Using a survival method for repeated cisternal taps in rats, we observed high levels of hypocretin-1 during the dark (active) phase (highest at CT 8h) and low levels during the light (rest) phase (lowest at CT 8 h), constituting a 40 % fluctuation across a 24 hour period. This fluctuation is similar to what seen in hypocretin peptide and prepro-hypocretin mRNA levels in the rat hypothalamus (3), suggesting that CSF hypocretin-1 levels may reflect hypocretin production in the brain. We further observed that food deprivation significantly increased CSF hypocretin-1 levels, a finding in agreement with data demonstrating upregulated prepro-hypocretin mRNA levels after 48 hr food deprivation. In conclusion, CSF hypocretin-1 measurement by repeated taps can be used to determine the physiological roles and/or pharmacological variation of hypocretin neurotransmission.

References:

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037.K

The Role of Histamine in a Hypocretin (orexin)-Deficient Sleep Disorder, Narcolepsy

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Introduction: Narcolepsy is a chronic sleep disorder which affects 0.03-0.18% of the general population. Studies in dogs and mice have led to the identification of genes (preprohypocretin and hypocretin receptor 2 [Hcrtr-2] genes) responsible for the disease. In humans, genetic mutations in hypocretin-related genes are rare (1), but hypocretin deficiency is functionally involved in most cases (1, 2). Hypocretins are excitatory neuropeptides located exclusively in the lateral hypothalamic area. Hypocretin-containing neurons send projections to most monoaminergic nuclei, such as adrenergic locus coeruleus, dopaminergic ventral tegmental area, and histaminergic tuberomammillary nucleus (TM). It is reported that intracerebroventricular (ICV) injection of hypocretin-1 enhances wakefulness in rats. Considering the fact that Hcrtr-2 is enriched in the TM (3), coupled with the fact that the histaminergic system plays an important role in the control of vigilance, it is likely that a deficit in histaminergic neurotransmission plays an important role in the pathophysiology of narcolepsy. It is also possible that the wake-promoting action of hypocretin may be partially mediated by the histaminergic system.

Methods: Brain tissue from 9 familial (Hcrtr-2 mutated) narcoleptic and 9 control Dobermans was used. The mean age of narcoleptic and control animals was 26.0±21 months old, and 27.7±22.1 months old, respectively. Histamine content, as well as monoamine content (dopamine and norepinephrine and dopamine turnover), was measured in the cortex, thalamus and hippocampus with a fluorometric HPLC system and with an HPLC with an electrochemical detector, respectively. In order to evaluate whether the wake-promoting effect of hypocretin is mediated by the activation of the histaminergic neurotransmitter system, we also measured changes in histamine content in the brains (cortex, brainstem, cerebellum) of rats (control n=5, hypocretin n=6) 2 hours after ICV injection of hypocretin-1 (5 nmol).

Results: Histamine content in the cortex (436±67 [SE] pmol/g) and the thalamus (884±100 pmol/g) was significantly lower in narcoleptic Dobermans compared to controls (733±93 pmol/g and 1749±227 pmol/g, respectively). Hippocampus levels (602±132 pmol/g and 793±196 pmol/g, respectively) were also decreased, but this decrease did not reach statistical significance. In the rat ICV study, hypocretin-1 significantly enhanced wakefulness (169.9 % of the vehicle treatment), and increased histamine levels in the cortex (124 % of the vehicle treatments) and brainstem (130 %), but did not significantly increase levels in the cerebellum (110%).

Conclusions: In narcolepsy, a hypocretin-deficient sleep disorder, a decrease in global histaminergic neurotransmission is suggested. In contrast, DA and NE neurotransmission in the brain regions tested were not altered. This may be consistent with our pharmacological finding that H3 antagonists, such as GT-2331 and thioperamide, significantly reduce cataplexy and sleep in narcoleptic Dobermans. In rat experiments, it is also suggested that the wake-promoting effect of hypocretin may be partially mediated by the enhancement of histaminergic neurotransmission. These results therefore suggest involvement of a hypocretin-histamine interaction in the regulation of vigilance in both normal and pathological conditions.
Narcoleptic Behavioral Arrests in Orexin Ligand and Orexin-2 Receptor Knockout Mice are Neurophysiologically Distinct

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Introduction: Orexin neuropeptide deficiency1 and mutations in the orexin-2 receptor2 are associated with narcolepsy, a sleep disorder characterized by sleep attacks, cataplexy, and sleep paralysis. Premature or direct transitions from wake to REM-sleep occur frequently in orexin knockout (orexin/-) mice and human narcoleptics, but are rare in orexin-2 receptor knockout (OX2R/-) mice. Behavioral arrests and dark-phase disturbance of vigilance states are also less severe in OX2R/- mice. Here we report distinct neurophysiologic correlates of behavioral arrests in orexin/- and OX2R/- mice.

Methods: Concurrent infrared videophotography/EEG/EMG1 was used to study neurophysiologic correlates of behavioral arrests. Restricted feeding schedules3 reliably elicited arrests in orexin/- and OX2R/- mice.

Results: Typical behavioral arrests in orexin/- mice (Figure 1) begin with muscle atonia and a wake-EEG that may last several seconds but rapidly become REM-like. Rarely, transitions to non-REM patterns occur. Episodes usually end with abrupt resumption of purposeful motor activity and transition to wake-EEG patterns. Occasionally, restoration of wake-EEG and EMG tone occurs while the mouse exhibits struggling movements. Gait disturbances frequently precede attacks and are associated with EMG attenuation and ambiguous mixed wake-REM-like EEG patterns. Frequent episodes of non-purposeful, phasic, rocking behavior occur during arrests in association with nuchal atonia and REM-like EEG. Indistinguishable rocking is also observed during normal REM-sleep in orexin/- mice. In contrast, typical behavioral arrests in OX2R/- mice (Figure 2) begin with rapid EMG attenuation and a brief wake-EEG that rapidly turns into non-REM activity often indistinguishable from normal onset of non-REM sleep. Progression to REM-like patterns is rarely observed. Struggling movements, gait disturbances, and REM-associated rocking are not observed in OX2R/- mice.

Conclusions: We found distinct neurophysiologic phenotypes associated with behavioral arrests in orexin/- and OX2R/- mice. While attacks and behavioral epiphenomena in orexin/- mice demonstrate prominent intrusion of REM-like activity into wakefulness, arrests in OX2R/- mice are predominantly non-REM-associated. Compared to clinical narcolepsy, arrests and gait disturbances of orexin/- mice are reminiscent of complete and partial cataplexy, respectively. Rocking in orexin/- mice is suggestive of Periodic Leg Movements, frequently reported in human narcolepsy; but its occurrence only during REM more closely resembles the clinical parasomnia REM-sleep behavior disorder (RBD). Reports have suggested that RBD and REM without atonia are observed in human narcolepsy. Struggling movements observed at the end of orexin/- arrests are suggestive of sleep paralysis. Many OX2R/- arrests resemble sleep attacks rather than cataplexy. Our findings imply that disrupted signaling of both OX1R and OX2R pathways is required for many behavioral and polysomnographic phenomena in mouse narcolepsy. The incomplete phenotype of the OX2R/- mouse suggests that the OX1R pathway contributes to regulation of REM-sleep gating and REM atonia.

References:
(3) Willie JT, Chemelli RM, Xiong Y, Yanagisawa M. A behavioral paradigm that elicits narcoleptic attacks in orexin knockout mice. Sleep 2000;23(Suppl.):A91-A92.

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039.A

Effect of Diurnal Variation and Behavioral State Changes on Extracellular Orexin-A Levels in the Rat Brain

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Introduction: The hypocretins/orexins are hypothalamic neuropeptides derived from a common orexin preprohormone. Original work on these neuropeptides suggested they may be involved in a wide range of functions, including feeding, energy homeostasis, neuroendocrine systems, and behavioral state control. Orexin containing neurons are exclusively located in the lateral hypothalamic area (LH), but they send projections throughout the CNS, including dense innervation of a number of brain structures involved in the regulation of sleep and wakefulness. Furthermore, recent reports clearly indicate that narcolepsy and cataplexy can be caused by dysfunctions of the orexin peptide-receptor system. Thus, genetically altered mice lacking the orexin gene exhibit narcolepsy-like behavior, including an increase in REM sleep, decreased wakefulness, and cataplexy-like episodes entered directly from periods of active movement. Similarly, dogs with a genetic form of narcolepsy have an abnormality in orexin type-II receptors. We recently found that microdialysis perfusion of antisense DNA for the orexin type-II receptor in the subcoeruleus produced an increase in REM sleep with cataplexy - like episode in rats, whereas orexin-A peptide perfusion in the cholinergic basal forebrain (BF) increased wakefulness. Finally, many human narcoleptic brains show loss of orexineric neurons in the LH, whereas narcoleptic patients have been shown to have undetectable CSF levels of orexin. Thus, the evidence is strong that the orexin system is involved in the patholgy of narcolepsy, suggesting that orexins may be involved in the regulation of natural changes in behavioral state. Although the precise role of orexin in the neurophysiology of sleep is unknown, the combined work suggests that endogenous orexin promotes wakefulness and suppresses the appearance of REM sleep. On the other hand, the absence, or reduction, of orexin peptide or orexin receptors is associated with a decrease in wakefulness and an enhanced expression of REM sleep. Sleepiness is determined both by the duration of prior wakefulness and by circadian influences. The present study was designed to test the hypothesis that endogenous orexin mediates the circadian influence on sleep & wakefulness.

Methods: To determine if extracellular orexin-A levels fluctuate as a function of circadian (diurnal) variation, and/or in response to changes in sleep & wakefulness state, the present study used microdialysis (MD) sample collection coupled to biochemical analysis by enzyme linked immuno-sorbent assay (ELISA). Guides for MD probes with membrane lengths of 2 mm (CMA/microdialysis) were stereotaxically implanted in anesthetized male Sprague-Dawley rats. Probes were later placed into two sites: the LH, an area that receives a dense innervation of orexin projections and also contains orexin perikarya (coordinates: AP -3.1, ML ± 1.5, DV -9.0); and the cholinergic zone of the BF, an area in which perfusion of orexin-A peptide has been shown to increase wakefulness (coordinates: AP -0.4, ML +2.5, DV-8.8). Samples were collected in freely moving rats during different times of day, and also during a 60 to 90 min period of forced wakefulness (MD flow rate of 1.5 ul/min). Rats were maintained on a schedule with lights on from 7 a.m. to 7 p.m. The detection of orexin-A by the ELISA assay (Phoenix Pharmaceuticals) is based on the competitive binding of biotinylated orexin-A & orexin-A in the samples to the primary antibody, which is linked to the immunoplate via the secondary antibody. Standard curves determined the assay to be linear from the lowest concentration of 0.05 ng/ml of orexin-A up to the highest of 1.6 ng/ml (R=0.99).

Results: MD probes placed in a 1 uM standard solution of orexin-A recovered 0.5 ± 0.3% of the orexin-A in the solution (N=3), indicating that orexin-A (MW =3,562) can pass through the dialysis membrane. Orexin-A was detectable in less than 50 ul of MD sample collected from probes placed in the LH. The concentration of orexin-A in the LH microdialysate from 1000h to 2200h was 0.8 ± 0.3 ng/ml (N=5). Relative to this time period (1000h to 2200h) LH orexin-A levels from 2200h to 1000h (mid evening to early morning) were 3-fold higher (N=5; p=0.05 Wilcoxon signed rank test). In contrast, a 60 min period of forced wakefulness (100% wakefulness) did not alter LH extracellular orexin-A levels relative to the preceding afternoon baseline period, where the wakefulness % was about 30% (N=2). The analysis of samples from the BF is pending.

Conclusions: ELISA can be used to measure extracellular levels of orexin-A in microdialysis samples collected from probes in the LH of rat. Sample times of under 30 minutes appear feasible which will allow for a finer analysis of the relationship between orexin-A levels and behavioral state change in future work. Current preliminary data indicate that orexin-A levels in the LH are not strongly determined by sleep & wakefulness state. Rather, the diurnal variation in LH orexin-A levels was more marked, supporting the hypothesis that unidentified mechanisms, linked to the circadian cycle, lead to the higher levels of extracellular orexin observed during the time of day when wakefulness is most prevalent and REM sleep is least likely to occur.

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040.A

Hypocretin-saporin Induced Lesion of the Lateral Hypothalamus Produces Narcoleptic-like Sleep in Rats

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Introduction: Narcolepsy, a disabling neurological disorder characterized by excessive daytime sleepiness, sleep attacks, sleep fragmentation, cataplexy, sleep onset REM sleep periods, and hypnagogic hallucinations, was recently linked to the neuropeptide, hypocretin (HCRT). HCRT neurons are located only in the lateral hypothalamus but electrolytic or neurotoxic lesions of this area have not produced sleep behavior consistent with narcolepsy (McGinty, 1969; Shoham and Teitelbaum, 1982). The inconsistent effects on sleep might have occurred because the appropriate neurons were not destroyed. In the present study, the ribosome inactivating protein, saporin, was conjugated to HCRT-2/orexin B and used to lesion HCRT receptor bearing neurons in the tuberomammillary nucleus (TMN). Because there is evidence that the HCRT neurons have an autoreceptor (Horvath et al., 1999), the toxin was also used to lesion HCRT neurons in the lateral hypothalamus.

Methods: Sprague-Dawley rats (400-450 g) were implanted under anesthesia with electrodes to record the electroencephalogram (EEG) and electromyogram (EMG). The temperature in the sleep recording room was 250°C and a 12:12h light-dark cycle (7AM-7PM lights on; 100 lux) was maintained. EEG and EMG recordings were collected for at least two weeks in all animals. The HCRT-saporin conjugate (490 ng/0.5 ml; Advanced Targeting Systems, San Diego, CA) or pyrogen free saline were delivered (Picospritzer; 0.5 ml) using a glass micropipette (tip diameter=20 mm) in the posterior hypothalamus at the area between 3.3 and 4.2 mm posterior to bregma.

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Results: A significant reduction in the numbers of TMN and HCRT neurons in the lateral hypothalamus was detected 3 to 5 days after toxin administration and complete loss occurred by 2 weeks. Rats with more than the 60% loss of the HCRT-containing neurons exhibited narcoleptic-like behavior, such as sleep onset REM sleep periods, nighttime increase in both SWS and REM sleep, sleep fragmentation, and diurnal rhythm blunting.

Conclusions: Our findings are consistent with the emerging evidence that loss of HCRT neurons underlies the multiple sleep disturbances that occur in narcolepsy. The HCRT-saporin conjugate provides a method of determining the contribution of a specific HCRT innervation in the regulation of behavior.

References:

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041.A

Genetic Ablation of Orexin Neurons Causes Narcolepsy in Mice

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Introduction: Orexins (hypocretins) are two recently described neuropeptides implicated in energy homeostasis and arousal. Prepro-orexin knockout mice have a phenotype remarkably similar to human and canine narcolepsy. Studies of post mortem human narcoleptic brains have further suggested that narcolepsy is due to specific destruction of orexin-expressing neurons in the lateral hypothalamus. We have produced transgenic mice where orexin neurons are specifically ablated by expression of a truncated Machado-Joseph disease gene product (ataxin-3) driven by the human prepro-orexin promoter, resulting in an over 99% removal of orexin-expressing neurons by 12 weeks of age. Here we report the behavioral and polysomnographic characterization of orexin/ataxin-3 transgenic mice, but none in wild-type littermate controls. The mean±SEM number of behavioral arrests (9±4.8 vs. 17±2 episodes/mouse/4 h) and the mean duration of these attacks (65±22 vs. 66±4 seconds) were very similar between the orexin/ataxin-3 transgenics and the orexin knockouts, respectively. Other behavioral epiphenomena seen in orexin knockout mice, including gait disturbance preceding and rocking/tottering during behavioral arrests, were also frequently observed in the orexin/ataxin-3 transgenics. Analysis of EEG/EMG recordings in the orexin/ataxin-3 transgenic mice reveal that their vigilance state parameters (Table 1) are strikingly similar to those reported for orexin knockout mice. Hypnograms of transgenic mice are characterized by premature entry into REM sleep and marked sleep stage fragmentation (Figure 1) indistinguishable from orexin knockout mice. Significant disruption of dark phase vigilance parameters with reduced wakefulness and increased sleep, with preserved light phase sleep architecture, was also remarkably similar to the knockout phenotype. A significantly higher frequency of premature entry into REM sleep during the dark phase as compared to light phase was observed in the orexin/ataxin-3 mice, also comparable to that found in orexin knockout mice. No sleep abnormalities were observed in wildtype mice.

Table 1

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<td>Episode duration</td>
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Values are expressed as mean±SEM. Significant differences between (Tg/+ and +/+) mice are indicated with two asterisks (P<0.01) or one asterisk (P<0.05).

Figure 1

A26
Conclusions: Genetic ablation of orexin-expressing neurons in orexin/ataxin-3 transgenic mice produces a narcoleptic phenotype indistinguishable from that of orexin knockout mice based on behavioral and polysomnographic evidence. This provides further evidence that narcolepsy is due to a physiologic dysfunction of the orexin neuropeptide system rather than possible developmental neurologic anomalies in orexin knockout mice.

References:

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Detailed Characterization of Sleep in Orexin Knockout Mice

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Introduction: Study of orexin knock out (orexin -/-) mice demonstrated a phenotype with many of the characteristics of narcolepsy 1. Our continuing analyses of the original EEG/EMG recordings from these mice have now provided a more complete picture of the sleep changes that result from the absence of orexin neuropeptides in this species. The significance of this phenotype requires a detailed EEG characterization as studies proceed on the functional importance of orexin, and, for example, as comparisons are made between the orexin -/- mouse and the orexin receptor (OX1R, OX2R, OX1R/OX2R) null mice.

Methods: The procedure for recording EEG/EMG signals from these mice has been described elsewhere1. Twenty-four hour continuous recordings were digitized on-line and archived for subsequent analyses: 1. The 24 h EEG/EMG recordings [N = 4 (-/-) and N = 4 (+/+); two 24 h periods/mouse] were visually scored into 4 sec epochs of awake, non-REM (NREM) and REM sleep to compare resulting sleep states with those originally reported after scoring based on 20 sec epochs. 2. The latency from the end of the previous period of wakefulness to each REM episode was calculated for all mice in the original study [N = 6 (-/-) and N = 6 (+/+) and mean REM latency histograms were derived for orexin -/- mice and wildtype controls. 3. Power spectra were determined by Fast Fourier Transform (FFT) for those REM periods which were immediately preceded by wakefulness and compared with REM periods that occurred normally after NREM sleep.

Results: Table 1 displays data for REM sleep during the dark phase, comparing the 20 sec and 4 sec epoch analyses. The 4 sec analysis showed a non-significant increase in REM time, combined with significant decreases in REM latency and mean episode duration, since episodes as short as 2 sec in duration were captured by this analysis. As expected, the 4 sec analysis also resulted in a reduced mean episode duration for all vigilance states compared with the previously reported data after 20 sec analysis: for example, during the dark period, the mean duration of wakefulness episodes was 116 ± 27 sec vs. 178 ± 23 sec after 4 sec epoch analysis compared with 351 ± 56 sec vs. 704 ± 88 sec after 20 sec epoch analysis in the orexin -/- and wildtype controls, respectively.

Therefore, the orexin -/- mice continued to show a more fragmented sleep pattern than the wildtype controls even after a more rigorous 4 sec analysis. Figure 1 displays the mean REM latency histograms for the orexin -/- and wildtype mice. Note that wildtype mice have no REM latencies less than 1 min and significantly fewer episodes with latencies less than 3 min. FFT analysis showed that REM periods directly preceded by wakefulness had power spectra that were indistinguishable from REM periods that followed normal NREM sleep, with prominent power in the theta (4.5 - 9 Hz) band, but a very different pattern from spectra recorded during periods of wakefulness.

Table 1

<table>
<thead>
<tr>
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<tr>
<td>4 second analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total REM time (min)</td>
<td>45.8 ± 3.5</td>
<td>24.9 ± 5.9</td>
</tr>
<tr>
<td>REM episode duration (sec)</td>
<td>76.9 ± 1.5</td>
<td>67.6 ± 4.2</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>3.8 ± 0.9</td>
<td>4.3 ± 0.3</td>
</tr>
<tr>
<td>Inter-REM interval (min)</td>
<td>19.3 ± 1.3</td>
<td>40.7 ± 6.7</td>
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<tr>
<td>20 second analysis</td>
<td></td>
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<tr>
<td>Total REM time (min)</td>
<td>41.3 ± 2.8</td>
<td>20.7 ± 4.5</td>
</tr>
<tr>
<td>REM episode duration (sec)</td>
<td>88.1 ± 5.1</td>
<td>76.2 ± 2.4</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>7.0 ± 1.2</td>
<td>8.8 ± 0.6</td>
</tr>
<tr>
<td>Inter-REM interval (min)</td>
<td>23.6 ± 2.6</td>
<td>49.6 ± 9.8</td>
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</table>

Figure 1

Conclusions: 1. Our original conclusions about the increased sleep fragmentation and hypersonolence in orexin -/- mice are unchanged by scoring EEG/EMG records into 4 sec epochs. 2. We propose to define a REM latency of less than 1 min as a sleep-onset REM (“SOREM”) period in mice. 3. EEG spectral power distribution during SOREMs in orexin -/- mice is identical to normal REM sleep with no evidence of an abortent EEG pattern. It is markedly different from waking EEG.

References:

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A Statistical Model of Cumulative Sleep Debt in Chronic Sleep Restriction

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Introduction: Chronic sleep restriction causes cumulative sleep debt, which results in increasing neurobehavioral performance deficits. The magnitude of these deficits depends on the cumulative amount of sleep loss, which is relative to the “duration of enough sleep” (i.e., to the amount of sleep needed each day to avoid neurobehavioral impairment). An additive model of sleep debt was evaluated, which postulated that each hour of sleep loss is equally important in determining the performance deficits resulting from chronic sleep restriction. The model was applied to data from 14 days of sleep restriction in a laboratory. It was assumed that the “duration of enough sleep” was normally distributed among the subjects, and this distribution was estimated from the available data.

Methods: Data from n = 24 subjects who spent 20 days inside a laboratory were used. After 3 baseline days, subjects underwent sleep restriction for 14 days. Nine subjects received 4h TIB (03:30-07:30); eight subjects received 6h TIB (01:30-07:30); and seven subjects received 8h TIB (23:30-07:30). Neurobehavioral performance was tested every 2h during wakefulness, and included a 10min psychomotor vigilance test (PVT) for which the daily average (09:30-23:30) of lapses (reaction times ≥ 500ms) per test bout was used to measure performance impairment (IMP), relative to baseline. Polysomnography (PSG) was recorded on all baseline nights, and on two out of every three nights throughout the 14-day restriction period. The PSG records were visually scored using conventional criteria, and total sleep time (TST) was assessed. For the days with no PSG recordings, TST values were estimated with linear regression over the other days of sleep restriction. Subsequently, cumulative TST (CTST) was determined for each day of restriction.

Results: The model was formulated as: IMPD = θ(λD - CTSTD), where D is the day of sleep restriction (1 through 14), λ is the normally distributed “duration of enough sleep” (in hours) and θ is the “rate of impairment” (i.e., the increase in lapses per test bout resulting from each hour of sleep loss). The model was fit to the data with mixed-model nonlinear regression; the mean and standard deviation (s.d.) of λ and the value of θ were estimated from the data. The estimated value for the “rate of impairment” was θ = 0.38 (lapses per hour of sleep loss), and the estimated mean ± s.d. for the “duration of enough sleep” was λ = 8.2 ± 2.1 (hours).

Conclusions: In this experiment, the average amount of sleep needed to avoid neurobehavioral impairment was found to be 8.2h, with a s.d. of 2.1h among individuals, and each hour of sleep loss during the 14 days of sleep restriction resulted in 0.38 additional lapses per PVT test bout on average, providing the model described the data sufficiently well. The following refinements are underway: (1) Statistical evaluation of goodness-of-fit for the model. (2) Re-estimation of the model allowing for individual differences in the “rate of impairment” by assuming a normal distribution for θ (which is estimated from the available data); it is expected that this will result in a smaller estimate for the s.d. of λ. (3) Application of the model to other neurobehavioral variables to scan its domain of applicability. (4) Selection of other independent variables such as cumulative slow-wave sleep and REM sleep, and combinations thereof, to identify the aspects of sleep architecture that best predict cumulative neurobehavioral performance deficits for this subject population under laboratory conditions of chronic sleep restriction.

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044.I

Chronic Sleep Restriction: Relation of Sleep Structure to Daytime Sleepiness and Performance

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Introduction: The 2-process model of sleep regulation considers EEG slow-wave activity (SWA) “the major marker of non-REM sleep homeostasis, as well as daytime alertness” (1). If SWA reflects both the rise in sleep propensity during waking and its dissipation during sleep, then greater amounts of SWA should reflect greater recovery of waking alertness, and SWA should be negatively correlated with neurobehavioral deficits due to sleepiness. This hypothesis was tested in a dose-response experiment of chronic sleep restriction.

Methods: N=35 healthy adults (M=28y; 29m) spent 20 days in the laboratory (3d baseline 8h TIB; 14d sleep restriction; 2d recovery 8h TIB). During 14d of sleep restriction, subjects were randomized either to 4h TIB (n=13), 6h TIB (n=13), or 8h TIB (n=9). Alertness was assessed every 2h each day (0730h-2330h), using a 30min computerized battery that included psychomotor vigilance test (PVT), digit symbol substitution test (DSST), Stanford Sleepiness Scale (SSS) and Karolinska Sleepiness Scale (KSS). Following robust model selection, linear regression analyses (PVT, DSST) or linear regression analyses after square root transform of the abscissa (KSS, SSS) were performed to describe each subject’s day-to-day change (slope) in each variable across the 14d (positive slope = increasing sleepiness). PSG was scored during the 14d restriction period for n=24 subjects (288 nights). Non-REM sleep EEG (C3-A1/A2) was subjected to power spectral analysis to determine SWA in the first 4h of sleep (for comparison of the 3 conditions on an equal time scale). Linear regression was performed to derive estimates for first night (acute) and subsequent average nightly changes across the 14d, in terms of intercepts and slopes, respectively for SWA and other sleep variables. Regression was then used to evaluate relationships of these slopes and intercepts with the slopes of sleepiness and performance variables, controlling for condition.

Results: The effects of cumulative sleepiness were evident in dose-response differences in the magnitude of positive slopes for PVT, DSST, SSS, and KSS among the 4h-TIB, 6h-TIB, and 8h-TIB conditions (P<0.05). Acute changes in the first night of sleep restriction, with significant differences among conditions (P<0.05), were observed for REM and SWA. Significant negative relationships were found between the slopes for SWS and KSS (P=0.007), and between the slopes for SWS and SSS (P=0.031). There were no significant relationships between SWA and KSS or SSS, or between SWS and PVT or DSST slopes. However, significant positive relationships were found between the slopes of SWA and PVT lapses (P=0.001), and between the slopes for SWA and DSST (P=0.041).

Conclusions: Although greater SWS slopes were associated with lower slopes in subjective sleepiness across days of sleep restriction, as predicted by the 2-process model, the opposite prevailed for performance. Significant positive associations were found for the slopes of SWA with the slopes of PVT and DSST, indicating that after the first night subjects who had greater increases of SWA in the first 4h of sleep across 14d also tended to have greater increases in neurobehavioral performance deficits, independent of restriction condition. This finding suggests that among individuals, SWA may be a marker of homeostatic sleep drive.
but not necessarily of the dissipation of that drive. REM and other features of sleep are currently being tested for their role in dissipation of homeostatic sleep drive.

References:

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045.I

Rapid Eye Movement (REM) Sleep Regulation in Humans: Selective REM Sleep Deprivation During Daytime Sleep

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Introduction: There is a long-standing interest in the mechanisms underlying REM sleep regulation (1). In contrast to the progress in clarifying the neurophysiological and neurochemical mechanisms involved in REM sleep, much less is known on the processes involved in its regulation. A recent selective REM sleep deprivation study, where nighttime sleep was interrupted (2), showed a dramatic rise in the number of interventions during the REM sleep deprivation nights. The rising trend in the number of interventions during selective REM sleep deprivation may be due to circadian and/or homeostatic factors. Here, in contrast to the earlier study (2), selective REM sleep deprivation was scheduled during daytime. The circadian drive for REM sleep is high in the morning and decreases during the daytime sleep episode.

Methods: Twelve healthy young men (24y ± 0.17; mean ± SEM) underwent a two-session protocol. One session consisted of baseline sleep (23:00-7:00h; B1, B2), a wake episode of 24 h followed by daytime sleep (7:00-15:00h; E1, E2) and recovery sleep (23:00-7:00h; R1, R2). During E1 subjects were repeatedly awakened to prevent REM sleep. The second session served as a control condition. In E2 an attempt was made to match total sleep time (TST) of E1. Polysomnographic recordings were obtained during the sleep episodes and sleep stages were scored according to standard criteria. The C3-A2 EEG derivation was subjected to spectral analysis. The data were subjected to ANOVA for repeated measures. Contrasts were tested by paired t-tests. The significance level was p<0.05.

Results: The REM sleep deprivation in E1 was successful with only 6.3 ± 1.0 min of REM sleep compared to 110.5 ± 5.4 min during baseline. TST was significantly shorter during daytime sleep episodes than during baseline (B1: 446.5 ± 4.2 min; E1: 330 ± 16.4 min). The number of interventions in E1 showed large interindividual variations (19.8 ± 2.2; range 9-34). The attempts to enter REM sleep tended to occur in clusters. The number of interventions per hour of sleep increased from the first to the second 2-h interval and differed little between interval 2 and 4 (see Figure). REM sleep rebound during recovery sleep (R1) was moderate. REM sleep rose by 7.7 ± 3.9% above baseline level, which was far less than the amount of REM sleep lost. TST during recovery sleep was similar to baseline (R1: 446.5 ± 4.2 min). REM sleep latency was not affected by increased REM sleep pressure. Minor changes of the REM sleep EEG power spectrum were observed.

Conclusions: The results suggest either a weak homeostatic drive for REM sleep or an antagonism of a rising homeostatic REM sleep propensity by a declining circadian REM sleep propensity. Moreover, the initial high “slow-wave pressure” due to sleep deprivation may counteract REM sleep propensity.

References:

Research supported by Swiss National Science Foundation grant 3100-063005.97 and Human Frontiers Science Program RG-81/96 and RG-0131/2000.

046.I

Individual Differences in Performance Degradation and Subsequent Recovery in Volunteers Allowed 3 Hours Sleep Time Over 7 Days

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Walter Reed Army Institute of Research

Introduction: Sleep deprivation and sleep restriction degrade cognitive performance and alertness. Efforts are underway to model the effect of sleep/wake history on subsequent alertness and performance for the purpose of creating a predictive tool to manage sleep and sustain performance. Typically these have been two process models with parameters set by optimizing fit to empirical data. Critical to successful parameterization is specification of the magnitude and form of differences between individuals in sensitivity to sleep deprivation, and whether these differences represent short-term individual states or enduring traits. The critical questions are: (a) To what degree does a single set of parameters for a given model predict individual performance; and (b) Are predictions substantially improved by individualizing the model parameters for each individual subject.

Methods: As part of a larger, sleep dose response study, eighteen volunteer subjects (12 men, 6 women; age range 24-55; mean age 39.3; median age 36.5) participated in a 14-day residential study of the effects of sleep restriction on performance. For the first 3 days subjects were allowed 8 hours in bed each night, and averaged (by PSG criteria) 7.0 hours of sleep each night. For the middle 7 days, subjects were allowed 3 hours in bed and averaged 2.87 hours of sleep each night. For the last 4 days subjects were again allowed 8 hours in bed each night, and averaged about 7.0 hours of sleep each night. Subjects took the 10-minute long Psychomotor Vigilance Task (PVT) every 2-3 hours while awake for a total of 4 administrations each day during the baseline and recovery periods and 6 administrations each day during the sleep restriction
Results: Mean performance for the 18 subjects on the PVT declined over the sleep restriction period with performance returning toward, but not reaching, baseline during the recovery period (Figure 1). There was considerable between-subject variability in response to the sleep restriction and subsequent recovery with some subjects showing little or no in decline in PVT performance across the 7 days of sleep restriction, others showing large consistent declines, and still others showing small mean declines with large increases in variability (Figure 2 – scatter plots). Further, a single parameter set optimized to fit the entire data set (all subjects, all groups) did not provide good fits to each subject individually (Figure 2 – dark gray lines). Optimizing the parameter set to subjects individually yielded better fit to that individual subject (Figure 2 – light gray lines).

Discussion:

Conclusions: Our findings clearly indicate substantial individual differences in sensitivity to the performance degrading effects of sleep restriction. It is apparent that optimal predictive value of the model will be realized through individualization of the model parameters. Still to be determined is whether the individual differences reflect short-term individual states or long term, enduring individual traits.

Table 1

<table>
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<tr>
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<th>Mean (s.d.) change score</th>
<th>ANOVA main effect TIB</th>
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<tbody>
<tr>
<td>DSST</td>
<td>5.47 (8.67)</td>
<td>16.67 (14.58)</td>
</tr>
<tr>
<td>PVT</td>
<td>5.93 (8.06)</td>
<td>17.14 (11.18)</td>
</tr>
<tr>
<td>KSS</td>
<td>1.70 (1.98)</td>
<td>3.79 (2.08)</td>
</tr>
<tr>
<td>VAS 1</td>
<td>7.97 (10.48)</td>
<td>20.57 (14.71)</td>
</tr>
<tr>
<td>VAS 2</td>
<td>8.39 (11.17)</td>
<td>18.69 (15.86)</td>
</tr>
<tr>
<td>VAS 3</td>
<td>7.69 (12.57)</td>
<td>13.50 (14.93)</td>
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Conclusions: The results indicated that subjects who received 14h TIB for recovery sleep has a greater improvement in neurobehavioral per-
Research supported by AFOSR grant F49620-1-0388, and NIH grants M01-RR00040 and K23-AG8672

048.I

The Effects of 40 Hours of Continuous Wakefulness on EEG Power and Flight Performance

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Introduction: Research has shown that waking, slow-wave EEG activity increases as a function of sleep deprivation (Pigeau, et al., 1987). Furthermore, it appears that accentuation of delta and/or theta activity is associated with decrements on cognitive tasks (Belyavin and Wright, 1987). However, few (if any) investigations have concurrently explored both the effects of sleep deprivation on EEG activity and the ability to perform a complex task such as flying a helicopter or a helicopter simulator.

Methods: Data collected from 32 subjects in 5 previously-conducted aviation-performance studies were combined to yield a sufficient number of cases for multivariate analyses. Four of these studies were completed in a simulator, and one was done in an aircraft. In each study, volunteers remained awake for 40 continuous hours. Flight performance was measured during 4 maneuvers—a right standard-rate turn (RSRT), a climb, a descent, and a left descending turn (LDT)—flown at 8 times (0900, 1300, and 1700) at baseline; and 0100, 0500, 0900, 1300, and 1700 under sleep deprivation). Twenty minutes following each 1-hour flight, EEG data were collected for power spectral analyses.

Results: A multivariate analysis of variance for session (with the 8 times indicated above) and variate (which included EEG delta, theta, alpha, beta; and flight performance on the RSRT, climb, descent, and LDT) indicated multivariate significance (p<.0001), as well as univariate significance on each of the 8 variates (p<.01) with the exception of EEG alpha and beta. The EEG effects were largely due to a deprivation-related linear increase in delta and theta. The flight effects were primarily due to a linear decrease in performance; however, the LDT revealed an increase in baseline performance followed by a deprivation-related decrease that concluded with an “end-spurt” recovery (a similar effect also occurred in the RSRT and descent).

Conclusions: These results demonstrate that the fatigue from sleep loss impacted delta and theta EEG power and objective measures of complex flight performance, and that this was the case when considering each variate separately and when evaluating their best linear combination. However, alpha and beta activity did not change across the sleep-deprivation period, suggesting that these EEG bands may not be particularly helpful for explaining the observed performance differences.

References:
(2) Pigeau RA, Heselegrave RJ, Angus RG. Psychophysiological measures of drowsiness as estimators of mental fatigue and performance degradation during sleep deprivation. In: Electric and magnetic activity of the central nervous system... 1987;AGARD CP-432, 21-1/21-16.

049.I

Individual Differences in the Effects of 47-50 hrs Sleep Loss on Mood and Cognition

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Introduction: Blagrove and Akehurst (2001) review work on neuroticism, extraversion, and external locus of control being associated with greater effects of sleep loss. Taylor and McFatter (1999) show neurotic extraverts have the worst performance on cognitive tasks after sleep loss, and Hill, Welch, and Godfrey (1996) found external LOC individuals (who see events as beyond their control) have a greater decrease in overall mood following 26-30 hours sleep loss than do internals (who perceive events that happen to them as under their own control). Studying 31 participants Blagrove and Akehurst (2001) found that deficits in mood due to 29-35 hours sleep loss correlated significantly with neuroticism (N), extraversion (E) and usual sleep length (USL), and had a quadratic relation with LOC. Logical reasoning deficits due to sleep loss correlated significantly with change in overall mood (r = .36), but not with the individual difference variables. The present study has the same design but with a sample subjected to 47-50 hours sleep loss.

Methods: The 17 sleep loss participants (male = 10, female = 7; mean age = 21.2 years, SD=2.3; mean usual sleep length = 8.5 hrs, SD=0.6) and 15 controls (male = 7, female = 8, mean age = 20.9 years, SD=2.4; mean usual sleep length = 9.0 hrs, SD = 0.6) were all healthy and good sleepers. Overall mood was assessed by the bipolar Profile of Mood States (POMS, Lorr & McNair, 1980); Logical Reasoning (LR) by number correct on an adaptation of Baddeley’s (1968) LR test, duration 10 minutes; LOC by Rotter’s (1966) questionnaire (higher scores represent externality), and E and N by the EPQ-RS. After a full night’s sleep baseline testing was at 14.00-17.00 on Day 1. Second testing was at 09.00-11.00 on Day 3. Sleep loss participants were thus deprived of sleep for 47-50 hours, controls slept as normal.

Results: Sleep loss led to significant deficits in overall mood (F(1,30)= 73.07, p<.001) and LR (F(1,30)=60.42, p<.001). (Sleep Loss and Control groups had baseline means (SD) for overall mood = 168.2 (17.0) and 142.9 (30.7) respectively, and for LR = 96.1 (31.0) and 96.1 (28.5) respectively. Control group had mean (SD) changes in mood = 0.6 (26.1) and LR = 15.7 (14.0), these changes had no significant correlations with the individual difference variables.) Table 1 shows the mean changes for the sleep loss group in overall mood and LR, and the Pearson r correlations of change scores with N, E, USL, and logical reasoning. Changes in LR and in overall mood did not correlate significantly.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change scores due to sleep loss</th>
<th>Correlations of change scores and individual difference variables</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Overall mood</td>
<td>-86.2</td>
<td>30.7</td>
</tr>
<tr>
<td>Logical reasoning</td>
<td>-30.3</td>
<td>18.8</td>
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* p<.05

Conclusions: The lack of significant correlations between individual difference variables and change in overall mood at 47-50 hours sleep loss contrasts with the significant correlations found by Blagrove and Akehurst (2001) at 29-35 hours, and is not due to floor effects on the POMS. The significant correlation of USL with cognitive deficits sug-
gests individual differences in sleep need.

References:

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050.1

Do Middle-aged Men and Women Differ in their Ability to Recuperate During the Day Following an Acute Sleep Deprivation?

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Introduction: Compared to men, middle-aged women report more sleep and fatigue complaints. However, when studied in the sleep laboratory, men tend to show less SWS and lower EEG slow-wave activity (SWA: spectral power between 0.5 and 4.5 in N-REM sleep) than women (1). These results led to the hypothesis that age might have differential effects in men and women during the middle years of life. Challenges to the sleep-wake cycle help to understand the mechanisms underlying gender and age differences. We have shown recently that people in their forties and fifties already show a heightened vulnerability to an abnormal phase angle between sleep and the circadian signal, in addition to an attenuation of the homeostatic recuperative response (2). The aim of this study was to evaluate gender differences in the effects of a 25 hours of sleep deprivation on daytime recovery sleep.

Methods: Thirty-three subjects were studied. They were separated into two groups according to their age: Young: (20-39 years, 8 women, 8 men) and Middle-aged (40-59 years, 8 women: 4 pre, 4 post-menopausal, 9 men). Peri-menopausal women and women using hormonal contraceptives or receiving hormonal replacement therapy were excluded. Pre-menopausal women were studied during the follicular phase of their menstrual cycle. All subjects came to the sleep laboratory for 4 consecutive nights and 2 days. Baseline sleep was recorded on the third night. The morning following the baseline night, subjects entered a mini-constant routine during which experimenters kept them awake in bed for the next 25 hours. The sleep recuperative episode started the morning after the 25 hours of sleep deprivation. Factorial ANOVAs with between group factors (age, gender) and repeated factors (sleep episode, cycle) were used to compare the effects of the sleep deprivation.

Results: Both age groups showed a decrease of sleep efficiency during daytime recovery sleep, but the Middle-aged subjects had a more abrupt decline than did the Young subjects (interaction group X night: p<0.02). No significant interaction was found between age group and gender or between age group, gender, and night. Slow-wave sleep was potentiated in both age groups following sleep deprivation. However, the rebound of SWS was less pronounced in the Middle-aged group than in the Young group (Interaction Group X Night: p<0.03). No significant interaction with gender was found. The Figures illustrate hourly mean SWA (and sem) for the first 180 minutes of N-REM sleep separately for women and men. The rebound of SWA following the sleep deprivation was less pronounced in the Middle-aged group compared to the Young group (interaction group X night: p<0.05). No interaction with gender was found.

Conclusions: These results suggest that middle-aged men and women do not differ in their response to sleep deprivation during daytime recuperative sleep. Compared to the young, both middle-aged men and women clearly show a higher vulnerability to an abnormal phase angle between sleep and the circadian signal, as measured with a steeper decrease of sleep efficiency during daytime sleep. The observed reduction of SWA following sleep deprivation in the middle-aged subjects suggests that the homeostatic recuperative drive is already attenuated in the middle years of life and that this attenuation is similar in middle-aged men and women.

References:
(1) Carrier J., Land S., Buysse, DJ, Kupfer DJ, Monk, TH The effects of age and gender on sleep EEG power spectral density in the middle years of life. Psychophysiology (in press).
(2) Gaudreau H, Morettini J, Lavoie HB, Carrier J Effects of a 25-hour sleep deprivation on daytime sleep in the middle-aged. Neurobiology of Aging (in press)

Research supported by Medical Research Council of Canada (Scholarship and grant MT-14999 to Carrier and post-doctoral fellowship to Gaudreau)
Sleep and Performance Consequences for Specialist Anaesthetists Working Twelve Consecutive Days.

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Introduction: Specialist anaesthetists may be required to work extended hours or on call. Thus, work demands may limit sleep opportunities. When sleep is restricted over consecutive days, a sleep debt accumulates and performance degrades (1). From a recent national survey, 27% of New Zealand specialists reported that their average working week exceeded what they believed they could do on an ongoing basis while maintaining patient safety (2). The present study examines the sleep and the reaction time performance of 24 specialist anaesthetists working 12 consecutive days.

Methods: Daily sleep totals were calculated from actigraphy across a 14-day study period (including two days off). For each individual, sleep loss (or gain) was calculated by subtracting daily sleep totals from baseline on nights when sleep was unrestricted. A 10-minute Psychomotor Vigilance Task (PVT) was used to measure reaction times pre- and post-duty. Analyses were undertaken using mixed model ANCOVAs, with individuals modelled as a random variable and terms variously included for shift type, time-on-duty (pre- or post-duty) and shift sequence (day- or night). Post hoc t tests examined simple effects, with adjustment for multiple comparisons using Holm’s sequentially rejective procedure.

Results: A significant shift type effect was found for sleep loss (F(2, 47) = 4.17, p < .05). Specialists lost sleep when working day shifts (t(130) = 2.71, p = .008), and day shifts followed by call (t(70.6) = 2.58, p = .012), relative to days off. On average, specialists obtained 0.6 h less than needed on day shifts, and 0.7 h less than needed on day shifts followed by call. Across the 12 working days, linear trends in pre-duty and post-duty reaction times differed (Table 1). From the regression slopes, pre-duty reaction times did not differ significantly across consecutive workdays. However, post-duty, median (t(174) = -3.69, p < .001), slowest (t(174) = -3.20, p < .01), and optimal reaction times (t (175) = -2.44, p < .05) became progressively slower. Figure 1 illustrates these findings graphically by plotting the estimates of pre- and post-duty median and optimal reaction times across the 12 days.

Table 1

<table>
<thead>
<tr>
<th>Performance Measure</th>
<th>Time on Duty Interactions</th>
<th>F(0,47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RT (1/RT)</td>
<td>9.67,1 (0.159)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Slowest 10% RT (1/RT)</td>
<td>3.91,1 (0.172)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Fastest 10% RT (1/RT)</td>
<td>6.02,1 (0.171)</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Specialists lost sleep on workdays and showed post-duty performance declines across consecutive working days, a likely consequence of cumulative sleep loss. However, specialists maintained their pre-duty performance across this period. These findings suggest that the standard hours of work of these specialist anaesthetists restrict sleep and may result in decreased safety margins as time on duty increases.

References:

Research supported by the New Zealand Health Research Council, Grant Nos. 97/241 and 98/391

Fluctuation of Subjective Alertness and Waking EEG During a 25-hour Sleep Deprivation in Young and Middle-aged Subjects

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Introduction: Both homeostatic and circadian processes modulate spectral components in the waking EEG (1). Spectral power in the alpha and theta ranges are particularly sensitive to the accumulation of wakefulness (2). It has been proposed that the wake-dependent modifications in the waking EEG and sleep EEG represent the same underlying homeostatic process (1). We have recently shown that compared to the young, middle-aged subjects show a reduced rebound of slow-wave activity (SWA: spectral power between 0.5 Hz and 4.5 Hz in N-REM sleep) following an acute sleep deprivation, suggesting an attenuation of homeostatic drive during the middle years of life (3). The aim of this study was to evaluate the effects of a 25-hour sleep deprivation on quantitative waking EEG and subjective alertness in young and middle-aged subjects. We predicted middle-aged subjects would show reduced wake-dependent modifications of these parameters compared to the young

Methods: Twenty-six subjects were studied. They were separated into two groups according to their age: 13 Young (20-39 years, 6 W, 7 M) and
Middle-aged (40-59 years, 7 W, 6 M). All subjects spent four consecutive nights and two days in the laboratory. On the morning following the third night, subjects entered a 25-hour mini-constant routine during which they were kept awake in bed. Waking EEGs with eyes open were recorded every two hours and subjective alertness was evaluated every 30 minutes with a visual analog scale. Waking EEGs (C3-A2; sampling rate: 256 Hz) were subjected to spectral power analysis (FFTs) for consecutive 2-sec epochs and a 0.5 Hz resolution. Averages were computed on artifact-free EEG signals (C3-A2). Two-way factor ANOVAs with one repeated measure (Time) followed by trend analyses have been used on log transformed data.

**Results:** Spectral power in theta and alpha frequency bands showed a significant time effect (p<0.0001 in both cases). Both theta and alpha frequency bands showed a significant linear trend (p<0.0001), increasing with accumulation of time awake in the young and the middle-aged subjects (see Figure 1). Subjective alertness showed a significant time effect (p<0.0001) with a significant linear trend (p<0.0001), young and middle-aged subjects showing a similar decrease of subjective alertness with time awake (see Figure 2). No interaction between Group and Time nor Group effect has been found for these parameters.

**Conclusions:** Middle-aged and young subjects showed similar time courses of subjective alertness and spectral power in theta and alpha frequency bands during a 25-hour sleep deprivation in constant behavioral and environmental conditions. The build up of homeostatic pressure seems to have no differential impact on the waking EEG in the middle-aged and the young subjects. These results are in contrast with the sleep EEG data showing a reduced rebound of SWA following a 25-hour sleep deprivation in the middle-aged population compared to the young (3). The functional relationship between wake-dependent modifications in the waking EEG and the sleep EEG is still unclear and deserves further investigation.

**References:**

Research supported by Medical Research Council of Canada (Scholarship and grant MT-14999 to Carrier and doctoral fellowship from Fond de Recherche en Santé du Québec to Drapeau)
Oral Presentations

053.O

Melatonin for Treatment of REM Sleep Behavior Disorder: Response in 8 Patients

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Mayo Clinic

**Introduction:** Clonazepam has been the treatment of choice for RBD. However, an alternative treatment is desirable for those with RBD refractory to clonazepam, for those who experience intolerable side-effects with clonazepam, and for those in whom clonazepam precipitates or aggravates obstructive sleep apnea (OSA). An open label trial of melatonin in RBD associated with Parkinson’s disease showed improvement of RBD in 5 out of 6 patients (1). There are no published data regarding melatonin for patients with RBD associated with other neurologic disorders.

**Methods:** The treatment response for RBD with melatonin was reviewed on all patients we have treated with this agent at Mayo Clinic Rochester from 1/00-11/00. The coexisting neurologic disorders, reasons for using melatonin, effective doses, and side-effects were also reviewed on all patients.

**Results:** Eight patients have been treated (all male, median age 70 years, range 53-81 years). The coexisting neurologic findings/disorders were mild cognitive decline with mild parkinsonism in 3 cases, dementia with Lewy bodies in 2, multiple system atrophy in 2, and narcolepsy in 1. The reasons for using melatonin in these cases were RBD refractory to clonazepam at 0.5 mg/night and increased forgetfulness at doses greater than 0.5 mg/night in 4 cases, reluctance to use clonazepam due to existing cognitive impairment in 2, impotence with clonazepam in 1, and presence of OSA in 1. With 4 patients continuing to use clonazepam at 0.5 mg/night, complete or near complete response to melatonin occurred in all patients (7 with 6 mg nightly and 1 with 12 mg nightly). One patient experienced headaches at 12 mg/night, otherwise no other side-effects with melatonin were reported.

**Conclusions:** Melatonin can be considered as sole or add-on therapy for treatment of RBD associated with a variety of neurologic symptoms and disorders.

**References:**

054.O

Striatal Dopamine Transporter Dysfunction in Idiopathic Clinical and Subclinical REM Sleep Behavior Disorder

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**Introduction:** There are clinical associations between REM sleep behavior disorder (RBD) and Parkinson’s disease (PD).

**Methods:** We therefore studied striatal presynaptic dopamine transporters with (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane (123I-IPT) using single-photon emission computed tomography (SPECT) in patients with idiopathic RBD (n = 8), patients with subclinical RBD (n = 9), controls without a history of sleep disorders (n=11), and patients with PD (stage Hoehn & Yahr I, n = 14).

**Results:** All patients with clinically apparent RBD had significantly symmetrically reduced striatal IPT binding (clinical RBD: IPT ratio: 3.2±0.4) compared with the controls (control IPT ratio: 4.3±0.2), but significantly higher striatal IPT binding compared with the striatum contralateral to the symmetric body side of the PD patients (PD: 2.5±0.3). SPECT of patients with subclinical RBD, which was defined as REM sleep without atonia and lack of complex motor behavior in the synchronized videotape also showed symmetrically reduced IPT uptake, which was intermediate (subclinical RBD: IPT ratio: 3.7±0.3): IPT uptake was lower compared with controls, but higher than in patients with clinical RBD. All results were statistically significant (p<0.027). Further studies are ongoing to quantify and further evaluate this finding.

**Conclusions:** We conclude from our preliminary results, that there is a continuum of striatal presynaptic dopaminergic dysfunction in patients with subclinical RBD, clinical RBD and PD.

055.O

Disorders of Arousal and Nightmares in Temporal Lobe Epilepsy (TLE)

*Silvestri RC*
(1) Brigham and Women's Hospital, (2) Harvard Medical School

**Introduction:** Sleep disruption is a common feature of temporal lobe epilepsy (TLE). Multiple arousals are usually dispersed through the night leading to severe sleep deprivation, cognitive impairment and resistance to treatment. Though non epileptic disorders of arousal have been reported in epileptic children, conversely, the possible ictal nature of recurrent parasomnias in TLE has not been extensively investigated.

**Methods:** A sleep questionnaire and diaries have been distributed to the (TLE) patients of a tertiary Center for Epilepsy in a Harvard Community Hospital. Patients identified by themselves or their families as presenting with disorders of arousal or recurrent nightmares underwent long term monitoring (LTM), with at least one full night of video-polygraphic recording. Recorded episodes have been classified according to sleep
stage, duration, behavioral component (motor/verbal/autonomic), EEG pattern and resemblance to the clinical/eegraphic pattern of a typical seizure. All patients had brain MRIs and baseline sleep deprived interictal EEG recordings.

Results: A total of 20 consecutive patients (6 M, 14 F; mean age 33.7, range 16-64) were identified over a 2 year sample of 168 reviewed cases; of these sixteen had confusional arousals, 14 recurrent nightmares, 2 sleepwalking and 4 night terrors, in different combinations. Brain MRI was negative in all but 6 affected by mesial temporal sclerosis (MTS). Twenty five episodes were documented in 10/20 patients: 20 confusional arousals, 3 night terrors, 1 sleep walking and 1 nightmare out of sleep stage 2, all corresponding to icctal eegraphic evidence of a TLE seizure, with a mean duration of 3 min (range 1.2-3.6). Optimization of drug regimen led to almost complete cessation of the episodes in all but the 3 unoperated MTS patients.

Conclusions: The possibility of misinterpreting nocturnal seizures as benign parasomnias is high in TLE, leading to insufficient seizure control, misdiagnosis and progressive cognitive impairment. An increased number of overnight recordings can be the premise for a better quality of life in these patients.

056.P

Sleep/Wake Patterns of Patients on Chronic Hemodialysis Via Ambulatory Polysomnography

Parker KP,1,2,3 Bliwise DL,2 Rye DB,2 Bailey J1
(1) Nell Hodgson Woodruff School of Nursing, (2) Department of Neurology, (3) Renal Division, Emory University

Introduction: Pathological sleep in the form of apneas and leg movements have been well described in hemodialysis (HD) patients. Considerable evidence suggests, however, that sleep regulation per se may also be disturbed. Excessive amounts of daytime sleep occurring in association with treatment, for example, may contribute to this dysregulation. We report here preliminary results from continuous, 24-hour ambulatory polysomnography (PSG) performed in patients before, during, and after HD.

Methods: The sample included 13 chronic HD patients who were free of other major chronic conditions and were not taking medications known to have CNS effects (see Table 1). All subjects had undergone one night of laboratory-based PSG that documented minimal evidence of primary sleep disorders - mean respiratory disturbance index (RDI) of 4.7 (5.2) and periodic leg movement index (PLMI) of 6.5 (12.6). The subjects underwent continuous ambulatory PSG (Oxford Instruments) for two 42-hour periods beginning at 6 PM the night before HD and ending at 12 PM the day following treatment. Data were collected regarding all sleep variables recorded and scored in a laboratory-based PSG except for RDI, PLMI, and brief arousal index (BAI).

Results: Data were pooled from all four nights - 2 nights before HD and 2 nights following HD. The daytime sleep was also pooled (2 days). The mean nocturnal total sleep time was 329.9 (± 73.5) minutes and the sleep efficiency was 71.3 (± 10.5)%. The percentage of time spent in each stage of sleep during the night was unremarkable. During the daytime, subjects slept an average of 115.2 (± 85.9) minutes with 30.3 (± 39.0) minutes of sleep occurring during the intradialytic period; 5.5% of the total daytime sleep was REM sleep. The remainder of the daytime sleep occurred following HD in all subjects. When the mean nocturnal and daytime sleep were considered together, subjects obtained an average of 445 minutes (7.4 hours) of sleep, 35% of which occurred during the day. The amount of total daytime sleep was negatively related to the nocturnal TST (r = -0.567, p = 0.022), indicating that increased daytime sleep was associated with decreased nocturnal TST.

Table 1 Sample Features (n = 13)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (+ SD) / Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
</tr>
<tr>
<td>ECOG</td>
<td>12.1 (± 4.1)</td>
</tr>
<tr>
<td>Cardio</td>
<td>69.2 (± 9.1)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>13.0 (± 2.3)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>34.6 (± 3.4)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>624.6 (± 521.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Based PSG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (minutes)</td>
<td>351.6 (± 45.6)</td>
</tr>
<tr>
<td>SE (%)</td>
<td>82.6 (± 0.2)</td>
</tr>
<tr>
<td>RDI (events/hour)</td>
<td>4.6 (± 5.2)</td>
</tr>
<tr>
<td>PLMI (events/hour)</td>
<td>6.5 (± 12.6)</td>
</tr>
<tr>
<td>BAI (events/hour)</td>
<td>17.2 (± 8.8)</td>
</tr>
<tr>
<td>MSLT minutes</td>
<td>12.6 (± 3.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ambulatory PSG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>nocturnal TST</td>
<td>329.9 (± 7.35)</td>
</tr>
<tr>
<td>nocturnal SE</td>
<td>71.3 (± 0.10)</td>
</tr>
<tr>
<td>intradialytic-TST</td>
<td>30.3 (± 39.0)</td>
</tr>
<tr>
<td>daytime TST</td>
<td>115.2 (± 85.9)</td>
</tr>
</tbody>
</table>

Conclusions: These results suggest that, in HD patients with minimal sleep pathology, significant amounts of sleep, including REM sleep, occur during and following treatment. This “displaced” daytime sleep is associated with shorter nocturnal sleep and may be interpreted as either a cause for or an effect of such nighttime sleep disruption. Because sleepiness during the dialytic procedure has been shown to be associated with body temperature changes (1), these results suggest a complex interaction between homeostatic and circadian factors and dialytic therapy, apart from the influence of sleep pathology.

References:
(1) Parker KP, Bliwise DL. Rye DB: Intradialytic subjective sleepiness and oral body temperature; Sleep, 23(7), 887-891.

Research supported by National Institute of Nursing Research RO1 NR 04340

057.P

Duration of Prescribed Hemodialysis Treatment Time Predicts Daytime Sleepiness Levels

Parker KP,1,2,3 Bliwise DL,2 Rye DB,2 Bailey J1
(1) Nell Hodgson Woodruff School of Nursing, (2) Department of Neurology, (3) Renal Division, Emory University

Introduction: Increased sleep propensity in the chronic hemodialysis (HD) population has been described for over 30 years (1). Although sleep apnea (SA) and periodic leg movements (PLMs) are very prevalent in this group, the extent to which these disorders versus renal disease per se and/or its treatment contribute to sleepiness remains to be established. In this analysis, we examined a variety of demographic, metabolic, sleep, and HD-related variables to determine their ability to predict objectively measured levels of daytime sleepiness.

Methods: The sample included 44 chronic, stable HD patients (see Table 1). Potential subjects with other major chronic conditions or those on medications known to have CNS effects were excluded from participation. All subjects underwent a laboratory-based PSG followed by a Multiple Sleep Latency Test (MSLT).

Results: We constructed four regression models composed of demographic (model #1), metabolic (model #2), sleep (model #3), and HD-
related (model #4) variables. (The number of variables in each model was limited to 4 because of concerns regarding subject-variable ratios. None of the variables in each model were significantly correlated.) We selected age, gender, race, and marital status as the demographic variables of interest because these factors are associated with sleep disorders in the general population. We selected BUN, creatinine, ferritin, and body mass index (BMI) as these are important indicators of metabolic status in renal failure patients and because the later two have been specifically associated with PLMs and SA. Total sleep time (TST), respiratory disturbance index (RDI), and periodic leg movement index (PLMI) were selected as the sleep variables because of their importance in overall sleep quality. Brief arousal index (BAI) was not included because it was significantly correlated with RDI. Finally, the HD related variables of duration of prescribed HD treatment time, treatment time of day (shift), KT/V (a measure of HD adequacy) were selected to identify treatment-associated effects on sleepiness. The first two models did not reach statistical significance in the prediction of MSLT scores. The sleep-related model accounted for 25.4% (p = 0.008) of the variance with RDI and PLMI being significant independent predictors of sleepiness levels. The HD-related model approached statistical significance and accounted for 15.7% (p = 0.080) of the variance. Duration of HD treatment time was negatively associated with MSLT scores. In addition, it was the only significant, independent predictor of MSLT scores in this model (see Table 2).

Table 1

<table>
<thead>
<tr>
<th>Parameter (mean ± SD*)</th>
<th>Entire Group N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.8 (±10.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>21</td>
</tr>
<tr>
<td>male</td>
<td>23</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
</tr>
<tr>
<td>married</td>
<td>25</td>
</tr>
<tr>
<td>single</td>
<td>15</td>
</tr>
<tr>
<td>divorced</td>
<td>4</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>black</td>
<td>35</td>
</tr>
<tr>
<td>white</td>
<td>9</td>
</tr>
<tr>
<td>BUN (mg%)</td>
<td>64.8 (±16.4)</td>
</tr>
<tr>
<td>Creatinine (mg%)</td>
<td>12.1 (±2.8)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35.8 (±3.3)</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>542.8 (±400.0)</td>
</tr>
<tr>
<td>Duration of HD treatment (minutes)</td>
<td>220.5 (±20.5)</td>
</tr>
<tr>
<td>KT/V**</td>
<td>1.5 (±0.3)</td>
</tr>
<tr>
<td>Time of treatment</td>
<td></td>
</tr>
<tr>
<td>shift 1 (6 AM to 10 AM)</td>
<td>18</td>
</tr>
<tr>
<td>shift 2 (10 AM to 2 PM)</td>
<td>13</td>
</tr>
<tr>
<td>shift 3 (2 PM to 6 PM)</td>
<td>13</td>
</tr>
<tr>
<td>TST (minutes)</td>
<td>335.7 (±66.3)</td>
</tr>
<tr>
<td>SE (%)</td>
<td>78.5 (±14.2)</td>
</tr>
<tr>
<td>RDI (events/hour)</td>
<td>13.3 (±20.8)</td>
</tr>
<tr>
<td>PLMI (events/hour)</td>
<td>21.9 (±35.6)</td>
</tr>
<tr>
<td>BAI (events/hour)</td>
<td>30.9 (±24.5)</td>
</tr>
<tr>
<td>MSLT (minutes)</td>
<td>10.2 (±4.3)</td>
</tr>
</tbody>
</table>

SD = standard deviation; ** KT/V = measure of HD adequacy based on treatment time, dialyzer clearance, and total body water

Table 2

<table>
<thead>
<tr>
<th>Models Derived to Predict Sleepiness (MSLT Scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models</td>
</tr>
<tr>
<td>R²</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Demographic</td>
</tr>
<tr>
<td>(1) Age</td>
</tr>
<tr>
<td>* Gender</td>
</tr>
<tr>
<td>* Race</td>
</tr>
<tr>
<td>* Marital Status</td>
</tr>
<tr>
<td>PLMI</td>
</tr>
<tr>
<td>#2 Metabolic</td>
</tr>
<tr>
<td>* BUN</td>
</tr>
<tr>
<td>* Creatinine</td>
</tr>
<tr>
<td>* Ferritin</td>
</tr>
<tr>
<td>* BMI</td>
</tr>
<tr>
<td>#3 Sleep Variables</td>
</tr>
<tr>
<td>* TST</td>
</tr>
<tr>
<td>#4 HD Variables</td>
</tr>
<tr>
<td>* Duration of HD</td>
</tr>
<tr>
<td>* PLMI</td>
</tr>
<tr>
<td>* KT/V</td>
</tr>
</tbody>
</table>

Conclusions: Conclusions: RDI and PLMI were significant predictors of MSLT scores. In addition, duration of HD treatment time was a significant, independent predictor of MSLT scores, suggesting that daytime sleepiness represents an iatrogenic effect of HD. These negative effects increase as procedure duration lengthens. To our knowledge, this is the first time that this phenomenon has been described.

References:

Research supported by National Institute of Nursing Research RO1 NR 04340 058.P

Excessive Daytime Somnolence and Increased REM Pressure in Myotonic Dystrophy

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Introduction: Myotonic Dystrophy (MD), the most common form of muscular dystrophy in adults, is a genetic multi-system disorder which is characterized by abnormalities of the muscular, endocrine, and central nervous systems. Excessive daytime sleepiness (EDS) is common in patients with MD and is a factor in compromising the quality of life in many MD patients. In the present study, eighteen patients with confirmed MD (by family history or genetic testing) who referred to the sleep lab were retrospectively reviewed.

Methods: In the present report, eighteen patients with MD presenting to Duke University Medical Center sleep disorders clinic between 1986-2000 were retrospectively reviewed. All patients underwent an in-lab overnight polysomnogram (OPSG) and 11 had a multiple sleep latency test (MSLT) performed the following day. Seven of these eighteen patients have been previously reported (Park and Radtke, 1995).

Results: Three of the eighteen patients studied had a respiratory disturbance index >15 (both central and obstructive events). In addition, three patients had an RDI between 5 and 15 and two had an elevated arousal index that was unexplained. Ten of eighteen patients had OPSGs without any sleep pathology identified that would contribute to the complaint of EDS. Eleven of eighteen patients underwent the MSLT the following...
day, six of whom had normal PSG and five with an abnormality noted on PSG. In the six MSLTs in patients with a normal PSG all demonstrated a mean sleep latency (MSL) of <8 minutes. Three had 2 or more naps with sleep onset REM sleep (SOREM), two had a single SOREM, and one had no SOREM noted. Similarly, in the five MSLT studies in patients with a PSG abnormality (although two had moderate to severe sleep disruption), a MSL of <8 was noted in 4. Two of these patients had two or more SOREMs, one had a single SOREM, and two had no SOREMs recorded.

Conclusions: The complaint of EDS in patients with MD is confirmed on MSLT evaluation (10/11 with MSL <8 min). Abnormal REM pressure is present in most patients with MD (5/11 with 2 or more SOREMs, 3/11 with a single SOREM, and 3/11 with no SOREM identified). Abnormalities on overnight PSG (elevated RDI, elevated arousal index) are not usually present and are not at a level that would likely contribute to the abnormal MSLT result. MD is a disorder that frequently manifests EDS and may demonstrate an MSLT result (shortened sleep latency with abnormal REM pressure) that is classically seen in narcolepsy.

References:

059.P

Marked REM Sleep Suppression Associated with Graves’ Disease in Prepubescent Girls

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Introduction: Recent findings have linked mechanisms involved in the regulation of the thyroid hormone axis to those involved in the regulation of sleep. By way of example, sleep deprivation in rats results in central nervous system suppression of the thyroid hormone axis (1), and narcoleptic dogs administered the central nervous system peptide, thyrotropin-releasing hormone, have reduced cataplexy (2). Over the years, scientists have periodically tested the possibility that thyroid hormones play a major role in the regulation and function of sleep. These studies mainly employed pharmacological manipulation of thyroid hormones in normal individuals to determine changes in the sleep response, or correlated variations in serum thyroid hormone concentrations with sleep stage amount. While their results suggest that sleep is not much affected, the brain has an exquisite ability to remain euthyroid during peripheral thyroid hormone excess or insufficiency. Contrarily, it is well recognized that thyroid hormone disease can profoundly affect central nervous system (CNS) function. Are these CNS effects affecting sleep? Two studies conducted over 25 years ago profiled sleep in hyperthyroid patients, but yielded conflicting results. Dunleavy and colleagues (1979) studied 4 thyrotoxic subjects, 50-60 years old, and found 2 to 6 times normal amounts of Stage 3 and 4 sleep. In the second study, by Passouant and colleagues in 1966, sleep was disrupted in hyperthyroid subjects, and sleep corresponding to Stages 3 and 4 was reduced. In the present study, we investigated the sleep of three preadolescent girls diagnosed with Graves’ disease, as a step toward providing a broader working framework for elucidating the linkage of thyroid hormones and sleep.

Methods: Three prepubescent girls, ages 7, 9, and 11, clinically diagnosed with hyperthyroidism were evaluated by overnight polysomnography within 2 weeks of the start of antithyroid therapy. The evaluations were conducted at the Le Bonheur Children’s Medical Center Pediatric Sleep Disorder Center in Memphis, TN. In addition to the clinical and laboratory diagnosis of hyperthyroidism, all three girls had abnormally high levels of thyroid stimulating immunoglobulin indicative of Graves’ disease. Sleep stage percentages were compared with published normative values for prepubescent girls (3).

Results: The principal finding was a reduction in REM sleep that was greater than 3 standard deviations below normal for girls of this age (Fig. 1). The reduction in REM sleep was accompanied by a trend toward more NREM sleep in each Stage 2, 3, and 4. Sleep efficiencies were 97.4%, 91.8%, and 91.3% for the 7-, 9-, and 11-year-old, respectively, compared with normal sleep efficiencies of 97 and 95% for 6-to-9- and 10-to-12-year-old girls, respectively.

Figure 1

Conclusions: The CNS effects of Graves’ disease on sleep in the three prepubescent girls whom we studied were manifested by a profound suppression of REM sleep. Abnormal thyroid hormone regulation is the prominent feature of thyroid disease, yet immunologic disturbances are at the root of Graves’ disease. Whether the endocrine branch or the immune branch may be mediating the central effects of thyroid hormone disease on sleep will be under study.

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060.P

Autonomic Functioning During REM Sleep Differentiates IBS Symptom Subgroups

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Introduction: Using the stages of sleep as a model to study autonomic functioning, we have identified autonomic abnormalities during rapid-eye movement (REM) sleep in IBS patients (Orr, et. al. 2000). It is not known whether sleep can also reveal symptom-specific differences in autonomic activity in IBS patients. Therefore, the present study was designed to investigate autonomic activity by means of heart rate vari-
ability analysis in a large sample of IBS patient which allowed stratification into different symptom subgroups.

**Methods**: Twenty-nine female IBS patients and 21 healthy women participated. We stratified our patient group into 14 patients with only lower bowel symptoms (IBS+L), and 15 patients with both lower and dyspeptic like symptoms (IBS+D). The protocol included a 30-minute quiet waking period followed by an overnight study in the sleep laboratory. Standard polysomnography was recorded to detect the various stages of sleep as well as the ECG in order to measure the beat-to-beat intervals of the cardiac cycle. Fifteen-minute segments were selected from waking, stage 2 of non-REM sleep, and REM sleep. Each segment was analyzed by spectral analysis to calculate the power in the low frequency (LF) band (.04 - .15 Hz), a measure of sympathetic activity, power in the high frequency (HF) band (.04 - .5 Hz), a measure of vagal tone, and the LF/HF ratio as an indicator of sympatho-vagal balance.

**Figure 1**

LF/HF Ratio Across Sleep Stages

- **Figure 1**: The LF/HF ratio, was significantly (p < .01) different across the states of consciousness (wake, non-REM, REM). Significantly (p < .01) higher LF/HF means were found during REM than wake and non-REM (p < .01) for all participants. However, there were no significant differences for wake and non-REM (p = .13). 2) IBS patients without functional dyspepsia (IBS+L) revealed significantly increased LF/HF ratios during REM sleep compared to controls (p < .01) and IBS+D patients (p < .01), see Figure 1. There were no significant mean differences between IBS+D patients and healthy controls during REM. 3) Although not significant, sympathetic tone (LF), was greatest in the IBS+L group and vagal tone (HF) was least which accounts for the dramatic increase in sympatho-vagal balance during REM.

**Conclusions**: IBS patients without dyspeptic symptoms have a greater sympatho-vagal balance during REM sleep. 2) These results clearly show that autonomic functioning, unique to REM sleep, differentiates these IBS symptom subgroups suggesting that autonomic functioning during REM sleep may be a useful biological marker distinguishing different subgroups of IBS patients.

**References**


**061.A**

Sleep-Like State in Zebrafish: Effects of Melatonin and Sedatives

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**Introduction**: In search for a viable vertebrate model for studying the molecular bases of sleep we chose to test the zebrafish (Danio rerio), a diurnal vertebrate with a clear circadian pattern of daytime activity and nighttime rest. Given that zebrafish provide an efficiency of large-scale genetic screens, multiple mutant phenotypes and current construction of genetic and physical maps, this species is one of the best candidates for studying the mechanisms of homeostasis and the molecular bases of behavior in lower vertebrates (1). We have analyzed whether the behavioral and pharmacological features of rest state in zebrafish larvae are comparable to those observed in mammals, by documented changes in locomotor activity and arousal threshold after rest deprivation. We also determined whether the physiological and pharmacological agents known to promote sleep in humans could change zebrafish behavior by testing the effects of the pineal hormone melatonin, benzodiazepine and barbiturate hypnotics on the activity and arousal threshold in zebrafish.

**Methods**: Larval zebrafish (D. rerio, Tubingen strain, 7-14 days old) were maintained under 12:12 light:dark cycle at 23°C and fed Paramecium daily. Locomotor activity was documented using automatic image analysis system, simultaneously monitoring a distance traversed by each of 60 fish during consecutive 15-sec intervals. Fish were housed in individual wells of a microplate and recordings were conducted under constant infrared illumination for up to 5 days. Rest deprivation was achieved by a continuous gentle vibration of a microplate containing fish and was scheduled either at daytime (ZT0-ZT6) or at night (ZT18-ZT24). Locomotor activity for 6 hours after rest deprivation was compared to basal recordings. Arousal threshold (AR) was measured by applying series of standardized mechanical stimuli to a microplate containing fish. The videorecordings of this procedure were visually scored and a number of stimuli necessary to induce locomotion in each fish was registered. Measurements were conducted starting ZT3 (daytime AR), ZT 15 (nighttime AR), an hour after rest deprivation or an hour after pharmacological treatment. Pharmacological treatments (sodium pentobarbital, diazepam and melatonin) were administered directly into individual wells containing larvae. Locomotor activity for 2 hours after treatment was compared to a 2-hour basal recording. Figure legend shows final concentration of each agent in the microplate wells. The control for each treatment contained corresponding vehicle solutions which did not change locomotor activity.

**Results**: Prolonged periods of quietness (>5 min) were associated with two main postures in larval zebrafish, either floating with head down or staying in a horizontal position close to the bottom of a chamber. Locomotor activity in zebrafish was significantly lower and arousal threshold higher at subjective night compared to daytime. Nighttime rest deprivation, in contrast to daytime rest deprivation, resulted in a significant decline in daytime locomotor activity of the fish and in a heightened arousal threshold, suggesting that zebrafish have a homeostatic control of rest behavior and can compensate for rest deprivation. Pentobarbital and diazepam treatment (10μM-100μM) resulted in a concentration-dependent decrease in zebrafish locomotor activity and increase in arousal threshold, with high doses completely eliminating spontaneous activity and larval response to external stimuli. Pretreatment with flumazenil, benzodiazepine receptor antagonist, blocked the effect of diazepam but did not modify the effect of pentobarbital. We have previously shown that increasing circulating levels of the pineal hormone melatonin to within physiological range can acutely promote sleep onset in humans and non-human primates, suggesting that it plays an important role in normal sleep regulation in diurnal species. Treatment with a wide range of melatonin doses (100nM-100μM) results in a robust rest-promoting effect in larval zebrafish, reducing motor activity and increasing arousal threshold. In contrast to diazepam and pentobarbital, even highest melatonin doses did not abolish spontaneous activity or arousal upon stimulation. Pretreatment with a specific melatonin receptor antagonist, luzindole, blocked the effects of melatonin, providing the first evidence that the acute rest-promoting effect of melatonin is linked to specific melatonin receptors. Pretreatment with flumazenil did not modify the effects of melatonin in zebrafish, implying that benzodiazepine receptors are not involved in this effect of the pineal hormone.
Conclusions: Our study reveals that zebrafish show species-specific rest postures, compensate for rest deprivation by rest rebound, have elevated arousal threshold during their habitual rest period and respond to conventional sedatives. These fundamental similarities between the behavioral features of sleep in higher vertebrates and the rest behavior in zebrafish suggest that rest in this lower vertebrate is a sleep-like state. Recent remarkable advances in studying the zebrafish genetics and development provide a unique opportunity for a genetic analysis of the sleep phenomenon and examination of molecular mechanisms of sleep regulation in vertebrates. Furthermore, sensitivity of rest process in zebrafish larvae to melatonin, known to promote sleep in humans and diurnal monkeys (2,3), and to conventional hypnotics might open the possibility of a more efficient screening for new hypnotic agents.

References:

062.A

Local Field Potential Recordings from Drosophila Mushroom Bodies and their Modulation by Activity State

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Introduction: In mammals, clearly recognizable changes in pattern and amount of brain electrical activity accompany changes in motor activity and arousal thresholds. It has recently been demonstrated that Drosophila melanogaster exhibit a sleep-like state (Hendrickx et al., Neuron, v25, 2000; Shaw et al., Science, v287, 2000). This state is characterized by motor inactivity and heightened arousal thresholds. We sought to determine whether changes in brain activity patterns in Drosophila are, as in mammals, closely associated with changes in motor activity.

Methods: The thorax and head of 4, 2-4 day old, female, Canton-S Drosophila were fixed to a small loop of tungsten rod. One twelve-micrometer wire was inserted into each optic lobe (OL) and another wire through the ocelli, to rest near the mushroom bodies (MB) and a ground wire was placed in the thorax. The preparation allowed free movement of limbs, wings and proboscis with the animal suspended from the tungsten loop. Motor activity was assessed by measuring interruption of an infrared light source by limb movements. Recordings of local field potentials (LFPs) in the virtual absence of movement and power-source artifacts were achieved by current amplification of signals, grounding of the animal, and a Faraday cage.

Results: The data presented herein are from differential recordings of the MB referenced to an OL wire. All animals exhibited a background of low-voltage fast activity 40 microvolts in amplitude interrupted, with varying frequency, by sharp field potentials (hereafter termed ‘spikes’) between 50 and 200 microvolts in amplitude and 5-50 ms in duration. Spikes were both positive and negative-going, and occurred in isolation as well as in bursts. These spikes were not caused by movement artifact since: 1. visual inspection indicated that these spikes could occur in the total absence of movement; 2. point-to-point correlation of rectified field-potential amplitude with movement was low. 3. spikes could be observed in mutant animals where reversible suppression of motoneuron synaptic transmission produced temporary paralysis. Conversely, potent suppression of spikes occurred in the presence of continued movement in mutant animals where synaptic transmission of MB neurons was reversibly suppressed. Each animal exhibited several long (> 5 minutes) periods of motor activity and inactivity. We compared LFPs recorded during active periods with those of inactive periods using power spectral analysis and by counting the occurrence of spikes larger than 50 microvolts in amplitude. Spectral power at frequencies between 10 and 100 Hz and spike frequency decreased during long periods of motor inactivity. No other correlation between LFPs and activity state could be discerned.

Conclusions: These results show that LFPs can be recorded from the brain of Drosophila and that such potentials are modulated by behavioral state. It remains to be determined whether the drop in spike-like field potentials during long inactive periods results from a generalized decrease in neuronal activity or a loss of synchronized MB neuronal activity.

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063.B

Correlation Between "Unihemispheric" Slow Wave Sleep and the State of Eyes in a Beluga Whale

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Introduction: Pronounced interhemispheric EEG asymmetry (IA) during slow wave sleep (or "unihemispheric" SWS) has been described in several species of Cetaceans (Mukhametov, 1984). Though it was clearly documented that dolphins can sleep with one eye open, the correlation between the pattern of EEG in each hemisphere and the state of eyes has not been established. In birds, which also exhibit short episodes of IA during sleep, such a correlation has been shown in several species (Rattenborg et al., 1999). Therefore, the aim of the present study was to examine the relationship between the state of the eyes and sleep in another species of Cetaceans - the beluga whale.

Methods: The study was carried out on an adult male beluga whale. EEG was recorded from two symmetrical pairs of electrodes implanted over two hemispheres. During this part of the study (4 consecutive days) the whale was in a pool (4.5x4.5x1.2 m) with sea water where its movement was restricted using ropes attached to a harness worn by the whale. This allowed us to observe and video tape the state of both eyes most of the time. EEG from two hemispheres was scored visually in 30 sec epochs as follows: 1) desynchronization; 2) intermediate synchronization; 3) high amplitude synchronization. The state of each eye was sampled alternately in 5-sec intervals (open, closed, intermediate) and then extrapolated for the whole 30 sec epoch.

Results: Only SWS with pronounced IA asymmetry was recorded in the beluga whale. The state of both eyes is presently compared in 4 states: waking (stage 1 in both hemispheres), bilateral intermediate SWS (stage 2 in both hemispheres), “right hemispheric high amplitude SWS” (stage 3 in the right hemisphere and stage 1 or 2 in the left hemisphere) and “left hemispheric high amplitude SWS” (stage 3 in the left hemispheres and stages 1 or 2 in the right hemisphere). As follows from the Figure, both eyes were mostly open during waking and they could be in any state during bilateral intermediate SWS (no difference between the state of two eyes, Chi-squared test; P>0.1). However, during right and left hemispheric SWS the eye contralateral to the sleeping hemisphere was mostly closed or in an intermediate state and the ipsilateral eye was mostly closed.
Role of Putative Cholinergic Neurons of the Laterodorsal Tegmental Nucleus in the Generation and Maintenance of Penile Erections during Paradoxical Sleep: Evidence from Single Unit Recordings

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Introduction: Penile erections are a characteristic phenomenon of paradoxical sleep (PS). Our previous data suggest an essential role of the forebrain in PS erectile control since such erections are eliminated by rostral brainstem transections or lateral preoptic cytotoxic lesions (1). Whereas the executive mechanisms of PS are located within the mesopontine tegmentum and rostral medulla, the brainstem control of forebrain PS erectile mechanisms remains to be elucidated. In the following study, we performed single unit recordings of the laterodorsal tegmental nucleus (LDT) while monitoring penile erections and sleep-wake states to determine if a subset of LDT neurons may play a role in PS-erectile control.

Methods: Three male rats were implanted for polygraphic recordings of cortical EEG, neck EMG, EMG of the bulbospongious (BS) muscles, and corpus spongiosum of the penis (CSP) pressure for penile erection monitoring as previously described (1). Single unit recordings were performed using glass micropipettes in awake head-restrained rats while recording sleep-wake states and penile erections. Putative cholinergic neurons can be differentiated from non-cholinergic neurons in this region by the duration of their action potentials (2). Recording sites were identified histologically by iontophoretic injection of pontamine sky blue from the recording pipette. Cholinergic LDT neurons were identified by staining for NADPH diaphorase. Statistical analyses of unit firing activity were performed using Student’s T-test.

Results: Previously described types of LDT neurons did not show any correlation with PS erectile activity. However, we identified two new types of putative cholinergic LDT neurons that increased their activity specifically in association with PS-related penile erections. The first type included tonic PS-on neurons that significantly increased their tonic activity up to 20 seconds before the onset of each PS-related erection from a baseline of 4.7 to 6.4 Hz (p<0.01), and then decreased their firing rate back to baseline during the erection. The second type included highly phasic PS-on neurons that significantly increased their firing rates from a baseline of 3.1 Hz prior to a PS-related erection to 4.3 Hz (p<0.001) during the portion of the erectile event that included the phasic BS muscle bursts and suprasystolic erectile tissue pressure peaks. Specifically, these neurons exhibited phasic bursts with an average maximum frequency of 15.1 Hz approximately 3 seconds before each BS muscle burst-CSP pressure peak complex (see Figure).

Conclusions: These data suggest that a subset of LDT neurons play an important role in PS erectile mechanisms. We hypothesize that the tonic PS-on neurons that increased their activity immediately preceding the erection may be involved in the generation of the PS erectile event, whereas the phasic PS-on/erection-on neurons may maintain the PS-related erection by generating the phasic perineal muscle bursts and erectile tissue pressure peaks. Given the major ascending projections from the LDT, we further hypothesize that these LDT neurons may in part modulate PS-related erections through their connections with essential forebrain erectile mechanisms using acetylcholine as a neurotransmitter.

References:

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Figure 1
Changes in Neurotransmitter Release in Motoneuron Pools During Pontine acetylcholine-induced Muscle Tone Suppression

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Introduction: The pontine inhibitory area (PIA) participates in the suppression of muscle tone and other aspects of REM sleep. Electrical stimulation applied to the PIA produces a global inhibition of skeletal muscle tone in the decerebrate cat and rat. Carbachol injected into the PIA produces long duration REM sleep-like periods, rapid eye movement, PGO spikes, muscle atonia and EEG desynchronization in the intact cat. We have found that acetylcholine (Ach) microinjected into the PIA also produces a short-term (5 min) muscle tone suppression in the decerebrate cat. This suppression of tone facilitates the measurement of neurotransmitter release in motoneuron pools during atonia. In this experiment, we measured monoamine and amino acid release in motoneuron pools during muscle tone suppression induced by PIA Ach microinjection in the decerebrate cat.

Methods: Experiments were performed on 2 young male and 2 female cats. Decerebration at the pre-collicular-post-mammillary level was performed under halothane anesthesia. Microdialysis probes were inserted into the hypoglossal nucleus (Type A-1-02, EICOM, Kyoto, Japan) and the spinal ventral horn (59-7005, Harvard Apparatus Inc.) 2 hours before sampling. A half microliter of Ach (1 M) was injected into the PIA, which was identified by electrical stimulation. Ten microliters of dialysate were collected from the hypoglossal nucleus and spinal cord during a 5 minute pre-injection, a 5 minute injection and a 5 minute post-injection period. The monoamine and amino acid levels in the perfusate were determined by HPLC with electrochemical detection (monoamine: 450 mV, DTA-300, EICOM; amino acid: excitation at 340 nm and emission at 440 nm, Soma-S-3350). The detection limit of our analysis system was 0.5 fmol per 20 ul injection for all transmitters.

Results: We found a significant change in neurotransmitter release in motoneuron pools during PIA Ach-induced tone suppression. Noradrenaline (NE) and serotonin release in the hypoglossal nucleus (NE: p<0.05, df=11; serotonin: p<0.05, df=11, t-test) and spinal cord (NE: p<0.05, df=9; serotonin: p<0.05, df=9, t-test) were significantly decreased during PIA Ach-induced atonia. However, dopamine release in motoneuron pools (hypoglossal nucleus: p=0.93, df=11; spinal cord: p=0.78, df=9, t-test) was unaltered during PIA Ach-induced atonia. In contrast, a significant increase in glycine (hypoglossal nucleus: p<0.01, df=13; spinal cord: p<0.05, df=9, t-test) and GABA (hypoglossal nucleus: p<0.05, df=13; spinal cord: p<0.05, df=9, t-test) release was found in motoneuron pools during PIA stimulation-induced tone suppression.

Conclusions: Our present study found that Ach injection into the PIA produced a significant decreases in NE and serotonin, but not dopamine, as well as a significant increases in glycine and GABA release in the hypoglossal nucleus and spinal cord. We suggest that PIA-induced muscle tone suppression is mediated through inhibition of noradrenergic and serotonergic activity, as well as activation of glycnergic and GABAergic neuronal activity. Thus, PIA induced muscle tone suppression appears to be linked to a combination of inhibition and disin facilitation produced by modulation of monoamine and amino acid release.

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Pontine Inhibitory Area is Required for Dorsal but not Ventral Ros- tromedial Medullary-induced Atonia

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Introduction: Activation of medial pontomedullary reticular formation elicits a global inhibition of skeletal muscle tone during REM sleep. In the rostromedial medulla, electrical stimulation in both of the dorsal nucleus gigantocellularis (NGC) and the ventral nucleus magnocellularis (NMC) induces atonia, whereas glutamate injection into the NMC but not the NGC produces atonia. Our previous study has shown that atonia induced by electrical stimulation of the NGC can be attenuated by trans-action at the pontomedullary junction and by pontine lidocaine injection. This work suggests that an ascending pathway is required for NGC inhibition of muscle tone. On the other hand, Magoun and Rhines (1946) demonstrated that spinal reflex inhibition induced by stimulation of the NMC is unaltered by pontomedullary transaction. The present study was designed to compare the differences of neurotransmitter release in motoneuron pools induced by NMC and by NGC stimulation, as well as the differences during NGC stimulation before and after pontine lido-caine injection that blocked muscle atonia.

Methods: Experiments were performed on 5 young adult cats. Cats were decerebrated at the pre-collicular-post-mammillary level under halothane anesthesia. Microdialysis probes were inserted into the hypoglossal nucleus (Type A-1-02, EICOM, Kyoto, Japan) and the spinal ventral horn (59-7005, Harvard Apparatus Inc.) 2 hours before sampling. Trains (300 ms with 100 Hz, 0.2 ms and 10-40 μA rectangular cathodal pulses) were delivered into the NGC and NMC through stainless steel microelectrodes (5710, A-M Systems, Inc.) once every 10 sec over a period of 5 min. A half microliter of 4% lidocaine was microinjected into the pontine inhibitory area, which was identified by electrical stimulation, bilaterally. Ten microliters of dialysate were collected from the hypoglossal nucleus and spinal cord during 5 minutes pre-stimulation, stimulation and post-stimulation periods before and after pontine lidocaine injection. The norepinephrine (NE) levels in the perfusate were determined by HPLC with electrochemical detection (450 mV system (DTA-300, EICOM).

Results: Electrical stimulation of the NGC and NMC suppressed activity in all muscles recorded. However, NGC but not NMC stimulation-induced atonia was attenuated by pontine lidocaine injection. We measured neurotransmitter release in motoneuron pools during NGC and NMC stimulation-induced atonia. Before pontine lidocaine injection, NE release in motoneuron pools was significantly decreased during NGC (p<0.05, df=35, t-test), but not NMC (p=0.32, df=33, t-test) stimulation. In contrast, the same stimulation in the NGC (p<0.05, df=27, t-test), but not NMC, elicited a significant increase in NE release in motoneuron pools after pontine lidocaine injection.

Conclusions: Our present study found that norepinephrine release in motoneuron pools was unaltered by NMC stimulation. However, NE release in the hypoglossal nucleus and spinal cord was significantly decreased during NGC stimulation-induced muscle tone suppression. Pontine lidocaine injection attenuated NGC, but not NMC stimulation-induced atonia. The same injection also caused an increase in NE release in motoneuron pools during NGC stimulation. We suggest that NGC, but not NMC-induced muscle tone suppression may be partially mediated through pontine-inhibition of noradrenergic neuronal activity and consequent disin facilitation of motoneurons.

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An Absence of Adenosine Effects in Laterodorsal Tegmental Neurons of A1R Knockout Mice Associated with Increased Wakefulness

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Introduction: Adenosine is known as a fatigue factor that inhibits cholinergic arousal centers through activation of adenosine A1 receptors (Rainnie et al., 1994). To investigate the role of adenosine A1 receptors (A1R) in sleep and waking we have disrupted the primary A1R coding exone in 129/olaHsd ES cells and developed A1R knockout (A1R-KO) mice in a C57BL background. Compared to their wild type siblings, the A1R-KO mice showed significantly greater amounts of time spent in wakefulness (Kaushal et al., 2000). Here, we extend these studies by investigating the effects of adenosine on in vitro neurons of the laterodorsal tegmentum (LDT) of A1R-KO mice compared to their wild type siblings.

Methods: Whole-cell patch-clamp recordings in brainstem slices were obtained from LDT neurons of both homozygous A1R-KO mice and their wild type siblings C57BL mice following EEG recordings to monitor behavioral state. Coronal slices, 400 micro-m thick, were prepared and incubated in oxygenated artificial cerebrospinal fluid (ACSF). The recordings were obtained in current and voltage-clamp mode by using an Axopatch-1D preamplifier and pClamp 7.0 software for data acquisition and analysis. Spontaneous excitatory postsynaptic currents (spEPSCs) were semi-automatically analyzed off line with Mini Analysis 4.0 software.

Results: Recordings were obtained on LDT neurons from both A1R-KO and their wild type siblings. Results from the wild type population showed that adenosine markedly reduces the spontaneous glutamatergic input to LDT neurons. Adenosine reduced the frequency of spEPSCs (figure below, left), without affecting the amplitude of these events (n = 2). However, application of adenosine (50-200 micro-M) did not induce any direct postsynaptic effects on the wild type LDT neurons. Current-clamp recordings showed no variation in the membrane potential and input resistance induced by adenosine (n = 3; Vh = -60 mV). Voltage-clamp recordings confirmed these results - no activation of inwardly rectifying potassium current was observed both during voltage step to -100 mV (Vh = -60 mV; n = 2) or during voltage ramp protocols from -100 to -35 mV (10 mV/s; n = 3). Recordings from A1R-KO mice showed no response of LDT neurons to adenosine. In these animals, following adenosine application (200 micro-M), neither reduction in the spEPSCs frequency (figure, right) and amplitude nor variations in the membrane conductance were observed (n = 2).

Conclusions: Unlike in rats where adenosine inhibits the LDT neurons by activation of postsynaptic receptors (Rainnie et al., 1994) and by inhibiting their glutamatergic inputs (Arrigoni et al.), in the mouse LDT nucleus, adenosine inhibitory action seems to be mediated only through the modulation of the excitatory input. However, like it has been reported for rats, adenosine inhibition of excitatory transmission in mouse LDT nucleus occurs by activation of adenosine A1 receptors as suggested by the results of recordings from A1R-KO mice.

References:

Adenosine A1 Receptors Mediate Inhibition of cAMP Formation in the Pontine, REM Sleep-Induction Zone in vitro

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Introduction: Microinjection of adenosine agonists into the caudal oral pontine reticular formation (PnOc) of the rat produces a long-lasting increase in REM sleep (Marks and Birabil, 1998). Both A1 and A2a adenosine receptor agonists can mediate this REM sleep response through independent mechanisms. The A2a mechanism is atropine-sensitive and appears to require participation of the cholinergic system, while the A1 mechanism is insensitive to atropine (Marks and Birabil, 2000b). Microinjection of the adenylyl cyclase inhibitor SQ22,556 in the PnOc also results in long-lasting increases in REM sleep (Marks and Birabil, 2000a). In that A1 adenosine receptors are coupled to G-proteins producing inhibition of this synthetic enzyme for cAMP, we hypothesize that A1 receptors mediate adenosine effects in the brainstem by reducing the production of cAMP. Here, we report on the dose-response relationship of an adenosine agonist selective for A1 receptors to inhibit forskolin increases in cAMP in tissue containing the pontine, REM sleep-induction zone.

Methods: Long-Evans Hooded rats were decapitated under ketamine anesthesia. Three consecutive, 300 m, coronal sections were cut
Conclusions: Adenosine A1 receptors mediate an inhibition of the production of cAMP in cells of the PnOc. Inasmuch as a direct inhibition of adenylyl cyclase in this region of brain induces a long-lasting increase in REM sleep, one mechanism of adenosine’s action in the REM sleep induction zone to increase REM sleep may be an A1 receptor-mediated inhibition of cAMP formation. Neurons expressing high constitutive levels of adenylyl cyclase are scattered throughout the pontine reticular formation and may be prime targets for the inhibitory action of adenosine in the regulation of REM sleep.

References:

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Effects of Bupropion SR on Anterior Paralimbic Function During Waking and REM Sleep in Depression: [18F]FDG PET Studies

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Introduction: REM sleep is reliably disturbed in depression. Antidepressant medications as a group tend to suppress REM sleep and increase the latency to REM sleep. In contrast, bupropion SR has been reported to enhance REM sleep. The antidepressant effects of bupropion SR are thought to be mediated by enhancement of monoaminergic neurotransmission, primarily noradrenaline and dopamine, in the absence of serotonergic enhancement. In preclinical studies, noradrenergic neurons slow, then cease firing across the transitions from wake to sleep, then from NREM to REM sleep. Dopaminergic neuronal firing, in contrast, is thought to be relatively constant across behavioral states. Therefore, effects of bupropion SR that are differentially expressed during REM sleep vs waking may result from its noradrenergic effects, whereas, effects common to waking and REM sleep may result from its dopaminergic activity. Functional neuroimaging studies of REM sleep in depression have shown a blunted activation of anterior paralimbic structures from waking to REM sleep. These structures are densely innervated by the mesolimbocortical dopaminergic pathways. We hypothesized, therefore, that the REM sleep enhancing properties of bupropion SR may result from a normalization of abnormal anterior paralimbic function in depressed patients. Within this framework, we performed waking and REM sleep-related PET studies before and after treatment with bupropion SR in depressed patients.

Methods: Twelve depressed subjects were entered into a trial that measured concurrent EEG sleep studies and [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET scans during both morning waking and the second REM period of sleep. Identical studies were to be performed following acute treatment with bupropion SR. PET studies used a 4-6 mCi dose of [18F]FDG. The time of injection was either following a 15-minute accommodation period (waking) or at the onset of the second REM period of sleep. A pixel-by-pixel ANCOVA (covarying for global metabolism) was performed to determine differences in relative metabolism in four conditions, waking and REM sleep both before and after treatment. Individual analyses looked at the main effects of treatment as well as the state (wake vs REM) by treatment (pre- vs. post) interactions. Based on prior analyses demonstrating healthy subject vs depressed subject interactions in anterior paralimbic activation from waking to REM sleep, our regional analyses were restricted to these regions.

Results: Nine subjects completed pre- and post-treatment waking PET studies. Five subjects completed pre- and post-treatment waking and REM sleep PET studies. Bupropion SR treatment was associated with reductions in clinical ratings of depression and no suppression of EEG measures of REM sleep. As predicted, bupropion SR reversed the abnormal failure to activate anterior cingulate cortex in depressed patients. This effect was restricted, however, to more superior portions of the anterior cingulate cortex and medial prefrontal cortex (supragenual areas). In secondary analyses, this effect was more related to a profound reduction in waking metabolism in the anterior cingulate cortex in the absence of a significant change in REM sleep metabolism. More inferiorly, in the anterior cingulate and medial prefrontal cortex (pregenual areas), there was both a waking and REM sleep treatment-related reduction in relative metabolism.

Conclusions: Bupropion SR reverses the abnormal pattern of relative glucose activation from waking to REM sleep in superior regions of
anterior cingulate and medial prefrontal cortex. More inferiorly, in pregenual areas, reductions were noted in both waking and REM sleep following treatment. We speculate that the effects that show a differential pattern between waking and REM sleep are related to noradrenergic effects of bupropion SR. This would be consistent with a role for the superior anterior cingulate cortex and in noradrenergic function in reducing cognitive sensitivity to confictual experiences. We speculate that the effects that are similar between waking and REM sleep are mediated by the dopaminergic effects of bupropion SR. This would be consistent for a role of the pregenual and medial prefrontal cortex and for dopaminergic function in reversing motivational deficits in depression. Future studies with additional antidepressant medications are required to help clarify the specificity of these effects to bupropion SR vs. effects related to recovery from depression.

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070.Q

Sleep Deprivation, EEG, and Functional MRI in Depression: Preliminary Data

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Introduction: Sleep deprivation (SD), an excellent model of antidepressant treatment, is easy to execute, fast-acting, and does not require medications. We are examining the effects of one night of partial SD (PSD) on quantitative perfusion functional MRI (fMRI), clinical status, and nocturnal polysomnography in medication-free depressed patients and matched controls. We hypothesize: 1) depressed responders’ baseline ventral anterior cingulate (BA 25 and ventral 24) / medial prefrontal cortical (BA 32) perfusion will exceed that of nonresponders and controls; 2) following PSD, perfusion in the ventral anterior cingulate (BA 25 and ventral 24) / medial prefrontal cortical (BA 32 and 10) areas will significantly decrease in responders only. We will also look for between-groups and within-groups differences in other regions where functional abnormalities have been reported in depression.

Methods: Subjects include unmedicated patients with current unipolar major depression and a baseline 17-item Hamilton Depression Rating Scale (HDRS17) > 16 and matched normal controls. Prospective subjects are excluded for contraindications to MRI or SD, significant comorbid psychiatric or substance use disorders; primary sleep disorders or deviant sleep cycle; or for any history of neurological or circulatory conditions which could affect sleep, EEG, or brain circulation. Subjects spend an adaptation night, a baseline night, a PSD night (in which they have to remain awake beginning at 3:00 a.m.,) and a “recovery” night in the sleep laboratory, with standard polysomnographic montage. Mood ratings, including the HDRS17, are administered at standard times throughout the study. Clinical response is defined by a ≥30% reduction in the modified HDRS17. On baseline and sleep-deprived nights, subjects receive high-resolution anatomical images and QUIPSS III spiral perfusion images. Since our pilot data feature only three subjects, we viewed maps of normalized perfusion.

Results: At baseline, the responder exhibited elevated perfusion in a large prefrontal area covering BA 24a and extending anteriorly into BA 10/32 and posteriorly into BA 25; the control’s maximal perfusion covered a markedly smaller area. The nonresponder had even lower normalized perfusion than the control, particularly ventrally. After PSD, the responder’s signal decreased over much of the area of initially high normalized perfusion; there was little change in the nonresponder’s scan.

Conclusions: While highly preliminary, our findings are consistent with previous SD studies.2 Common findings include a) baseline activity of responders greater than nonresponders in parts of BA 24a and 32; b) baseline activity of nonresponders less than controls in ventral BA 24a and 32; c) baseline activity of responders greater than controls in subgenual cortex; and d) decreased activity of responders in portions of BA 32 following SD.

References:

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071.Q

Predictive Value of the Delta Sleep Ratio for Sleep Deprivation Response in Major Depression

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Introduction: The quick but short-lasting improvement of depressive symptoms by sleep deprivation (SD) in about 60% of patients with a major depressive disorder is well established, but the mechanisms of action are still not clear. Recent studies suggest that changes in NREM sleep, especially in slow wave activity (SWA), could be associated with the therapeutic outcome of SD. The distribution of SWA across the first two NREM sleep episodes, expressed as the ratio of SWA in the first to the second NREM episode (termed delta sleep ratio), has previously been shown to be relevant for the clinical outcome of psychotherapy (Küpf er et al., 1990) and pharmacotherapy (Ehlers et al., 1996) in depressed patients.

Methods: In the current study, spectral analysis of NREM sleep EEG directly prior to SD was performed to determine whether spectral sleep EEG parameters predict SD response. 16 pair matched and drug free patients with a major depressive disorder, 8 responders and 8 nonresponders to SD (response criterion: 50% reduction on the 6-item HAMD score), were included. Average EEG spectral power was calculated for the whole night before SD and for single NREM episodes.

Results: While whole-night averages of spectral power did not differ significantly between subgroups, SD responders showed a steady decrease of SWA across successive NREM episodes (cf. figure), whereas in non-responders an increase from the first to the second episode was observed. This resulted in a significantly different distribution of SWA across NREM episodes as determined by the delta sleep ratio (quotient of SWA in the first to the second NREM episode).

Conclusions: While highly preliminary, our findings are consistent with previous SD studies. Common findings include a) baseline activity of responders greater than nonresponders in parts of BA 24a and 32; b) baseline activity of nonresponders less than controls in ventral BA 24a and 32; c) baseline activity of responders greater than controls in subgenual cortex; and d) decreased activity of responders in portions of BA 32 following SD.
Conclusions: With regard to psycho- and pharmacotherapeutic results it is hypothesized that low and high values of the delta sleep ratio characterize subgroups of depressed patients with different neurobiological alterations, which could be relevant for further scientific and therapeutic approaches.

References:

072.Q

Sex Differences in the Time Course of SWA in Depressed and Healthy Adolescents

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Introduction: Although numerous studies have suggested that slow-wave sleep deficiencies characterize major depressive disorders (MDD) (1), few analyze the time course of slow-wave activity (SWA), presumed to reflect homeostatic sleep regulation (2). A recent large-scale study of 76 depressed and 55 healthy adults indicated that the time course of SWA was abnormal in men, but not women, with MDD (3). Men with MDD showed both a lower accumulation and a slower dissipation of SWA across NREM sleep. Thus, homeostatic regulation of sleep appears to be impaired only in men with MDD. The present study contrasted the time course of SWA in depressed and healthy adolescent boys and girls to determine if SWA abnormalities were also evident in early onset MDD and were sex-dependent.

Methods: The sample included 16 outpatients (13-18 years of age) with MDD who were symptomatic but unmedicated and 16 healthy controls (13-18 years of age) with no personal or family history of psychopathy. Eight males and eight females were included in each group. Participants spent two consecutive nights in the lab. Power spectral analysis was used to quantify SWA (0.5 - 4Hz) in 30 sec epochs. Data were then averaged in each successive NREM period (Stage 2, 3 and 4). Repeated-measures ANOVA compared group and sex differences across NREM periods. Exponential regression analyses were used to evaluate the SWA time course separately for each group.

Results: The ANOVA revealed a significant group by sex by NREM period interaction. Means indicated that SWA power in the first NREM period was lower in girls than in boys in each group, but was lowest girls with MDD. Exponential regressions indicated that asymptotic SWA, the initial accumulation, was marginally lower in girls with MDD compared to healthy girls (p<.07), but the rate of decay (the dissipation of SWA) was virtually identical in the two groups of girls. SWA accumulation did not differ between MDD and healthy boys but the rate of decay was significantly slower in the boys with MDD (p<.05).

Conclusions: The dissipation of SWA appears to be abnormal in adolescent boys with MDD, but not in girls. This outcome suggests that the SWA impairment observed in men with MDD occurs early in development and likely reflects a sex- and disease-dependent component in SWA regulation. These data provide further support that the pathophysiology of MDD differs in men and women and that these sex differences are also evident in early onset MDD.

References:

Research support by NIMH MH6953 and the Bob Smith Center for Pediatric Research.

073.Q

Sleep Microarchitecture in Females at Risk for Depression

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Introduction: Major depressive disorders (MDD) are more prevalent in women, run in families and are associated with a variety of sleep abnormalities, particularly those derived from sleep microarchitecture (1,2). Low temporal coherence, reflecting a breakdown in the synchronization of sleep EEG rhythms, has been shown to characterize children and adults with MDD and to persist into clinical remission. Thus, low coherence may be a vulnerability marker for MDD (2). As such, it should also be evident in those at high-risk for MDD.

Methods: Sleep studies were conducted on 41 high-risk adolescent (12-15) girls, who had a maternal history of depression. An age-matched control group of girls (N=40) with no maternal depression were also
Results: Temporal coherence was significantly lower in the high-risk group (p<.05). Regression analyses correctly classified 71% of the high-risk group and 95% of controls. In addition, 22/41 (54%) of the high-risk group had coherence values that were 2 sds below controls. Upon follow-up, 11/41 (27%) high-risk girls showed depressive symptoms, 6 who met DSM-IV criteria for MDD. Most importantly, all 11 girls had extremely low coherence values. Only 1/40 (2.5%) control girls showed evidence of depression at follow-up and was identified as a false positive by the regression analysis.

Conclusions: Low temporal coherence of sleep EEG rhythms is evident in girls at high-risk for depression, even before symptoms are revealed. Coupled with previous findings in children and adults with MDD, low coherence appears to be a vulnerability marker of the illness.

References:

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Daytime Sleep in Depression
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Introduction: Sleep abnormalities such as reduced slow-wave sleep and short REM latency are often reported in studies of depression, though these abnormalities are not necessarily consistent or entirely specific to depression (1). Notably, daytime naps can reduce slow wave sleep and REM latency in the nocturnal sleep which follows. Although some 24-hour sleep recordings have been done in hospitals (2), it seems valuable to examine how napping may be related to depression in the community.

Methods: To examine the issue of daytime napping in major depression, data for 440 postmenopausal women were analyzed from an ancillary study of the Women’s Health Initiative. Each woman wore an Actilume recorder of wrist activity and illumination. Except for bathing, Actilumes were usually worn for an entire week at home and in the community. Sleep-wake was inferred from wrist activity, using an algorithm which has been validated for 24-hour studies in this age group (3). Nocturnal in-bed sleep periods were determined from daily sleep logs, supplemented by the illumination recordings which usually allow precise identification of lights-off and lights-on. Sleep both in-bed and out-of-bed was averaged for available days for each subject. Further, from a 24-hour cosine fit to sleep/wake data, the circadian quotient of sleep (24-hr. amplitude over mesor) was computed as an index of the circadian organization of sleep. Shortly after the recordings, each woman was interviewed by the author to determine psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID- I / NP).

Results: Of the 440 women, 12 were found to have current major depressive disorders (MDD) during the recordings, and 31 were found to have current mood disorders of any kind (including MDD, dysthymia, minor depressive disorders, and mood disorders due to other medical conditions.) Women with MDD and women without MDD both averaged 360 min. of sleep during nocturnal sleep periods. Out of bed, women with MDD averaged 62 min. of sleep versus 31 min. for those without MDD (p<.05 by one-tailed Mann-Whitney test). Similarly, those with any current mood disorder averaged 46 min. of sleep out-of-bed, whereas those without any mood disorder averaged 31 min. (NS). For those with MDD and also for the group with any current mood disorder, the circadian quotients were significantly lower than for the unaffected groups (p<.05 by one-tailed Mann-Whitney tests).

Conclusions: These observations indicate an impairment of the circadian organization of sleep/wake associated with depression, characterized by increased daytime sleep. The major limitations of the study are the impression of monitoring sleep/wake from wrist activity and the relatively small number of participants with current MDD. These results support the hypothesis that short REM latency and reduced slow wave sleep in depression result from daytime napping, rather than from pathophysiological processes specifically tied to MDD. Future studies of sleep in depression should always incorporate 24-hour monitoring to control for daytime napping, which might not be appreciated without objective recording.

References:

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The Effects of Vagus Nerve Stimulation (VNS) on Sleep in Depression
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Introduction: Numerous studies have demonstrated that major depressive disorders (MDD) are characterized by a variety of sleep and quantitative EEG abnormalities (1). Moreover, it appears that some of the sleep disturbances are not normalized by antidepressant therapies. A recent study has demonstrated the efficacy of vagal nerve stimulation (VNS) in treatment-resistant depression (2). Since the vagus nerve has extensive projections via the nucleus tractus solitarius to many brain regions, including the reticular formation, parabrachial nucleus and locus coeruleus, it is not unreasonable to expect VNS to impact on sleep (3). The purpose of this preliminary study was to investigate the effects of VNS on sleep and biological rhythms in EEG in four treatment-resist-
ant depressed patients.

Methods: Sleep studies were performed at baseline and after 10 weeks of VNS delivered by a NeuroCybernetic Prosthesis (NCP™). Changes in sleep macroarchitecture, based on standard stage scoring (i.e. total sleep time, % sleep stages, REM characteristics, etc.) and microarchitecture, based on quantitative EEG analyses (i.e. temporal coherence, periodicity and amplitude of EEG rhythms) were evaluated (1).

Results: Pre-treatment, baseline sleep studies revealed severe sleep abnormalities, as shown in Table 1 below. Note that baseline sleep was more disturbed than that usually reported in non-treatment-resistant patients. Sleep microarchitecture was also particularly abnormal at baseline, with severely dampened ultradian EEG rhythms. After VNS self-reported sleep quality improved after in all patients. Sleep microarchitectural changes included less non-restorative Stage 1 sleep and intermittent wakefulness, accompanied by increased Stage 2 sleep. The most dramatic effect, however, was on the strength or amplitude of EEG rhythms. Large increases were found for the amplitude of beta, theta and delta rhythms, to near normal levels. See Table 1.

Table 1

<table>
<thead>
<tr>
<th>Sleep EEG Measure</th>
<th>Pre-VNS (Baseline)</th>
<th>Post-VNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sleep Period</td>
<td>422.6 (78.9)</td>
<td>455.9 (83.6)</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>15.2 (4.4)</td>
<td>31.4 (17.2)</td>
</tr>
<tr>
<td>REM Latency</td>
<td>142.4 (22.7)</td>
<td>157.3 (41.7)</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>33.4 (16.7)</td>
<td>22.3 (12.3)</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>46.1 (10.4)</td>
<td>58.2 (9.7)</td>
</tr>
<tr>
<td>% SW</td>
<td>0.6 (0.9)</td>
<td>0.5 (0.7)</td>
</tr>
<tr>
<td>% REM</td>
<td>12.8 (0.9)</td>
<td>14.3 (2.3)</td>
</tr>
<tr>
<td>% Awake</td>
<td>7.0 (8.9)</td>
<td>4.7 (4.4)</td>
</tr>
<tr>
<td>Av Rhythm Strength (Beta &amp; Delta)</td>
<td>1442.3 (198.1)</td>
<td>2441.7 (328.1)</td>
</tr>
</tbody>
</table>

Conclusions: Unlike most antidepressant medications, VNS treatment improved both subjective and objective sleep characteristics and reversed the dampening of EEG rhythms. These effects may be of clinical benefit, since persistent sleep disturbance increases the risk of relapse and recurrence. This study also suggests that sleep abnormalities in treatment-resistant depression may differ from those who are not resistant to treatment. A follow-up study is underway to confirm our findings.

References:

076.Q

Sleep and Remission from Depression: What Changes and What Does Not

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Introduction: Aproximately half of those suffering from major depression do not seek help yet 60-70% experience remission within a year. Little is known about the nature of the changes and the mechanisms responsible. This study tests 3 hypotheses: 1. Remission is more likely when mood improves following sleep, 2. Overnight mood regulation is less likely in the presence of reduced REM latency, and 3. Sleep disturbance remains when other symptoms improve.

Methods: Volunteers undergoing divorce recruited for an 8 month sleep study, meeting criteria for major depression on SCID-NP, Hamilton Rating Scale (HRS)=18, and Beck Depression Inventory (BDI)=14 slept for 2 consecutive nights on 4 occasions (Months 1,2,4,8). Night1 was a sleep through (ST) Night 2 each REM was interrupted for dream recording (RI). Subjects completed Profile of Mood States (POMS) test before and after each lab night. At follow-up (FU),SCID,HRS,BDI were repeated. Of 12 who have completed the study, 9 were in remission on all criteria and 3 unchanged. Depressed were compared to a group of 60 normal volunteers who slept for 2 nights only (ST and RI) with POMS before and after each.

Results: 1.Depressed HRS at screening Mean= 23.25 (3.57) FU Mean= 9.25 (9.68) t=4.69,df 11,p.001. BDI Mean= 26.00 (8.78) FU= 12.16 (3.01) t=5.44,df 11, p.000. Overnight change in POMS Total Negative Mood score (TNM) correlated significantly with change in HRS r=.623 and BDI =.608. Multivariate test of overnight change in TNM by group (Dep vs Norm) and condition (ST vs RI)yielded significant within subjects, group*condition effect df 1, mean square 2091.01. F=6.374,p=.014. Error df 70, mean square 328.07.(Dep TNM change Night 2= -13.08 Normal TNM change Night 2= 1.83).2.Over the 8 months Depressed had 93 nights of PSG, TNM was lower on 56 mornings than previous night. REM latency was reduced (<65 min) for 11 of 12 subjects on 1 or more of their 8 nights. Chi square for Mood Improved vs Mood Same or Worse following nights when REML was Normal was greater than for REML reduced (<65 min) at X2=4.93,df 1, p.05.3.4. Of 12 subjects still endorsing at FU the BDI items most common at screening: 1. Disturbed Sleep N= 12, FU N= 8, Appetite N= 12 FU N= 8, Irritability N= 11 FU N= 5, Sense of failure N=11 FU N= 4, Concentration N= 11 FU N= 3, Sadness N=11 FU N= 1.

Conclusions: Remission from untreated depression is related to overnight reduction in negative mood. This is less likely to occur on nights when the depression marker of reduced REML is present. Self-reported vegetative signs of depression, including sleep, are less likely to improve when subjects meet criteria for remission suggesting continued vulnerability to this disorder(1).

References:

Research supported by NIMH 50471.

077.A

Microdialysis Perfusion of Adenosine A1 Receptor Antisense Oligonucleotide in the Basal Forebrain Increases Wakefulness and Decreases NonREM Sleep Both in Spontaneous Bouts and Following Sleep Deprivation.

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Introduction: The cholinergic magnocellular regions of the basal forebrain (BF) are known to regulate behavioral states. Majority of neurons in the BF exhibit their highest discharge activity during wakefulness and reduce their discharge activity during nonREM sleep, and are thought to
Methods: Antisense: A 21 base pair phosphorothioate ODN antisense (5’-gatgtaggg gcagtagtg g-3’) was custom synthesized (Gene Link Inc, Hawthorne, NY). To control nonspecific effects, the same sequence was randomized and used as A1 receptor non-sense ODN. Surgery and Implantation: Adult male Sprague-Dawley rats were anesthetized for implantation of standard sleep recording electrodes and two bilateral microdialysis guide cannulas targeted for the BF (Paxinos and Watson, 1997). After post-operative recovery, microdialysis probes (CMA-11; 2 mm length) were lowered through both the guide cannulas. After 12 hrs of probe-insertion recovery, the experiment was begun. Throughout the experimental procedures, the rats were were maintained in 12:12 light:dark cycle with food and water ad lib. The behavior of the animals was continuously digitized and recorded (Stellate Systems) till the experiment was complete. Spontaneous sleep recordings: The experimental protocol consisted of 5 days of continuous behavioral state recording with 3 days of treatment: Control Day: Artificial CSF (ACSF) was continuously and bilaterally perfused for 8 hours (1000 h to 1800 h). Antisense (or non-sense) Day 1 and 2: The protocol was the same as the ACSF day except that 20 µM of antisense (non-sense) to the A1 receptor was perfused continuously for 8hours (1000 h to 1800 h) instead of ACSF. Post Antisense (or Nonsense) Day 1 and 2. Behavioral state recordings were carried out for the next two days without any perfusion/treatment. Sleep Deprivation: The sleep deprivation experiment lasted for 3 days. The protocol for each day of the experiment was: Perfusion Day 1 and 2: ACSF or 20 µM ODN (antisense or non-sense) was continuously perfused for 8 hours (1000 h to 1800 h) each day. Sleep Deprivation day: There was no treatment/perfusion on the sleep deprivation day, instead the animals (ACSF or ODN (antisense or non-sense) treated) were sleep deprived for 6 hrs (13.00 h to 19.00h) by gentle handling. Following sleep deprivation the animals were allowed to have ad lib recovery sleep, from 19.00 - 07.00 hr. Behavior of the animals was continuously recorded both during sleep deprivation and during recovery sleep. Data analysis and histology. Once the experiment was completed the animals were sacrificed, and the brains processed for histology. The electrographic data were classified into three different behavioral states: Wakefulness, non-REM sleep and REM sleep and scored separately for the light period and the dark period.

Results: Our preliminary data suggest that antisense to the AD A1 receptor increased wakefulness and decreased nonREM sleep both during the light (inactive) and dark (active) periods. Further antisense treatment (N=3 rats; or ACSF for N=2 control rats) markedly diminished recovery sleep for the first four hours, especially after the first hour. During the first four hours of recovery sleep the mean wakefulness increased from 41% in control (ACSF) animals to 75% in AD antisense treated animals. NonREM sleep on the other hand decreased from 45% in control to 18% in antisense treated animal during first four hours of recovery sleep (Fig 1). This is consistent with the time course of return of AD concentrations to baseline in other experiments in our lab.

Conclusions: Preliminary data of this study further strengthen the role of AD in the regulation of behavioral state. Our data further indicate that AD in the BF mediates its sleep inducing effects via the A1 receptor. We believe these data further suggest antisense technology is both scientifically valuable and feasible.


This work was supported by the Department of Veterans Affairs (RWM) and by the National Institutes of Health Grant R37MH39683 (RWM) and KO1MH01798 (MMT).

078.A

Intracellular Calcium is Mobilized by Adenosine Acting via the A1 Receptor in the Basal Forebrain Cholinergic Neurons, but not in Non-cholinergic Neurons

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Introduction: The levels of extracellular adenosine are increased during prolonged wakefulness both in rat and cat basal forebrain (Basheer et al.,1999; Porkka-Heiskanen et al.,1997). Previously, we have shown that increase in extracellular adenosine in basal forebrain can induce DNA binding activity of transcription factors like c-Fos and NF-kB via A1 adenosine receptor (Basheer et al., 1999; 2000). However, the signal transduction pathway involved in transducing the adenosine effects via A1 adenosine receptor to intracellular proteins like transcription factors
is not yet clear. Both inhibition of adenylate cyclase via Gi and activation of phospholipase C (PLC) can occur by A1 receptor occupancy. PLC activation can in turn mobilize intracellular Ca++ and activate protein kinase C. In order to determine if adenosine can mobilize internal calcium via A1 adenosine receptor in basal forebrain neurons we performed intracellular calcium imaging using two photon microscope in response to adenosine in real time.

**Methods:** Male Long Evans rats (weight 300-350g) were used. Acute brain slices from anesthetized rats were prepared by sectioning (200 micron thick) the brain in carboxygenated ACSF. For calcium assays, acute sections were loaded with 10 µM calcium orange for one hour at room temperature. A BioRad MRC 1024ES multi-photon Imaging system (BioRad, Hercules, CA)was used for quantitative fluorescence imaging of samples in epifluorescence mode. Labeled neurons in the brain sections were identified by XYZ scanning generally at depths of 30-70 µm. The 512 x 512 pixel images were collected in direct detection configuration at a pixel resolution of 0.484 µm with a Kalman 3 collection filter. Images were reconstructed and processed using the BioRad LaserSharp and Metamorph (Universal Imaging, West Chester, PA) software. The data are presented as the average of at least three blinded experiments performed on different days; both intra and inter-experimental variability were less than 2%.

**Results:** Treatment of slices with adenosine resulted in significant increases in intracellular fluorescence when compared to untreated controls. A similar response was also observed with the A1 selective agonist CHA. The calcium response was blocked by A1 antagonist, CPT (Kruskall-Wallis One-way analysis on ranks H(4)=80.6, p<0.0001, Dunn’s post-hoc test p<0.05 between the control vs adenosine and CHA, Fig 1) The increase in internal calcium with adenosine or CHA was independent of the presence of calcium in the medium indicating the intracellular calcium response was due to mobilization of internal stores. Moreover, after depleting the internal sources of calcium using thapsigargin, there was no response to adenosine (one way ANOVA on ranks, H(4)=97.8, p<0.0001, Dunn’s post-hoc analysis p<0.05 between control vs adenosine and CHA , and Thapsigargin treated vs adenosine, fig 2), even in calcium containing medium. Remarkably, ChAT immunohistochemistry showed that all the calcium responding neurons in BF were ChAT positive, although not all ChAT-positive neurons responded.

**Figure 1**

![Figure 1](image1.png)

**Conclusions:** Our data indicate that adenosine can mobilize intracellular calcium via A1 adenosine receptors in BF. Immunolabeling of calcium responding neurons show that such a selective functional response to adenosine occurs in the cholinergic neurons in basal forebrain. We posit that mobilization of internal calcium in cholinergic neurons may underlie the regulation of intracellular proteins like activation of transcription factors and subsequent expression of other genes.

**References:**


This work was supported by the Dept of Veterans Affairs and NIMH grant MH39683 to RWM.

079.A

**Wakefulness-inducing Effects of Microdialysis Perfusion of Histamine in the Basal Forebrain of Freely Moving Rats**

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**Introduction:** Several lines of evidence implicate both the cholinergic and non-cholinergic wakefulness-related neurons of the magnocellular region of the basal forebrain (BF), as well as the histaminergic neurons of the tuberomammillary nucleus (TMN) in the process of cortical activation that occurs during wakefulness. It is known that the cholinergic zone of the BF receives histaminergic projections from the TMN (2). Extracellular single unit recording has shown that neurons in the cholinergic BF and the histaminergic neurons of the TMN exhibit their highest firing rates during wakefulness in free moving cats and rats. Microdialysis studies done in our lab indicate that levels of extracellular histamine follow a similar pattern across behavioral states in the ventral forebrain region (3). In vitro studies have shown that histamine excites the cholinergic neurons of the BF (1). It was thus hypothesized that the histaminergic neurons excite the cholinergic neurons of the BF to induce wake-
fulness and cortical arousal. To test this, we carried out local perfusion of histamine in the cholinergic BF.

Methods: Nine adult male Sprague-Dawley rats were anesthetized for implantation of guide cannulas for microdialysis probe along with standard sleep recording electrodes. These guide cannulas were targeted towards the cholinergic horizontal diagonal band (HDB) at coordinates: AP - 0.40; ML 1.8 and DV 7.5 (according to Paxinos and Watson rat brain atlas). They were then divided into 2 groups; one group (n=4) received low concentration (1, 3 and 10 µM) and the other (n=5) received high concentration (100, 500 and 1000 µM) of histamine perfusion. To determine if the observed behavioral effects of histamine perfusion in the basal forebrain were site-specific, microdialysis guides were also targeted at a control site, the centromedian thalamic nucleus (N=3; 500 µM histamine perfusion), at the following coordinates: AP -3.3; ML 0.0 and DV5.5. After post-operative recovery and habituation to the recording chamber, the microdialysis probe (CMA-11; 1 mm length, 0.24 mm diameter) was lowered through one of the guide cannulas. After 12 h of recovery from probe insertion, the experiments were begun. ACSF was continuously perfused while behavioral states were simultaneously recorded for 6 h (1100 h to 1700 h). The following day same protocol was followed except that histamine was perfused for 2 h (1300 h to 1500 h) at the doses described above. The 3 doses were counterbalanced with 1 week between administration. Behavioral states were classified into 3 different states: wakefulness (W), non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). Once the experiment was completed the animals were sacrificed and processed for histological verification of the perfusion sites.

Results: The 3 highest histamine doses produced a significant dose dependent increase in wakefulness, 100 µM (t(4)=5.36, p<0.005); 500 µM (t(4)=6.24, p<0.003) and 1000 µM (t(4)=10.92, p<0.0004) and a significant reduction in NREM 100 µM (t(4)=5.79, p<0.004); 500 µM (t(4)=6.52, p<0.002) and 1000 µM (t(4)=8.87, p<0.0009) during the histamine perfusion period as compared with ACSF. Though REM showed marked reduction, esp. at 500 and 1000 µM dose, it was significant only at 500 µM (t(4)=3.37, p<0.02). The 3 lower concentration groups (1, 30, 100 µM) and the thalamic control site group did not show any significant changes in behavioral states in response to histamine perfusion.

Conclusions: The data suggest that histamine acting on the BF cholinergic zone may play an important role in regulating wakefulness and cortical arousal. The site of action of histamine in inducing arousal appears site specific. As prior in vitro work indicates that histamine excites BF cholinergic neurons, the present behavioral effects of histamine perfusion in the BF could be mediated by the histamine-responsive cholinergic neurons in the BF. However, the cellular effect of histamine on the cortically projecting non-cholinergic BF neurons is unknown, and this population of neurons could also contribute to the behavioral effects observed herein.

References:

This work was supported by the Department of Veterans Affairs (RES and RWM) and by the National Institutes of Health Grant R37MH39683 (RWM) and KO1MH01798 (MMT).

080.A

Lesions of Histaminergic Neurons do not Produce Hypersomnolence
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Introduction: The tuberomammillary nucleus (TMN) resides in the posterior hypothalamus, and is thought to play a crucial role in arousal because TMN neurons are the sole source of the wake-promoting neurotransmitter histamine. Furthermore, antagonists at the histamine H1 receptor are sedating in humans, while large electrolytic lesions of the posterior hypothalamus produce hypersomnolence (1). Loss of TMN neurons has been hypothesized to underlie the hypersomnolence following electrolytic posterior hypothalamic lesions. However, this hypothesis has not been adequately tested because electrolytic lesions also damage fibers of passage, while excitotoxins such as ibotenic acid may on average kill only a third of TMN neurons in the rat (2), which may not be sufficient to produce changes in sleep. To examine whether complete TMN lesions produce hypersomnolence, we lesioned the TMN using a novel toxin: orexin conjugated to the ribosomal toxin saporin (ORX-SAP). This toxin targets orexin receptor bearing cells, such as the TMN which abundantly expressed orexin type 2 receptors.

Methods: ORX-SAP, ibotenic acid, or saline was injected bilaterally into the TMN using stereotaxic coordinates: AP -4.2, DV -8.9, RL ±0.7. Rats were instrumented for EEG/EMG, and sleep-wake behavior was recorded for 1-2 weeks after surgery. Rats were then formalin perfused, and brains were cut on a freezing microtome. Sections were immunostained for adenosine-deaminase (a marker of histaminergic neurons) and orexin, and Nissl counterstained. EEG/EMG recordings were scored using ICEUS software (M. Opp, Univ. Michigan).

Results: In 5 rats that received ORX-SAP injections, 50-95% of TMN neurons were ablated. Nissl counterstains showed that neurons surrounding the TMN were lesioned to a similar extent. In a second group of 6 rats that received IBA, only 20-60% of TMN neurons were ablated, even though nearly all posterior hypothalamic neurons surrounding the TMN were lesioned. Preliminary analysis shows that neither IBA nor ORX-SAP lesioned animals show changes in total NREM or REM sleep time at 2-4 days, 7 days, or 10 days after lesions.

Conclusions: The novel toxin ORX-SAP kills TMN neurons much more effectively than ibotenic acid, which preferentially spares many TMN neurons. Although Nissl stains showed that ORX-SAP also kills non-histaminergic neurons surrounding the TMN, we could control for the effects of this damage via comparisons with the ibotenic acid lesions. Preliminary analysis of EEG/EMG recordings indicates that nearly complete ORX-SAP lesions of the TMN do not produce hypersomnolence, nor do ibotenic acid lesions ablating areas surrounding the TMN. Hence, the hypersomnolence reported after previous electrolytic lesions of the posterior hypothalamus may have been due to loss of other cell types, perhaps the orexin neurons, not loss of the TMN.

References:

DVA Research, NS30140, AG15853, HL60922.
The GABA<sub>A</sub> Agonist Gaboxadol Persistently Increases Sleep Maintenance and Intensity During Subchronic Administration to Rats

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Introduction: Many hypnotics, such as benzodiazepines, are agonistic modulators of γ-aminobutyric acid<sub>A</sub> (GABA<sub>A</sub>) receptors. Such compounds increase the ability to fall and stay asleep, but inhibit rapid eye movement (REM) sleep and deep non-REM sleep. Tolerance to their hypnotic action may develop rapidly and withdrawal effects are not uncommon. Previous findings in rats<sup>1</sup> and humans<sup>2</sup> demonstrate that the GABA<sub>A</sub> receptor agonist gaboxadol (4,5,6,7-tetrahydroisoxazolo[4,5-c]pyridin-3-ol) (also abbreviated as THIP) promotes deep non-REM sleep and increases non-REM sleep continuity. The aim of this study was to assess its potential for the development of tolerance and occurrence of rebound phenomena during subchronic treatment in rats.

Methods: Under deep halothane anaesthesia 17 adult male Wistar rats were implanted with 4 epidural electrodes for recording of the electroencephalogram (EEG) and further 2 electrodes were inserted into the neck muscle for electromyogram (EMG) measurement. All animals received intraperitoneal injections at the onset of darkness on nine consecutive days. Nine of the animals were injected with vehicle (0.9 % saline) on the first and last two days of the experiment and with gaboxadol (3 mg/kg) during the 5-day treatment period (gaboxadol group), whereas the other eight animals received vehicle injections throughout the experiment (placebo group). Recordings of the EEG and EMG were made during the first 6 h after each injection.

Results: During the baseline recordings, animals of the placebo and the gaboxadol group exhibited similar sleep patterns. After the first gaboxadol injection, rats displayed more non-REM sleep, longer non-REM episodes, and higher levels of slow wave activity in the EEG within non-REM sleep than the animals of the placebo group. These effects were sustained during all treatment days. REM sleep was not affected. After drug withdrawal, the sleep patterns of the gaboxadol and the placebo group were practically identical again.

Conclusions: The results of this study suggest that gaboxadol does not produce tolerance toward its sleep effects during subchronic treatment and abrupt drug withdrawal does not seem to be associated with sleep disturbances. These findings confirm and extend the existing information suggesting that gaboxadol may be promising for treatment of insomnia.

References:

The Effects of a Glutamate Receptor Antagonist on Sleep Depend on the Time of Administration

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Introduction: Several lines of evidence indicate that excitatory amino acids (EAA) have an important role in the regulation of sleep (1). Accordingly, the most abundant EAA in the central nervous system (CNS), glutamate, has been demonstrated to have an effect on the regulation of sleep and the modulation of the circadian rhythm. Glutamate, via the N-methyl-D-aspartate (NMDA) receptor, is also the strongest stimulus for the production of nitric oxide (NO) by neurons (2). Previously, the inhibition of NO production has been shown to have a complex phase-dependent effect on sleep (3). The aim of the present study was to determine if the effects of a non-competitive NMDA receptor agonist, MK-801, on sleep are also phase-dependent.

Methods: Male Sprague-Dawley rats (370-520 g) were implanted with EEG and EMG electrodes. The rats were kept on a 12:12 h light-dark cycle, light onset at 1000 h. On the control days, all rats received saline intraperitoneally (ip, 2 ml/kg) at either dark onset or light onset and sleep was recorded for 23 h. Dark onset: On the experimental day, the rats (n = 8) received 0.25 mg/kg MK-801 ip and sleep was recorded starting at 2200 h. Light onset: On the experimental day, the rats (n = 7) received 0.25 mg/kg MK-801 ip and sleep was recorded starting at 1000 h. Food and water were provided ad libitum.

Results: Systemic injection of 0.25 mg/kg MK-801 at light onset completely suppressed non-rapid eye movement sleep (NREMS) for the first 2 h. This effect was followed by a positive rebound in NREMS, which remained significantly elevated during the transition from the light period (LP) to the dark period (DP). Rapid eye movement sleep (REMS) was initially suppressed for 6 h following injection, with a large positive rebound occurring from h 9-16. Slow-wave activity (SWA) showed a 150 % increase from baseline after NREMS reappeared, i.e., during the second 2 h of the LP, and remained elevated throughout the remaining LP and the first 2 h of the DP as it returned to baseline levels. Systemic injection of 0.25 mg/kg MK-801 at dark onset caused tendencies towards decreased sleep for the first 2 h period. After sleep returned to baseline, there was a significant increase in NREMS and REMS during h 5-6. REMS was slightly elevated during the last 2 h of the DP and during the first 4 h of the LP. SWA showed a significant increase during h 3-4 and remained slightly elevated for the next 6 h. Previous trials using 0.01 mg/kg or 0.05 mg/kg MK-801 were performed with no appreciable effects.

Figure 1

Figure Legend: The effects of 0.25 mg/kg MK-801 on the sleep of rats after dark onset and light onset injections. The data points represent 2-h averages in sleep and slow-wave activity (SWA). Open symbols: Average of 2 baseline days. Solid symbols: MK-801 day. Solid bars: Dark periods. Arrows: Time of injections. Asterisks: p < 0.05.
Conclusions: The effects of MK-801 on sleep depend on the time of administration. The effects of MK-801 on NREMS and REMS after dark onset and light onset administration closely resemble the phase-dependent effects of NO synthase inhibitors on sleep. These findings are in line with our hypothesis that NO may play a role in the effects of EAAs on vigilance.

References:

This work was supported by NIH (NS-30514).

083.A

Functional Mapping of the Human NonREM Sleep EEG

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Introduction: Sleep has long been assumed to be a global process. Increasing evidence indicates, however, that sleep may be also local and use dependent. EEG power spectra exhibit site-specific and state-related differences in specific frequency bands. The spatial distribution of EEG spectral power over the scalp as a function of frequency had been investigated only on the basis of few derivations along the antero-posterior axis. The aim of this study was to provide topographic data for the human nonREM sleep EEG under baseline conditions and for recovery sleep following sleep deprivation.

Methods: Eight male volunteers (21-25 years) were recorded during a baseline night and recovery sleep following 40 h of wakefulness. Power spectra were computed from 27 derivations (extended 10-20 system; average reference). Mean power maps of the nonREM sleep EEG were calculated for 1-Hz bands between 1.0 and 24.75 Hz. The effect of sleep deprivation on EEG topography was assessed by computing the recovery/baseline ratio of power spectra and analyzed by statistical parametric mapping (univariate comparisons at each electrode). Cluster analysis was applied to investigate topographic segregation into distinct frequency bands.

Results: Power maps showed a frontal hyperactivity in the 1.0-4.75 Hz and 10.0-12.75 Hz range, maximal power at posterior derivations between 5.0 and 8.75 Hz, and a maximum over the vertex in the 13.0-15.75 Hz band. Absolute power maps of baseline are illustrated for the delta and spindle frequency range in the left panels of Figure 1 (maximal and minimal power is indicated). Cluster analysis grouped maps with similar spatial patterns, thereby defining frequency bands with a good correspondence to the classical delta, theta, alpha, sigma and beta bands. Sleep deprivation increased power between 1.0 and 10.75 Hz and decreased power above 11.75 Hz. However, the topographic distribution was little affected. The largest increase in the 1.0-10.75 Hz range occurred predominantly at frontal derivations, the maximal decrease in the 13.0-15.75 Hz band at the vertex derivations. Maps of the power ratio recovery/baseline are depicted for the delta and spindle frequency range in the right panels of Figure 1 (maximal and minimal ratios are indicated).

Conclusions: Five frequency bands exhibiting a distinct topographical distribution could be discriminated in the nonREM sleep EEG. The different topographies may reflect separate generators. The increased sleep propensity after prolonged waking is reflected by an increase of low-frequency power in frontal derivations. This observation is consistent with a high need for recovery of frontal, heteromodal association areas of the cortex.

The study was supported by the Swiss National Science Foundation grant 3100-053005.97 and the Human Frontiers Science Program grants RG-81/96 and RG-0131/2000.

084.T

Influence of Anticipatory Anxiety on Sleep in Behaviorally “Anxious” and “Non-Anxious” Mice

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Introduction: Anxiety may have a role in certain types of sleep disturbances. Fear conditioning is thought to produce anticipatory anxiety (Davis 1992), and we have found that training in the fear conditioning paradigm suppresses REM in normal Sprague-Dawley rats (Sanford et al., 2000). Thus, fear conditioning could provide an animal model for studying how anxiety affects sleep. Inbred mouse strains exhibit different levels of reactivity to aversive environmental stimuli, which is thought to reflect anxiety. Differential responsiveness to fear conditioning among strains could provide clues to the neural and genetic bases of anxiety and its influence on sleep. We identified mouse strains that differ on behavioral measures of anxiety (e.g., zero maze, open field), and examined the effects of fear conditioning on sleep across strains. The present results illustrate the efficacy of this approach in two inbred strains.

Methods: Mice (BALB/cJ and C57BL/6J; n=8 per strain) were implanted with transmitters (DataSciences ETA10F20) for recording sleep via telemetry. After baseline sleep recording sessions, the mice were trained to associate a cue (tone) with footshock (15 cue - shock pairings on 4 consecutive days). Sleep and activity were recorded after fear conditioning (cue and shock presented between 0700 and 0900 h). Two days after the last fear conditioning session was completed, the mice were presented with the cue alone in their home cage (cue presented at 1200 h), and sleep and activity were recorded. Behavioral state was visually scored (10 sec epochs).

Results: Fear conditioning selectively suppressed REM in mice compared to time matched baseline recordings. The suppression of REM was
significantly greater in the reactive BALB/cJ strain compared to the less reactive C57BL/6J strain. Post-training exposure to the cue alone suppressed REM in much the same manner as exposure to the footshock. Again, the more reactive strain exhibited a greater suppression of REM (Table 1). The effect of the conditioned cue was relatively selective for REM. NREM was minimally affected.

Table 1

<table>
<thead>
<tr>
<th>Sleep parameters over 6 h during baseline and after cue. Recording periods are matched for circadian time. Mean (SEM)</th>
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<tr>
<td>C57BL/6J</td>
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<tr>
<td>Total NREM (min)</td>
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<td>Total REM (min)</td>
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<td>REM Episodes</td>
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<td>REM Duration (min)</td>
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*p<.05; **p<.01; ***p<.001

Conclusions: Mouse strains that differ on behavioral indices of anxiety exhibit differences in sleep. Reactive, “anxious” mice show greater suppression of REM during conditioned fear training. “Anxious” mice also show greater suppression of REM when presented cues associated with shock. Therefore, emotionally-laden stimuli associated with an aversive event can suppress REM in much the same way as exposure to the event itself. Applying the conditioned fear model of anticipatory anxiety to inbred mouse strains may provide a way to examine the genetic and neural mechanisms underlying the influence of anxiety on sleep.

References:

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085.J

Apolipoprotein E ε4 Predisposes to Sleep Disordered Breathing in the Normal Adult Population

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Introduction: Apolipoprotein E (ApoE) is a protein involved in lipid metabolism. It has three allelic variants (ε2, ε3 and ε4). The ApoE ε4 variant is a well known risk factor for Alzheimer’s (AD) and cardiovascular disease (CD). AD patients are also reported to have increased sleep disordered breathing (SDB), EEG slowing and disturbed nocturnal sleep. In this study, we hypothesized that genetic variation at the level of ApoE could contribute to SDB and/or sleep abnormalities in the general population.

Methods: A population-based random sample (ref.1) of 791 middle-aged adults (42.2% female, 49.4±0.28 years old, Body Mass Index (BMI): 30.1±0.22) was used. Nocturnal polysomnography (1-3 times per subject, separated by 4 years for a total of 1344 sleep studies) was performed to evaluate apnea-hypopnea index (AHI), sleep architecture, and the number of periodic leg movements. EEG slowing index was derived from eye-opened awake EEG prior to nocturnal polysomnography. Cholesterol, triglycerides, and glucose were also measured. ApoE genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (ref.2). Statistical analysis (SAS software, SAS Institute, Cary, NC) included logistic and linear regression modeling whenever most appropriate. Models were adjusted for age, sex, BMI and ethnic heritage. AHI was used as a binary outcome using a cutpoint of 15, which is often used to indicate clinically significant SDB.

Results: Allele frequencies for ε2, ε3 and ε4 were 0.071, 0.780 and 0.149, respectively. LDL (134±2.2 for ε4+ and 128±1.2 for ε4-, p=0.034) and triglycerides (162±7.2 for ε4+ and 140±3.2 for ε4-, p=0.046) were increased, while HDL (44.0±0.81 for ε4+ and 47.8±0.55 for ε4-, p=0.045) was decreased in ε4+ subjects. Although there was only a little change in sleep architecture and no change in EEG slowing index, the probability of moderate to severe SDB (%AHI ≥ 15) was significantly increased in subjects with versus without ApoE ε4, independent of age, sex, BMI and ethnic heritage (11.98% for ε4+ and 6.98% for ε4-, p=0.01). Mean AHI was also significantly increased in subjects with (6.5±2.62) versus without ApoE ε4 (4.8±0.34). These effects were proportional to ApoE ε4 dosage.

Conclusions: Our results are the first to report a polymorphism that influences sleep apnea. SDB has been reported to cluster in families (ref.3), and ApoE ε4 might be one of the multiple genetic factors involved in genetic susceptibility to this common syndrome. The observation of increased SDB prevalence in subjects with ApoE ε4 may have broad consequences. The deleterious effect of ApoE ε4 on lipid metabolism, together with the established cardiovascular impact of SDB could have synergic effects. SDB and ApoE ε4 may also interact centrally to impair cognition. Not only ApoE ε4 increases plaque density, thus resulting in neuronal loss, but also SDB induces sleepiness and has been suggested to damage the brain irreversibly through long-term hypoxemia. Further studies will be needed to confirm and extend on these important findings.

References:

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086.J

Heritability of Sleep-Disordered Breathing in Elderly Male Twins

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Introduction: Several twin studies have suggested that self-reported snoring has a genetic component, and studies of familial aggregation have demonstrated that physiologically recorded sleep apnea has a strong genetic basis (1,2). To date, no studies with physiological monitoring have estimated the heritability of sleep-disordered breathing (SDB). The present study reports on the heritability of several measures of SDB assessed in a community-dwelling sample of elderly male twins.
Methods: Subjects in the present study are 53 monozygotic (MZ) and 40 dizygotic (DZ) World War II male–male veteran twin pairs, ages 70 to 80, residing in California and throughout the southeastern U.S. Overnight SDB was recorded using the EdenTrace II. Two indices, the Respiratory Disturbance Index (RDI) and the oxygen desaturation index (O2DI) were scored, blind to subjects’ identity, zygosity, and pair relatedness. Hypopnea was defined by a drop in airflow or tidal volume of 50% below average amplitude for at least 10 seconds, accompanied by a 4% or greater drop in oxygen saturation. To determine the relative contributions of genetic and nongenetic influences to individual differences in SDB, we compared twin-pair similarities for RDI and O2DI in MZ and DZ twins. A significantly greater MZ than DZ intraclass correlation (ICC) was considered an indicator for the presence of genetic influences.

Results: The ICCs for RDI were .44 in MZ and .15 in DZ twin pairs; for O2DI the ICCs were .47 in MZ and .26 in DZ twins (both P < .05). To estimate the genetic and nongenetic components of variance for these measures, we used structural equation modeling of the observed variance-covariance matrices for MZ and DZ twins. Estimates of the genetic component of variance (heritability) with corresponding 90% confidence interval were .40 [.21 to .61] for RDI and .47 [.27 to .70] for O2DI.

Conclusions: Despite numerous age-dependent risk factors that operate in the elderly to promote a high prevalence of SDB in this age group, we detected a significant heritability for both RDI and O2DI. These results suggest that, even into old age, sleep-disordered breathing is determined in part by genetic factors.

References:

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087.J

Changes in Hipocampal Susceptibility to Severe Hypoxia Following Long-Term Exposures to Intermittent or Sustained Hypoxia

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Introduction: The clinical syndrome of obstructive sleep apnea (OSA), a condition characterized by repeated episodes of upper airway obstruction and hypoxia during sleep, affects 7-8% of the middle age population, and is associated with increased prevalence and severity of stroke (1,2). Acute hypoxia-ischemia (AHI) of hippocampal slices has served as a reliable stroke model, whereby recovery of synaptic function from AHI depends on the duration and severity of hypoxia (3). We hypothesized that functional recovery from AHI would be reduced in rats exposed to intermittent hypoxia such as occurring in OSA patients.

Methods: Young adult male Sprague Dawley rats were exposed to 7 days of either intermittent hypoxia (IH) which consisted of alternating room air and 10% O2 either every 90 sec or to chronic hypoxia (CH: 10% O2). Control animals were exposed to normoxic conditions. Hipocampal slices were harvested from these animals, and were exposed after equilibration to AHI for 12 min. The overall percentage of slices demonstrating functional recovery (assessed as the return of evoked potentials in the CA1 region to a standard stimulus of the Shaeffer collaterals) was calculated for each animal, and the mean percentages were then computed for each experimental group.

Results: In control animals, 55±12% of the hippocampal slices demonstrated functional recovery after AHI (n=9). Similarly, 51±7% of slices recovered after 7 days of CH (n=9; P< NS vs. control). However, in animals exposed to IH for 7 days, reduced functional recovery to AHI was apparent (40±4%; n=9; P <0.02 vs. control or CH).

Conclusions: These findings suggest that IH, but not CH, induces enhanced vulnerability to a standard AHI exposure as evidenced by diminished capability for functional recovery. We speculate that in OSA patients, episodic hypoxia underlies increased vulnerability to an acute AHI episode such as seen in stroke.

References:

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088.J

MRI White Matter Hyperintensities in Older Adults with OSA

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Introduction: White matter hyperintensities on MRI often represent cerebral ischemia. These changes can occur with “normal” aging, but may also be exacerbated by hypertension. Though hypertension is common in apnea and cerebral blood flow is known to decrease during apneic events, no studies have examined the ischemia of small vessels in the brains of apneics.

Methods: Eight participants over the age 65 were recruited from a pool of patients seen at a clinical sleep laboratory for suspected apnea. White matter hyperintensities were measured in patients with severe (S; n=4) and minimal apnea (M; n=4). No participant had a neurologic disorder, psychiatric disorder, or diabetes. Groups were equivalent in age, BMI, and gender (2 women and 2 men). All participants in the severe group, and two in the minimal group, were treated with only one medication for hypertension. MRI acquisition was performed on a Siemens 1.5 T unit using a volume head coil. FLAIR images were obtained with a slice thickness of 5 mm. Images were analyzed using NIH Image software. Intensities were sampled from white matter, gray matter, and hyperintense tissue to generate a histogram of intensity values. Histograms were used to select a range of intensities thought to represent disease for each participant. A single cutoff hyperintensity level was chosen to insure interrater reliability. Two blinded raters quantified all images independently and interrater reliability was measured (r=0.94-0.99). Average number of pixels per slice falling within the identified hyperintensity
range served as the dependent variable after correcting for whole brain size.

**Results:** The severe group had significantly greater white matter hyperintensities than did the minimal group (Table 1). The effect was still quite large after covarying age, though statistically significant at only a trend level (F = 2.782, p = .085). Figure 1 shows a sample of white matter hyperintensities from each group.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Minimal</th>
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<th>p</th>
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<tr>
<td><strong>Age</strong></td>
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<td><strong>RDI</strong></td>
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<tr>
<td><strong>BMI</strong></td>
<td>34.0±4.21</td>
<td>31.9±4.93</td>
<td>-0.65</td>
<td>.271</td>
</tr>
<tr>
<td><strong>Hyperintensities</strong></td>
<td>172.0±81.5</td>
<td>69.4±41.8</td>
<td>-2.24</td>
<td>.033</td>
</tr>
</tbody>
</table>

**Figure 1**

**Conclusions:** Findings suggest that patients with severe apnea may have significantly more small vessel ischemic brain disease than those with minimal apnea. Though these findings have been seen with "normal" aging, none of the participants in this study was over the age of 70. Though the mechanism of the development of white matter hyperintensities is not fully understood, these findings suggest that apnea may contribute to patients' susceptibility to brain abnormalities that are commonly associated with hypertension.

**References:**


**Methods:** Blood samples were collected after an overnight fasting from 28 OSA patients (Age: 49.8±11.7 years, BMI: 29.1±4.5 kg/m², RDI: 28.9±19.1) and 20 healthy volunteers (Age: 46.4±10.9, BMI: 25.6±2.8). Six patients (Age: 49.3±9.1, BMI: 31.5±4.8, RDI: 56.6±8.1 before CPAP and 14±4.9 after CPAP) were on CPAP treatment for 3 months after which they were studied in the sleep lab for two consecutive nights, a night with and a night without CPAP. Flow cytometry was employed in order to determine integrins (CD11b, CD11c) and lectins (CD15, Lewis X) expression and intracellular oxidation of hydroethidium (HE), indicating the production of reactive oxygen species (ROS). This was determined in resting and in phorbol-myristate acetate (PMA) activated monocytes in whole blood. Leukocyte adhesion to human cultured coronary artery endothelial cells (HCAEC) was analyzed by 51Cr release assays.

**Results:** There was an increase in the number of monocytes expressing CD15 and CD11c molecules in monocytes of OSA patients as compared to controls (10.2±1.5% vs. 1.3±1.2% and 55.3±16.9% vs. 32.5±12.2%, p<0.001, respectively). Increased levels of ROS production were observed in CD11c+ monocytes of OSA patients. Both basal production of ROS by CD11c+ monocytes (OSA: 88.5±51.9 Mean Fluorescence Intensity (MFI) Units vs. Control: 38.9±39.9 MFI units), and number of CD11c+ cells participating in oxidation of HE (OSA: 40.7±20.1% vs. Control: 20.2±4.4%), were significantly higher in OSA patients p<.001 in both). In response to PMA activation, respiratory burst activity was also significantly higher in monocytes of OSA patients producing 432.4±144 MFI units in comparison with 207.8±106 MFI units in control (P=0.0007). The monocytes of OSA patients were more adherent to HCAEC than control monocytes (index of adhesion 4.2±1.5 vs 2.5±0.5, p=0.02). Both selectin and integrin ligands were found to be involved in OSA monocytes adhesion to HCAEC. In agreement with these results, removing CPAP treatment for one night increased the percentage of CD15+ and CD11c+ monocytes participating in the basal ROS production in comparison with the treatment condition, and dramatically enhanced the monocytes adhesion index to HCAEC (4.4±0.75 vs 1.5±0.7).

**Conclusions:** We conclude that phenotypic changes in monocytes from OSA patients reflect a state of cellular pre-activation in-vivo. This pre-activation may enhance endothelial cell/monocyte interactions resulting in damage to the endothelium which may trigger atherogenic processes. Our preliminary data on CPAP treatment suggest that effective CPAP treatment in OSA patients downregulates adhesion molecules expression.

**This study was supported by a grant from the Israeli Academy of Sciences to L Lavie and P Lavie**

**Introduction:** Sleep apnea syndrome is associated with increased cardiovascular morbidity. Although several mechanisms have been proposed to explain this association, the exact nature of this association is yet to be determined. We hypothesized that the repeated apnea-related hypoxia may result in oxidative stress in sleep apnea patients. Oxidative stress is responsible for enhancement of adhesion molecules expression in the endothelium and leukocytes, and consequently for endothelial cell damage. These are considered to play a major role in cardiovascular morbidity. There are several families of adhesion molecules: selectins are responsible for the initial steps in leukocyte adherence to the endothelium, and integrins play a role in leukocytes adhesion to stimulated endothelium at the sites of injury. The focus of the present study was to identify adhesion molecules on blood monocytes of OSA patients in comparison with controls, and to correlate their expression with adhesion properties and parameters of oxidative burst. We also studied the effects of CPAP treatment on some of these parameters.

**Methods:** Blood samples were collected after an overnight fasting from 28 OSA patients (Age: 49.8±11.7 years, BMI: 29.1±4.5 kg/m², RDI: 28.9±19.1) and 20 healthy volunteers (Age: 46.4±10.9, BMI: 25.6±2.8). Six patients (Age: 49.3±9.1, BMI: 31.5±4.8, RDI: 56.6±8.1 before CPAP and 14±4.9 after CPAP) were on CPAP treatment for 3 months after which they were studied in the sleep lab for two consecutive nights, a night with and a night without CPAP. Flow cytometry was employed in order to determine integrins (CD11b, CD11c) and lectins (CD15, Lewis X) expression and intracellular oxidation of hydroethidium (HE), indicating the production of reactive oxygen species (ROS). This was determined in resting and in phorbol-myristate acetate (PMA) activated monocytes in whole blood. Leukocyte adhesion to human cultured coronary artery endothelial cells (HCAEC) was analyzed by 51Cr release assays.

**Results:** There was an increase in the number of monocytes expressing CD15 and CD11c molecules in monocytes of OSA patients as compared to controls (10.2±1.5% vs. 1.3±1.2% and 55.3±16.9% vs. 32.5±12.2%, p<0.001, respectively). Increased levels of ROS production were observed in CD11c+ monocytes of OSA patients. Both basal production of ROS by CD11c+ monocytes (OSA: 88.5±51.9 Mean Fluorescence Intensity (MFI) Units vs. Control: 38.9±39.9 MFI units), and number of CD11c+ cells participating in oxidation of HE (OSA: 40.7±20.1% vs. Control: 20.2±4.4%), were significantly higher in OSA patients p<.001 in both). In response to PMA activation, respiratory burst activity was also significantly higher in monocytes of OSA patients producing 432.4±144 MFI units in comparison with 207.8±106 MFI units in control (P=0.0007). The monocytes of OSA patients were more adherent to HCAEC than control monocytes (index of adhesion 4.2±1.5 vs 2.5±0.5, p=0.02). Both selectin and integrin ligands were found to be involved in OSA monocytes adhesion to HCAEC. In agreement with these results, removing CPAP treatment for one night increased the percentage of CD15+ and CD11c+ monocytes participating in the basal ROS production in comparison with the treatment condition, and dramatically enhanced the monocytes adhesion index to HCAEC (4.4±0.75 vs 1.5±0.7).

**Conclusions:** We conclude that phenotypic changes in monocytes from OSA patients reflect a state of cellular pre-activation in-vivo. This pre-activation may enhance endothelial cell/monocyte interactions resulting in damage to the endothelium which may trigger atherogenic processes. Our preliminary data on CPAP treatment suggest that effective CPAP treatment in OSA patients downregulates adhesion molecules expression.

**This study was supported by a grant from the Israeli Academy of Sciences to L Lavie and P Lavie**
Effect of Intermittent and Sustained Hypoxia on Long-Term Potentiation in the CA1 Hippocampal Region of the Rat

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Introduction: The major neurocognitive manifestations of obstructive sleep apnea (OSA) include excessive daytime sleepiness, psychosocial maladjustments, and mental impairment in terms of thinking, perception, memory, communication, or the ability to learn new information. However, sleep fragmentation may not be the only factor associated with these problems since disturbances in the ability to maintain wakefulness were inversely correlated to the degree of hypoxemia (2). In addition, reductions in general intellectual measures and executive and psychomotor tasks were attributable to the severity of hypoxemia while other attention and memory deficits were related to impaired vigilance (3). Thus, the role of episodic hypoxia in the neurocognitive deficits of OSA is unclear.

Methods: Young adult male Sprague Dawley rats were exposed to 7 days of either intermittent hypoxia (IH) which consisted of alternating room air and 10% O₂,5 either every 90 sec or to chronic hypoxia (CH; 10% O₂). To assess whether IH modifies sleep architecture, 6 chronically instrumented rats were exposed to IH while sleep measures were recorded. Control animals were maintained in normoxia. LTP was elicited in the CA1 region of the hippocampus by pulse train stimulation of the Schaffer collaterals at 100 Hz for 2 sec, and was defined as the ability to sustain augmented evoked potentials to a standard pulse stimulus for 15 min.

Results: IH reduced both REM and NREM during day 1 followed by rebound increases in sleep in day 2, and no further deviations from pre-IH sleep measures thereafter. LTP could be obtained in 80% of slices prepared from control rats (n=19). After 7 days CH, LTP was elicited in 64% of slices (n=12; P<0.05 vs. control), and could only be obtained in 47% of IH-exposed rats (n=12; P<0.05 vs. CH).

Conclusions: We conclude that 7 day exposures to both CH and IH reduce the ability to sustain LTP, that this effect is particularly prominent after IH, and is independent from sleep fragmentation or deprivation.

References:

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Sleep Apnea - Performance and Magnetic Resonance Spectroscopy

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Introduction: Sleep Apnea (SA) occurs in 25% of middle aged men resulting in sleep fragmentation and varying degrees of nightly repetitive oxygen desaturation. There are associated performance decrements with SA, which include daytime sleepiness, fatigue, memory loss and an inability to concentrate. One previous study has observed altered cerebral MR spectra (MRS) in sleep apnea but no subjective or objective measures of performance were reported(1). To measure the relationship between brain metabolism, attention and performance we obtained MRS from subjects with and without SA.

Methods: 38 male subjects (age range 24-64 years, RDI range 4-112) were studied in the following protocol. Subjects presented at 1600 hours following a caffeine/alcohol free day and completed the Neurobehavioural Assessment Battery (NAB, University of Pennsylvania, AusEd driving simulator plus questionnaires relating to mood and sleep quality. Subjects underwent an overnight sleep study followed by a MR scan at 0700 the next morning. H Spectra were obtained at 1.5T using GE Signa scanner from the white matter of left and right frontal lobes (2x2x2), the left hippocampus [Hip(1x1x1)] and the medulla[Med(1x1x2)]. Spectrum acquired included 28 scans 128scans, TE136 & TR1500ms, Ratios of N-acetamino aspartate (NAA), NAA/choline, Choline/creatinine, NAA/creatine and lactate were measured. The evening testing protocol was repeated.

Results: A Spearman correlation matrix was run with sleep variables, MR data and performance outcomes. MRS variables and objective performance measures showed associations with oxygen desaturation and arousal indices, but not total apnea time or RDI. Objective performance measures including memory, predominantly correlated with NAA/Creatine in the frontal lobes & NAA/choline in the hippocampus. Lactate signals were identified in 2 SA subjects who do not appear to differ in subjective and objective performance indices. A regression was run with significant correlations using a variable measuring total time spent in disordered breathing (total apnea time). A curvilinear relationship was found between total apnea time and PVT parameters and subjective sleepiness measurements.

Table 1: Correlation Matrix Metabolite Ratios with Sleep Variables and NAB (Spearman 2 tailed)

<table>
<thead>
<tr>
<th>Variable</th>
<th>NAA/Choline RF</th>
<th>HIPP/NAA/Choline</th>
<th>HIPP/Choline/LF</th>
<th>Choline/Cre LF</th>
<th>HP/Choline/Creat</th>
<th>Med/Choline/Creat</th>
<th>Choline/Cre</th>
<th>% SWS</th>
<th>MRS Slowest 10%</th>
<th>MRS TETcorrect</th>
<th>MRS TETcumd1</th>
<th>MRS PVTsme2</th>
<th>MRS SAST total rate2</th>
<th>MRS Min desat</th>
<th>MRS CH</th>
<th>MRS % SWS</th>
<th>MRS KSS</th>
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</thead>
<tbody>
<tr>
<td>rho</td>
<td>.52 &lt;.012</td>
<td>.65 &lt;.004</td>
<td>.71 &lt;.002</td>
<td>-.52 &lt;.006</td>
<td>-.69 &lt;.012</td>
<td>.51 &lt;.004</td>
<td>-.45 &lt;.019</td>
<td>-.64 &lt;.041</td>
<td>.76 &lt;.028</td>
<td>.42 &lt;.032</td>
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<tr>
<td>p</td>
<td>.022</td>
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<td>.012</td>
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<td>.027</td>
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</tbody>
</table>

Key: DSST-Digit symbol Substitution Task number correct PomsV-Profile of Mood States VigourSAST-Subtraction Addition TaskPWT- Psychomotor Vigilance task mean slowest 10%-sum of errors. TET cum-Timed Estimation Task cumulative deviationMin desat-minimum desaturation% SWS = Percent in Slow Wave SleepKSS – Karolinska Sleepiness Scale

Conclusions: Cerebral bioenergetics in SA is related to indices of oxygen desaturation or arousal index (with regional differences), but not
with indices of apnea frequency or time spent in apnea, MRS is correlated with subjective sleepiness, mood variables, and objective performance decrements. Although less data was collected for the hippocampus and medulla, highly significant correlations were found between hippocampal and medullary MRS ratios and performance variables. These findings provide biologic support for the view that performance changes in sleep apnea are not related to simple measures of apnea (RDI & apnea time) but appear to involve more complex mechanisms.

References:

092.J

Right to Left Shunting Through Patent Foramen Ovale Can Occur During Obstructive Sleep Apnea

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Introduction: Patent foramen ovale (PFO) can potentially give rise at ischemic stroke by means of paradoxical embolization. In obstructive sleep apnea syndrome (OSAS) right to left shunting (RLS) can occur through PFO during periods of nocturnal apnea due to elevated right-side pressures. The aim of our study was to evaluate the prevalence of PFO by means of transcranial Doppler (TcD) in patients with obstructive sleep apnea syndrome (OSAS) and investigate the presence of RLS during sleep of these patients.

Methods: 78 consecutive subjects with OSAS (mean age 53 ± 12 years) and 89 normal controls (mean age 48 ± 9 yrs.) underwent TcD with injection of agitated normal saline solution mixed with 1 ml of air (contrast medium, CM). The test was performed with patients at rest and during Valsalva maneuver (VM). 10 patients with OSAS (mean age 53 ± 11 years) and prior diagnosed PFO underwent also TcD with CM during sleep.

Results: PFO was present in 21 of 78 patients with OSAS and in 13 of 89 control patients. Seventeen of 21 patients with OSAS showed PFO only during VM with respect to 12 of 13 subjects of the control group. Prevalence of PFO in OSAS was statistically different respect to the control group (p<0.05). During sleep RLS was present in 9 of 10 patients and only when an obstructive apnea occurred with a length major than 17 seconds. In 1 of 10 patients only hypopneas occurred and no RLS could be shown.

Conclusions: Prevalence of PFO in subjects with OSA is significantly higher than in normal controls, however the difference is small. The shunt is frequently present only during VM. In patients with OSAS and concomitant presence of PFO, RLS can occur during sleep. PFO could increase in patients with OSAS the risk for stroke, especially in case of high apnea-hypopnea index.

093.A

Warm-Sensitive Neurons are Co-Localized With Sleep-Active Neurons in the Preoptic Hypothalamus

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Introduction: The anatomical distribution of preoptic area (POA) sleep-active neurons was recently characterized using c-Fos immunostaining as a marker of neuronal activation. Segregated sleep-active neurons were found in the ventrolateral POA (VLPO) and in the rostral and caudal median preoptic nucleus (MnPN) (1-2). Previously, it was found that warm-sensitive neurons (WSNs) were hypnogenic since excitation of these neurons by local warming could induce sleep onset, tonically augment sleep, and increase delta activity within sleep (3). Further, WSNs are sleep-active (3). Therefore, we hypothesized that VLPO and MnPN sites containing segregated sleep-active neurons would also contain WSNs.

Methods: Ten rats were surgically prepared for chronic EEG, neck EMG, and brain temperature (Tbr) recording using standard techniques. After recovery from surgery and chamber adaptation, 3 hr. polygraphic recordings were carried out from CT 1-4 at a control (23.0 °C) or elevated ambient temperature (Ta). We previously found that WS activation during sleep was equal to that induced by an approximately 2.0 °C local stimulus during waking (3). Accordingly, we exposed animals to a Ta (37.0-39.5 °C) adjusted to raise Tbr by no more than 2.0°C, relatively mild brain warming. Wakefulness was maintained by tones or cage vibration. At CT 4, animals were anesthetized, perfused and subsequently prepared for c-Fos immunostaining (2). A person blind to treatments mapped c-fos immunostained cells in the MnPN and VLPO sites using standardized grids (2).

Results: In the elevated Ta, mean Tbr increased from 37.7 to 39.3 °C. Tbr was unchanged in the control Ta. Following induction of an elevated Tbr, MnPN and VLPO sites exhibited marked (7-10 fold) and highly significant increases in c-Fos immunostaining compared to animals without heat exposure (Table 1, * p< .01, heat wake vs control wake, 2-tailed t tests). C-fos expression occurred although animals were awake during most of the recording period (Table 1). The numbers of neurons exhibiting c-Fos immunostaining after heat exposure exceeded levels found previously following sustained sleep (Table 1).

Table 1

<table>
<thead>
<tr>
<th>C-Fos Counts Per Grid and % Sleep (standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat Wake (n=6)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Rostral MnPN</td>
</tr>
<tr>
<td>Caudal MnPN</td>
</tr>
<tr>
<td>VLPO</td>
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<tr>
<td>% Sleep</td>
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</tbody>
</table>

Conclusions: This study supports a hypothesis that WSNs are co-localized with sleep active neurons in VLPO and MnPN hypothalamic sites, but these may not be identical. Since WSNs identified by c-Fos in VLPO and MnPN sites were not sleep-dependent, they may be distinct from sleep-active neurons. Alternatively, since brain or whole body warming increases the propensity for subsequent sleep (e.g.,3), we hypothesize that the induction of c-Fos in these sites is a marker of hypnogenic drive in sleep-active neurons. This must be confirmed. Using electrophysiological methods, we found previously that a majority of WSNs identified by local transient warming were sleep-active neurons(3). The present findings suggest that WSNs identified by sustained whole animal warming greatly outnumber sleep-active neurons. Non-specific effects of mild warming must be ruled out.

References:
Research supported by Supported by the NIH (MH 47480, HL 60296), and the Veterans Administration

094.A

Effects of Interleukin-1 beta on Sleep- and Wake-related Preop-tic/Anterior Hypothalamic Neurons in Unrestrained Rats.

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Introduction: Extensive evidence suggests that the preoptic/anterior hypothalamic area (POAH) is critically involved in sleep regulation (1). Extracellular neuronal recording, as well as studies using c-fos as a marker of cellular activation have identified sleep- and wake-related neurons in the POAH. Many lines of studies suggest that the cytokine interleukin-1beta (IL-1beta) promotes non-rapid eye movement (NREM) sleep (2). The POAH is one of the sites where microinjection of IL-1beta promotes NREM sleep. However, the neuronal types in the POAH that are affected by IL-1beta administration are not known. We hypothesized that IL-1beta promotes NREM sleep, at least in part, by the activation of sleep- and/or inactivation of wake-related neurons in POAH. In this study, we recorded sleep-wake discharge profile of the POAH neurons in freely behaving rats and simultaneously assessed influences of IL-1beta on their spontaneous sleep- and wake-related discharge by delivering IL-1beta adjacent to the recorded neurons using microdialysis.

Methods: Six Sprague-Dawley rats were surgically implanted with (a) EEG and EMG electrodes for chronic recording of sleep-wake states; (b) five pairs of microwires into POAH for recording extracellular neuronal activity, and (c) a guide cannula at ~0.5 mm lateral to the microwires for delivery of IL-1beta adjacent to the recorded neurons with a microdialysis probe (membrane length, 1 mm; outer diameter, 0.22 mm; molecular cut off size: 50 kDa). The sleep-wake discharge of POAH neurons was continuously recorded through (a) 3-5 sleep-waking episodes during baseline (artificial cerebrospinal fluid perfusion), (b) microdialysis perfusion of IL-1beta (rat recombinant IL-1beta; total IL-1beta delivered 2.5-3.0 ng), and (c) during wash out. A 50% or greater change in NREM/wake ratio was used as a criterion to classify neurons as wake-related (WRNs), sleep-related (SRNs), and state-indifferent (SINs).

Results: Of 18 POAH neurons studied, eight were SRNs, four were WRNs and 6 were SINs. Effects of IL-1beta on SRNs were heterogeneous. IL-1beta increased the discharge of 5 and decreased the discharge of 2 SRNs during both waking and NREM sleep. One SRN was not affected. The mean discharge of SRNs increased during waking (1.70 ± 0.84 vs 4.11 ± 1.82) and NREM sleep (5.63 ± 2.20 vs. 8.99 ± 3.60). IL-1beta suppressed the discharge of all four WRNs during waking (4.84 ± 1.37 vs. 1.49 ± 0.16) and NREM sleep (2.04 ± 0.94 vs. 0.92 ± 0.28). IL-1beta did not affect discharge of SINs during both waking (7.4 ± 2.15 vs. 7.35 ± 3.38) and NREM sleep (6.42 ± 2.35 vs. 6.99 ± 3.21).

Conclusions: These preliminary results suggest that in naturally awake and sleeping animals, IL-1beta exerts excitatory effects on a majority of SRNs and an inhibitory influence on WRNs in POAH. These results support a hypothesis that at least in part, SRNs and WRNs in the POAH mediate the sleep-promoting effects of IL-1beta.


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095.A

Sleep Induction by Microinjection of Ethanol Into the MPA is Prevented by a Benzodiazepine Receptor Antagonist

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Introduction: Microinjections, into the medial preoptic area (MPA) of a wide variety of hypnotic compounds, including triazolam, pentobarbital, progaglandin D2, and ethanol, have been shown to shorten sleep latency, suggesting that this may be an neuroanatomic site mediating pharmacologic sleep induction (1). At a molecular level it is less certain how these agents act, but one hypothesis is that most of them directly or indirectly influence the function of the GABAa/benzodiazepine receptor complex. Although ethanol is known to enhance GABA-stimulated chloride ion flux in the receptor complex, other hypotheses suggest that it induces sleep by altering neuronal membrane fluidity. In this study we have assessed its mechanism of action by administering it alone and in combination with flumazenil, a benzodiazepine receptor antagonist which has little or no effects on membrane fluidity or voltage-dependent calcium channel function.

Methods: Nine male Sprague-Dawley 225-250 gm rats were anesthetized and surgically implanted with electrodes for recording the EEG and EMG according to standard techniques, and were housed in cages with a 12:12 L:D cycle such that lights come on at 8:00 AM. After a one week recovery period, they were microinjected with one of the six treatment conditions at 10:00 AM on the day of the study. All animals received all treatments in random order, in studies separated by at least 3 days. Treatment conditions were: vehicle for ethanol and vehicle for flumazenil, ethanol 0.24 uM and vehicle for flumazenil, ethanol 0.47 uM and vehicle for flumazenil, vehicle for ethanol and flumazenil 0.95 ug, ethanol 0.24 uM and flumazenil 0.95 ug, and ethanol 0.47 uM and flumazenil 0.95 ug, each in 0.5 ul. Doses of ethanol are derived from Ticho et al. (2), while the dose of flumazenil has previously been found in our own work to have no effects on sleep when given by itself, yet block sleep induction by triazolam microinjections (3). Two hour sleep recordings were performed, and scored in 30 sec epochs by an investigator blind to the experimental conditions. Statistical analysis was performed by a repeated measures analysis of variance (ANOVA) and post-hoc Least Significant Difference tests on measures which showed a significant effect.

Results: As seen in the Table, both doses of ethanol, given with vehicle for flumazenil, significantly reduced sleep latency, and tended (p<0.06) to increase total sleep time. Flumazenil at this dose given in combination with vehicle for ethanol had no significant effect on any sleep measure. When ethanol and flumazenil were given in combination, sleep latency was not significantly different than the control condition (injection of vehicle for both compounds).

Table 1

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Sleep latency</th>
<th>Total sleep</th>
<th>NREM sleep</th>
<th>REM sleep</th>
<th>Wake after sleep onset</th>
<th>REM latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle/Vehicle</td>
<td>16.06±1.49</td>
<td>73.78±4.97</td>
<td>72.39±4.90</td>
<td>1.39±0.52</td>
<td>32.61±4.52</td>
<td>81.00±6.46</td>
</tr>
<tr>
<td>Vehicle/E-2.4</td>
<td>9.97±1.16</td>
<td>81.04±3.55</td>
<td>80.61±3.78</td>
<td>1.32±0.48</td>
<td>28.26±3.67</td>
<td>85.44±5.06</td>
</tr>
<tr>
<td>Vehicle/E-4.7</td>
<td>7.50±1.12</td>
<td>84.94±2.40</td>
<td>83.72±2.15</td>
<td>1.56±0.33</td>
<td>27.67±3.98</td>
<td>82.72±5.87</td>
</tr>
<tr>
<td>Vehicle/F-2.4</td>
<td>12.44±1.88</td>
<td>75.44±3.38</td>
<td>73.92±4.48</td>
<td>1.56±0.47</td>
<td>33.44±3.90</td>
<td>86.12±6.00</td>
</tr>
<tr>
<td>Vehicle/F-4.7</td>
<td>13.05±1.48</td>
<td>75.32±4.98</td>
<td>73.72±4.80</td>
<td>1.59±0.84</td>
<td>31.94±5.26</td>
<td>85.00±6.69</td>
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<td>E-2.4/E-2.4</td>
<td>16.02±2.14</td>
<td>71.94±4.75</td>
<td>70.11±2.69</td>
<td>1.39±0.72</td>
<td>33.61±4.45</td>
<td>83.30±5.98</td>
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<td>E-4.7/E-4.7</td>
<td>16.00±2.41</td>
<td>71.94±4.75</td>
<td>70.11±2.69</td>
<td>1.39±0.72</td>
<td>33.61±4.45</td>
<td>83.30±5.98</td>
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</table>

Abbreviations: Veh=Vehicle; E=flumazenil 0.95 ug; F=flumazenil 0.24 uM; E=flumazenil 0.47 uM; All values represent mean±SEM minutes.
Conclusions: In humans, flumazenil has been reported to reverse some EEG changes induced by ethanol, but to have little effects on measures of intoxication. In rodents it may block ethanol-induced reductions in exploration and release of beta-endorphin in some brain regions, but may have little effect on behaviorally-measured intoxication. In the present study we have found that flumazenil blocks sleep induction by ethanol microinjection into the MPA. One implication of these findings is that at this dose range, some of ethanol’s actions-specifically, sleep induction—may result from altering function of the GABAA-benzodiazepine receptor complex.

References:


This work was partially supported by NIH grants 2PO I AG 11412-03 and K07 BL03640.

096.A

Ventrolateral preoptic area lesions block the hypnotic effect of pentobarbital in the medial preoptic area

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Introduction: Microinjection, electrophysiological and lesion studies demonstrate a role of the medial preoptic area (mPOA) of the anterior hypothalamus in sleep/wake regulation. Recent c-fos and electrophysiological data indicate that a group of neurons in the ventrolateral preoptic/anterior hypothalamic neurons endogenous and pharmacological sleep regulation in the VLPO. Furthermore, VLPO lesions are followed by the persistent reduction of NREM or REM sleep, depending on the location of neuronal damage. In this study, we microinjected pentobarbital (PB) into the mPOA of rats with VLPO lesions to test the hypothesis that the VLPO modulates pharmacological responsiveness of the mPOA.

Methods: Twenty male Sprague-Dawley rats (250-300 grams) were implanted with bilateral microinjection guide cannulae in the mPOA (A-P -.5; M-L ±.5; D-V -.8). Eleven of these rats received bilateral radiofrequency lesions to the VLPO (A-P -.5; M-L ±.5; D-V -9.0) and eleven of these rats received bilateral microinjection guide cannulae in the mPOA (A-P -.5; M-L ±.5; D-V -8.0). In the sham group, both doses of PB significantly decreased sleep onset latency (p .001) and wake time after sleep onset (p .01), while they increased NREM (p .001) and total sleep time (p .001) compared to vehicle and versus PB injections in lesion rats (all values significant at p .001). In the lesion group, there were no differences on any sleep measure between vehicle and PB trials. Table 1 presents group values and significance levels.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Wake</th>
<th>SOL</th>
<th>NREM</th>
<th>TST</th>
<th>WASO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>58.95</td>
<td>22.39</td>
<td>65.93</td>
<td>66.22</td>
<td>33.50</td>
</tr>
<tr>
<td>Veh</td>
<td>58.78</td>
<td>22.39</td>
<td>65.83</td>
<td>66.22</td>
<td>33.50</td>
</tr>
<tr>
<td>LD</td>
<td>60.90</td>
<td>22.41</td>
<td>65.82</td>
<td>66.18</td>
<td>33.50</td>
</tr>
<tr>
<td>HD</td>
<td>63.42</td>
<td>22.82</td>
<td>65.00</td>
<td>65.68</td>
<td>42.37</td>
</tr>
</tbody>
</table>

Conclusions: These results demonstrate that the sleep inducing effects of PB in the mPOA are prevented by bilateral VLPO lesions. In previous studies from our laboratory, microinjections of triazolam and PB had potent sleep inducing effects in the mPOA but had no effect in the VLPO. These combined results suggest that the VLPO may represent an important effector mechanism for pharmacological sleep regulation in the mPOA. In contrast to a previous study using ibotenic acid (3), baseline (vehicle) sleep was not significantly reduced in our lesion group. A possible explanation is the slightly more dorsal placement of lesions in our study (Figure 1), suggesting anatomical specificity with regard to endogenous and pharmacological sleep regulation in the VLPO.

References:


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Poster Symposia

097.L

Beliefs and Attitudes About Sleep Before and After Participation in a Group Cognitive-Behavioral Insomnia Treatment Program

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Introduction: The faulty beliefs held by many insomnia patients about the origins and consequences of their sleep problem may exacerbate the condition. One means of evaluating the cognitions of insomniacs is through the use of the Beliefs and Attitudes About Sleep Scale (BAS), a 30-item visual-analog rating scale, developed by Morin et al. (1993). The psychometric properties of the BAS were recently examined by Espie et al. (2000) who found the BAS to have three reliable subscales. This study investigated whether patient ratings on these scales were lower (reflecting more adaptive thinking) following group CBT treatment and if they predicted treatment success.

Methods: Participants included 60 patients (30 men; mean age 48.1

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The insomnia treatment literature clearly indicates that behavioral treatments for primary insomnia are both efficacious and durable. This conclusion has been reached based on numerous studies using pre-post study design. Rate of change during treatment has been evaluated less frequently. We have reported previously that cognitive-behavioral therapy (CBT), outperforms relaxation therapy (RT) and placebo control (PC) during the second week of treatment and this advantage persists through the end of a six week treatment. (1) The present study is designed to compare the specific weekly rate of change among behavioral treatments for sleep maintenance insomnia.

**Methods:** Patients recruited to participate in this trial were middle-aged and older adults with moderate to severe primary sleep-maintenance insomnia. The methods used in this study have been described previously (2). Briefly, prospective subjects were screened to meet criteria for primary sleep-maintenance insomnia. Subjects were randomized to 6 weeks of cognitive-behavioral therapy (CBT), relaxation therapy (RT) or placebo (PC) and kept sleep logs each night throughout the protocol. Data for the present study were derived from these nightly sleep logs. This analysis focuses on wake after sleep onset (WASO) which is the primary outcome measure of interest. The statistical procedure used in the present analysis is hierarchical linear modeling (HLM)(3). When this technique is used, change is represented in a two level regression model. At the first level, a regression equation is calculated for each subject to generate 1) an intercept which indicates an individual’s baseline WASO and 2) a slope which indicates an individual’s rate of change in WASO each week during treatment and 3) a quadratic term which indicates acceleration or deceleration in change over time. At the second level a regression equation is calculated using these individual intercepts and slopes become the outcome variables and predictors are entered to explain the individual variability in the baseline mean, rate of change as well as the acceleration/deceleration in the change in WASO.

**Results:** The results presented here are for a sample of 71 subjects (CBT=23, RT=24, PC=24). The mean age of these subjects (34 females; 37 males) was 54.8 yrs. (SD = 11.8 yrs.). Results indicated that both CBT (p<.001) and RT (p=.003) had significant weekly decreases in WASO whereas PC did not (p=.074). Furthermore, CBT therapy has a significant deceleration in the rate of change (p<.001) whereas RT did not (p=.086). The linear decrease in WASO for RT was 7.4 minutes/week. The rate of decrease in CBT changed each week as follows: 25.4, 18.9, 13.1, and 7.3 minutes/week. Interestingly, when baseline trait anxiety was entered into the regression model as predictor of outcome, only CBT remained significant. This finding indicates that when baseline levels of anxiety are equivalent, RT no longer has a significant rate of change effect. This suggests that RT may be specifically addressing anxiety which may be interfering with sleep maintenance. The rate of change effect for CBT remained significant even when baseline level of anxiety are statistically equivalent suggesting that CBT is addressing specific sleep mechanisms, other than anxiety, which perpetuate sleep maintenance insomnia.

**Conclusions:** These results confirm our previous findings that cognitive-behavioral therapy for primary sleep-maintenance insomnia has a more rapid and larger treatment effect than either progressive muscle relaxation or placebo control. In addition our finding indicate that RT may be useful to reduce anxiety which may be interfering with sleep and CBT may be more specific to sleep mechanisms perpetuating insomnia.

**References:**

**Research supported by NIH R0148187 awarded to Dr. Edinger**
A Pilot Study of the Sleep EEG Power Spectral Effects of Behavioral Therapy in Primary Insomniacs

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Introduction: Cognitive Behavioral sleep therapy (CBT) has been demonstrated to be a highly effective treatment for primary insomnia leading to significant improvements in polysomnographic sleep variables (Morin et al., 1994). Yet, the underlying neurophysiologic changes which are associated with these improvements remain unknown. Frequency spectral analysis of the sleep EEG has been employed to study the neurophysiology of sleep alterations and treatments in more depth than can be achieved with standard polysomnographic analysis (Armitage, 1995), however this technique has not yet been applied to CBT. As a result, we carried out this pilot study in which we assessed the changes in sleep EEG spectral analysis associated with CBT in primary insomniacs.

Methods: The subjects were 10 primary insomniacs who received CBT and who were part of a larger study comparing CBT, progressive muscle relaxation, and placebo control (Edinger et al., 1992). The subjects underwent standard polysomnography prior to and after CBT including 2 EEG channels (C3-M2 and Cz-Oz) which were used for spectral analysis. The polysomnographic data was scored manually and artifacts, and arousals were eliminated. The data underwent FFT in 2 second epochs. Six frequency bands were employed: Delta (0.5-3.5 Hz), Theta (4.0-8.0 Hz), Alpha (8.5-12 Hz), Sigma (12.5-16 Hz), Beta (16.5-30 Hz), and Gamma (30.5-60 Hz). Exploratory Spearman correlation coefficients between the changes in power spectral amplitude from pre-treatment to post-treatment and the changes in standard polysomnographic variables were carried out.

Results: A decrease in WASO and in micro-arousals and improved sleep efficiency were associated with a decrease in higher frequency spectral amplitude in slow-wave sleep (WASO - Alpha: R=.07, p<0.04; Sigma: R=.07, p<0.02; Sleep Efficiency - Alpha: R=-.75, p<.02; Sigma: R=-.66, p<.04; Micro Arousals: Alpha: R=.82, p<.007; Beta: R=.8, p<.01). Also a decrease in sleep onset latency with CBT was associated with an increase in REM spectral amplitude (Theta: R=.85, p<.004; Alpha: R=-.87, p<.0003; Sigma: R=.7, p<.05).

Conclusions: This exploratory study suggests that polysomnographic evidence for improved sleep with CBT is associated with diminished Alpha, Sigma, and Beta Frequency activity in slow-wave sleep and greater Theta, Alpha, and Sigma EEG amplitude in REM sleep. While REM spectral amplitude findings have not been reported in conjunction with disrupted sleep, the slow-wave findings are consistent with prior reports that greater Alpha, Sigma, and Beta activity in slow-wave sleep is associated with disrupted sleep. These preliminary findings indicate that improvement in sleep disruption with CBT is associated with reduction of this higher frequency slow-wave activity.

Insomniacs with Comorbid Depression Achieved Comparable Improvement in a Cognitive Behavioral Group Treatment Program as Insomniacs without Comorbid Depression

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Stanford University

Introduction: Sleep disturbance is one of the diagnostic criteria for mood disorders and it is a common complaint in persons with depression. While it has been historically assumed that mood disorders cause changes in sleep pattern, recent studies found that persistent insomnia is a risk factor for the development of clinical depression. Existing controlled trials for cognitive behavioral intervention for insomnia have typically excluded persons with co-morbid conditions and those using hypnotics or other medications that affect sleep. This study is a part of an outcome study evaluating the efficacy of a multi-component cognitive behavioral group treatment program for insomnia & 2 in a heterogeneous sleep clinic sample. This present study focuses on comparing treatment efficacy in patients with co-morbid depression with those who were not depressed.

Methods: Participants were 62 patients (31 men, age = 48.5 ± (17.3) selected from the first consecutive 78 patients (39 men, age = 48.0 ± (16.7)) who completed the 7-session group insomnia treatment program at Stanford Sleep Disorders Clinic. Eighteen patients were excluded because they did not have baseline measure of depression. All participants were asked to complete the Beck Depression Inventory (BDI) at baseline and at the end of treatment. Thirteen persons were identified as having mild to moderate depression (D) at baseline based on a cut-off BDI score of 14 (M = 18.8 ± (8.3), range 14-26). The remaining 48 were identified as not depressed (ND; BDI = 8.3 ± (3.3), range 0-13). Sleep measures were derived from daily sleep diaries. All subjects had at least 5 days of sleep diary data for both baseline and post treatment. Because only 31 participants (4 D and 31 ND) completed a BDI at the end of treatment, there were insufficient data to evaluate whether improvement in sleep was related to improvement in depression in the D group.

Results: Selected measures, group mean ± (SD), are reported in the table below. The D group significantly differed (p = .032) from the ND group on age (40.7 ± (12.7) and 50.6 ± (17.8), respectively) and baseline BDI scores. Between group t-tests showed that the two groups were not statistically different in any of the sleep variables at baseline, except for lower sleep quality rating (p = .005) in D. Repeated-measure (baseline and post-treatment) ANCOVA, using age as covariate, showed that both groups improved significantly in terms of sleep latency (SL; p = .008) and time in bed (TIB; p = .003). There was a significant Group x Time interaction (p = .048) for sleep quality with greater improvement in the D group. All other sleep measures were improved with comparable magnitude in both groups.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>ND</td>
</tr>
<tr>
<td>TIB</td>
<td>8.4 (1.1)</td>
<td>8.1 (1.0)</td>
</tr>
<tr>
<td>TST</td>
<td>6.5 (1.7)</td>
<td>6.6 (1.2)</td>
</tr>
<tr>
<td>SL</td>
<td>48 (61)</td>
<td>31 (27)</td>
</tr>
<tr>
<td>WASO</td>
<td>84 (57)</td>
<td>73 (49)</td>
</tr>
<tr>
<td>#WASO</td>
<td>3.0 (2.6)</td>
<td>2.3 (1.6)</td>
</tr>
<tr>
<td>#Onset</td>
<td>2.8 (2.6)</td>
<td>2.4 (2.3)</td>
</tr>
<tr>
<td>#Maint</td>
<td>4.9 (1.7)</td>
<td>4.8 (2.0)</td>
</tr>
<tr>
<td>Quality</td>
<td>4.3 (2.1)</td>
<td>5.8 (1.5)</td>
</tr>
</tbody>
</table>

References:

Baseline and post-treatment values of sleep variables. #WASO = number of awakenings after sleep onset #Onset = number of sleep onset insomnia (SL ≥ 30 min) out of 7 days #Maint = number of sleep maintenance insomnia (WASO ≥ 30 min) out of 7 days Sleep quality was rated on a 10-point Likert scale, 1 = very poor, 10 = excellent.
Conclusions: The results indicate that cognitive behavioral group treatment for insomnia is effective in a tertiary clinical setting even for patients with elevated BDI scores. Both D and ND achieved comparable and statistically and clinically significant improvement on sleep at the end of treatment.

References:

101.L

The Efficacy of Cognitive Behavioral Treatment for Insomnia in a Tertiary Clinical Setting

Manber R, Loewy D, Black J, Kuo T, Palombini L, Koester U
Stanford University

Introduction: Existing studies document the efficacy of cognitive behavioral group interventions for insomnia 1. These controlled studies have typically excluded individuals with co-morbid conditions or those using hypnotics. In contrast, this is an evaluation of the efficacy of cognitive behavioral group treatment for insomnia provided to a non-select sleep clinic sample of patients referred by their sleep clinician for the treatment of psychophysiological insomnia.

Methods: Participants were 78 patients (39 men) between the ages of 16 and 83 (mean 48 ± 17 years). Sleep diaries were completed at baseline and throughout treatment. Treatment consisted of 7 group sessions. The treatment included education, relaxation, coping with stress and worry, stimulus control, sleep restriction, cognitive therapy, light exposure (when indicated), and relapse prevention. Treatment also included a gradual taper of hypnotic medication for patients who stated a wish to do so. At baseline, 41% of the participants had sleep onset insomnia, 81% had sleep maintenance insomnia, 38% had both sleep onset and sleep maintenance insomnia, and 9% did not have either. Sleep onset insomnia was defined by at least 3 nights of difficulty initiating sleep (at least 30 minutes). Sleep maintenance insomnia was defined by at least 3 nights of difficulty maintaining sleep (at least 30 minutes of wake after sleep onset). Sixty nine percent of the participants were taking prescribed hypnotic medications, 14% were taking over the counter preparations (e.g., melatonin, valerian, antihistamines), and 9% were taking antidepressants.

Results: There were significant improvements in latency to sleep onset, time awake after sleep onset, sleep efficiency, and sleep quality, but not in total sleep time (Table 1). Sleep quality was rated on a five point Likert scale anchored at 1=very poor and 10= excellent. The results were clinically significant in that 65% of the participants with sleep onset insomnia at baseline and 24% of patients with sleep maintenance insomnia at baseline no longer met criteria at the end of treatment. Overall 43% of the patients who met criteria for sleep onset insomnia or for sleep maintenance insomnia at baseline no longer met criteria for at least one of the two problems. Of the 42 patients who have used hypnotic medications at baseline, 48% have discontinued the use of medication by the end of treatment and an additional 19% had reduced the frequency or the dose of medication by at least half. There was no significant difference in rates clinical improvement between those who began group treatment on or off hypnotic medications. Those who have discontinued the use of hypnotic medication experienced significantly greater improvement in sleep.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>t (p&lt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (minutes)</td>
<td>37 ± 36</td>
<td>24 ± 19</td>
<td>3.2 (.002)</td>
</tr>
<tr>
<td>WASO (minutes)</td>
<td>79 ± 51</td>
<td>42 ± 29</td>
<td>6.9 (.0001)</td>
</tr>
<tr>
<td>TST (hours)</td>
<td>6.5 ± 1.3</td>
<td>6.6 ± 1.2</td>
<td>0.7 (ns)</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>0.80 ± 0.15</td>
<td>0.85 ± 0.15</td>
<td>4.2 (.0001)</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>5.4 ± 1.7</td>
<td>6.2 ± 1.6</td>
<td>4.5 (.0001)</td>
</tr>
</tbody>
</table>

Baseline and post treatment values of sleep parameters. Sleep quality was rated on a ten point Likert scale anchored at 1=very poor and 10= excellent.

Conclusions: The results indicated that cognitive behavioral group treatment for insomnia is effective in a tertiary clinical setting. Treatment was equally effective for those who began treatment on or off hypnotic medications.

References:

102.U

Effect of Individualized Social Activities on Sleep in Dementia

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Introduction: Sleep disturbance is a highly prevalent, disabling symptom in nursing home residents with cognitive impairment. Their nocturnal sleep is light and fragmented with frequent transient arousals and awakenings. While awake they may disturb other residents by screaming or wandering into their rooms. Frequent short daytime napping episodes interfere with daytime functioning and nighttime sleep. Nocturnal sleep disturbance and excessive daytime napping in cognitively-impaired (CI) elders may reflect a reduction in the purposive social activities that previously sustained their daytime alertness and promoted their nocturnal sleep. Further, living in under-stimulating settings may induce excessive napping in CI elders during the day with a subsequent adverse impact on the homeostatic sleep drive. Thus the specific aim of this study was to determine the effect of individualized social activities, timed to decrease daytime napping, on nocturnal sleep in CI elders.

Methods: Our research team conducted a randomized controlled trial of an individualized daytime social activity intervention, prescribed from a comprehensive assessment of individual elder’s interests, on nocturnal sleep in CI elders. Following collection of baseline actigraphy data for 5 days and nights, we randomly assigned the 139 participants to 1-2 hours of social activities daily from 9 a.m. - 5 p.m., in 15-30 minute sessions, for 21 days, to a control group. Criteria for inclusion were a diagnosis of dementia and <85% of the night asleep plus >30 minutes of daytime sleep during the five-day baseline period. For the purposes of this study, night began at the resident’s bedtime and ended when they got out of bed in the morning, or if they were bedfast, at their final morning awakening. The time of day the nursing assistants administered the activities was based on each resident’s patterns of daytime napping.
Examples of individualized activities included music, cooking, arts and crafts, and games. We collected post-test measures of sleep using actigraphy during the last 5 days and nights of the experimental or control conditions.

**Results:** Mean baseline percent nocturnal time asleep was 54.95% (sd = 20.96) while minutes of nocturnal sleep ranged from 21 to 648 minutes (mean = 353.18 minutes). Residents in the experimental group (n=71) engaged in the social activities and, when compared to the control group (n=68), their minutes of daytime sleep significantly decreased (p=.001), but their percent nocturnal time asleep did not improve (p = .93). Because of the extended time participants were confined to bed (mean = 10.64 hours), the study inclusion criteria of <85% of the night asp closely approached a number of residents who slept ≥6 hours at night. Based on the assumption that the intervention was designed to improve sleep in CI residents with nocturnal sleep disturbance, we reanalyzed the data using only participants who slept less than 50% (5 ½ or fewer hours) at night (Table 1). The results showed that those in the experimental group fell asleep 37.5 minutes faster (p = .03) and were awake 63.6 minutes less (p = .04), and their percent nocturnal time asleep increased from 26.12% to 33.45% (p = .08). The sleep of the control group was unchanged.

**Table 1**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline Days 17-21</th>
<th>Control Days 17-21</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime Sleep</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minutes slept*</td>
<td>101.95</td>
<td>103.48</td>
</tr>
<tr>
<td>% Time Asleep</td>
<td>26.12</td>
<td>33.24</td>
</tr>
<tr>
<td>Minutes asleep</td>
<td>165.66</td>
<td>211.84</td>
</tr>
<tr>
<td>Minutes awake*</td>
<td>460.09</td>
<td>422.82</td>
</tr>
<tr>
<td>Latency to sleep onset*</td>
<td>88.22</td>
<td>49.74</td>
</tr>
</tbody>
</table>

* = p < .05, p value for the interaction of group by time

**Conclusions:** These results suggest that limiting daytime napping by increasing social activities will not improve nocturnal sleep in CI elders with mildly disturbed nighttime sleep. However, for CI elders with severely disturbed sleep, limiting daytime napping by increasing social activities may significantly improve their nocturnal sleep.

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103.L

**Dose Response Effects of Behavioral Insomnia Therapy: How Many Sessions Are Enough?**

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(1) VA Medical Center, (2) Duke University Medical Center

**Introduction:** Cognitive-Behavioral Therapy (CBT) has emerged as an increasingly popular nonpharmacological insomnia treatment. Although CBT’s efficacy has been well documented,1,2 little is known about this treatment’s dose-response curve. However, the recent growth of managed care and capitation models of health care delivery have provided significant impetus to determine the lowest effective dose of treatments like CBT. This report describes findings obtained thus far in our ongoing CBT dose-response study designed to address this issue.

**Methods:** Prospective enrollees are being screened via structured interviews, medical examinations, TSH testing, and ambulatory polysomnography. Consenting individuals between the ages of 40 and 75 who meet DSM-IV criteria for Primary Insomnia and have an average wake time after sleep onset (WASO) ≥ 60 min. are being enrolled. Prior to treatment, participants complete a baseline assessment including sleep logs (2 weeks), actigraphy (one week), and multiple symptom-related questionnaires. They are then randomized to a waiting list control group or to one of four active treatment conditions in which they are provided varying numbers of therapist-guided CBT sessions. Those assigned to the two low-dose conditions are provided one (week 1 only) or two (weeks 1 and 5) sessions whereas as those assigned to the two high-dose conditions are provided four (weeks 1, 3, 5 & 7) or eight (weekly) sessions during an 8-week treatment period. During the treatment phase, all participants, including those in the waiting list group, complete logs, actigraphy, and symptom-related questionnaires each week. Subsequently, those who have received one of the active treatment doses complete 3 and 6-month follow-up assessments during which they repeat all measures taken at baseline. Those initially placed on the waiting list, are randomized to one of the active treatment conditions once they complete the 6-month period without treatment. These individuals also complete 3 and 6-month follow-ups after they complete their respective active treatment conditions.

**Results:** To date, 55 study patients have been enrolled and assigned to treatments. Of these, 40 (23 F; 17 M) patients (M_ageS = 54.5 yrs.; SD = 9.8 yrs.) have completed all study requirements for the 8 week treatment phase whereas 20 (11 F, 9 M) have completed the 3-month follow-up (FU). Among the more interesting findings obtained thus far were those derived from an analysis comparing the responses of women and men to the varying treatment doses. An analysis of covariance (ANCOVA), which adjusted for baseline differences, showed a significant dose x gender x time effect (F [16,216] = 1.99, p < .025) for our primary sleep log outcome measure, wake time after sleep onset (WASO). Figures 1a & 1b show selected time points for the trends contributing to this interaction. Women appear to show greater WASO decreases with greater numbers of therapist-guided CBT sessions. For men, however, low dose treatment seems better than high dose treatment.

**Figure 1**
Conclusions: With data available for slightly less than half of the 90 patients we hope to enroll in this protocol, we are detecting differential treatment responses of women and men to varying treatment doses. The contrasting responses noted could reflect the contrasting attitudes of women and men toward seeking interventions like behavioral insomnia therapy. The planned enhancement of our study sample should help us determine the stability of this finding.

References:

Research supported by National Institute of Mental Health - Grant # MH48187-04A1.

104.L

Treatment Regimen and Self Administration of Hypnotics

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Introduction: Previous studies have shown that insomniacs self-administer hypnotics at high rates. Given the concern that prolonged nightly use may lead to dependence, some advocate intermittent treatment. This study determined whether prior experience with different treatment regimens (i.e., instructions and capsule availability) would alter hypnotic self-administration.

Methods: Sixty-four healthy men and women with (n=32) and without (n=32) insomnia, 21-55 yrs, self administered placebo or triazolam (0.25 mg) after different prior treatment regimens. To qualify insomniacs had complaints for >1 yr, estimated nightly sleep as <6.5 hr, and had a sleep efficiency of <85% without apnea or leg movements on diagnostic NPSGs, while normals had estimated nightly sleep of >7 hr and sleep efficiency of >85%. Each subject was randomly assigned to one of three treatment regimens enforced for 11 nights: a capsule each night (HS), a capsule as needed (PRN), or a capsule every third night (INT). On 14 subsequent nights they chose to self-administer a capsule or not, placebo during one week and triazolam (0.25 mg) the other (counterbalanced in order). On all study nights, with the exception of the screening night, subjects slept at home. In the morning subjects completed a post sleep questionnaire that asked about their sleep that night and morning alertness. Logistic regression analyses were done on pairs of morning-nights using the 9 morning sleep and alertness variables to predict the next night capsule self-administration (morning 1 vs night 2, morning 2 vs night 3 etc).

Results: Insomniacs self-administered more capsules than normals and triazolam was self-administered more often than placebo. For both insomniacs and normals treatment regimen had a minimal effect on rate of capsule self-administration (see Figure). During the treatment regimen phase triazolam significantly improved self-ratings of sleep relative to placebo, improving ease of falling asleep, total sleep time, number of awakenings, speed of returning to sleep, and global quality of sleep. As seen on the table, during the choice phase, the variation in self-rated sleep and morning alertness predicted the self-administration of a capsule on the following night, regardless of whether the capsule was active drug or placebo. More difficulty concentrating, more morning sleepiness, less sleep time and longer sleep latency predicted choosing a capsule the next night.

Conclusions: As in our previous laboratory studies, insomniacs self-administered capsules at higher nightly rates than normals. But, the self-administration rates in this at-home study were lower than the previous lab studies (50% vs 60-80%). The treatment regimens had little impact on capsule self-administration. Self-rated sleep and morning alertness was predictive of capsule self-administration. Overall the data of this study are consistent with the view that hypnotic self-administration by insomniacs is therapy-seeking behavior and not drug abuse.

Research supported by National Institutes of Health (NIDA) grant No R01 DA05086 awarded to Dr. T Roehrs.

105.L

Does Cognitive-Behavioral Insomnia Therapy Really Alter Dysfunctional Beliefs About Sleep?

Edinger JD,1,2 Wohlgemuth WK,2 Radtke RA,2 Marsh GR,2 Quillian RE2
(1) VA Medical Center, (2) Duke University Medical Center

Introduction: Cognitive-behavioral therapy (CBT) has emerged as one of the most promising behavioral treatments for chronic insomnia. Presumably this treatment reduces dysfunctional beliefs which underlie and support sleep-disruptive habits. Unfortunately, research supporting this assumption has yet to be conducted. This study assessed the degree to which dysfunctional sleep-related beliefs change specifically in response to CBT, and determined whether such cognitive changes correlate with improvements in other core insomnia symptoms.

Methods: Following thorough screening, 75 (35F; 40M) consenting Primary Insomnia sufferers (M_age = 55.2 yrs; STD = 10.7 yrs.) with sleep maintenance complaints were enrolled in this double-blind, placebo-controlled, randomized clinical trial. Prior to treatment, all study patients completed a psychometrically refined 10-item version of the
Dysfunctional Beliefs and Attitudes About Sleep Scale (DBAS-R)\(^1\) as well as two weeks of baseline sleep logs, one night of home PSG and an Insomnia Symptom Questionnaire (ISQ).\(^2\) They then were randomized to CBT (n = 25), progressive relaxation training-RT (n = 25) or a quasi-desensitization placebo control-PC (n = 25). After 6 weekly, individual sessions of their respective treatments, study patients again completed all pre-treatment measures. CBT and RT patients then underwent a similar assessment (excluding PSG) 6 months later. Immediately following treatment, PC patients were debriefed and a subset accepted randomization to an additional 6 sessions of CBT (n = 9) or RT (n = 6). These patients then completed post-treatment and follow-up assessments.

Results: Pre- and post-treatment data were obtained from 70 (23 CBT, 23 RT and 24 PC) enrollees; follow-up data were obtained from 46 (24 CBT and 22 RT) enrollees. Figure 1 shows the changes in mean DBAS-R scores (averaged score across 10 items) for each treatment group across time points. Analyses of covariance adjusting for baseline DBAS-R scores and subsequent Bonferroni-corrected post-hoc tests showed that the CBT group had significantly greater pre-to-post-treatment reductions in their dysfunctional beliefs about sleep than did each of the other two treatment groups. Analyses conducted to compare baseline to follow-up changes of all CBT- and RT-treated patients showed that those who received CBT had significantly larger decreases in their DBAS-R scores than did those in the RT group. Table 1 shows Pearson correlations between changes in the DBAS-R and changes in other outcome measures at post-treatment (Post-Tx) and follow-up (F/U). These data show that the cognitive changes reflected by the DBAS-R were correlated with improvements shown on both objective and subjective measures of insomnia symptoms, particularly in the CBT group.

Figure 1

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>ISQ (PSG)</th>
<th>WASO (PSG)</th>
<th>Efficiency (PSG)</th>
<th>Quality (Logs)</th>
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</thead>
<tbody>
<tr>
<td>CBT</td>
<td>Post-Tx</td>
<td>.60**</td>
<td>.45*</td>
<td>-.45*</td>
<td>-.10</td>
</tr>
<tr>
<td></td>
<td>F/U</td>
<td>.63**</td>
<td>---</td>
<td>---</td>
<td>-.46*</td>
</tr>
<tr>
<td>RT</td>
<td>Post-Tx</td>
<td>.47*</td>
<td>-.03</td>
<td>.21</td>
<td>-.02</td>
</tr>
<tr>
<td></td>
<td>F/U</td>
<td>.68**</td>
<td>---</td>
<td>---</td>
<td>-.18</td>
</tr>
<tr>
<td>PC</td>
<td>Post-Tx</td>
<td>.03</td>
<td>.55**</td>
<td>-.55**</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>F/U</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>Post-Tx</td>
<td>.46**</td>
<td>.39**</td>
<td>-.31*</td>
<td>-.08</td>
</tr>
<tr>
<td>Sample</td>
<td>F/U</td>
<td>.62**</td>
<td>---</td>
<td>---</td>
<td>-.25</td>
</tr>
</tbody>
</table>

* = p < .05; ** = p < .01

Conclusions: These results suggest CBT is effective for reducing dysfunctional beliefs about sleep and such changes are associated with other positive outcomes in insomnia treatment. The significant correlations noted for the RT and PC groups suggest that sleep improvements may also lead to changes in such beliefs in the absence of cognitive therapy. Nonetheless, these changes appear to be an integral part of improvement in behavioral insomnia treatment.

References:
(1) Wright HR, Lack LC, Morin CM, Edinger JD. Dysfunctional Beliefs and Attitudes about Sleep Questionnaire: preliminary factor analysis. Sleep, 2000; 23 (Suppl. 2): A3 8 1.

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106.L

The Effects of Trazodone on Sleep in Patients Treated with SSRIs Antidepressants

Kaynak D,\(^1\) Pelin Z,\(^1\) Oztürk L,\(^1\) Uysal O,\(^2\) Gözükirmizi E,\(^1\) Denktas H,\(^1\) Kaynak H\(^1\)

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Introduction: SSRIs (Selective Serotonin Re-uptake Inhibitors) can fall to treat preexisting insomnia, exacerbate it or cause new insomnia while alleviating other symptoms of depression. Trazodone has been reported to be an effective hypnotic for patients with antidepressant associated insomnia. These clinical reports are limited by the lack of polysomnographic sleep recordings and the absence of a placebo control. The aim of the present study is to evaluate the effects of trazodone on subjective and objective measures of sleep in depressed insomnia patients treated with different SSRIs.

Methods: It’s a double blind placebo controlled study, investigated whether trazodone would improve sleep in depressed patients whose depressions have been treated with SSRIs but in whom SSRI-induced insomnia had subsequently developed. 12 female patients aged 20-50 years were recruited from outpatient sleep clinic. They all had the diagnosis of major depression according to the DSM 4 criteria, were currently being treated with SSRIs for at least 3 weeks and had complaint of new, exacerbated or untreated insomnia. They were given either trazodone or placebo in a double blind crossover design. Each phase lasted 7 days with a washout period of 7 days between them. PSG were repeated at 3rd, 9th and 17th, 23rd nights after treatment with either trazodone or placebo. TST, percentage of stage 1, 2, 3+4 and REM sleep, sleep latency, REM sleep latency, SEI, SCI, number of awakenings, number of stage shifts and mean duration of each cycle were evaluated as PSG parameters. Sleep was assessed by Pittsburgh Sleep Quality Index at the beginning and at the end of the study. Psychological evaluation was done by Hamilton Depression Rating Scale before baseline night and repeated after 9th and 23rd nights with treatment of trazodone or placebo. Both subjective and PSG data were analysed by Wilcoxon matched pair signed-rank test.

Results: Trazodone significantly increased TST (from 382 + 58 to 435 + 34, p <.01), percentage of stage 3+4 (from 20 + 9 to 28 + 14, p <.05), SEI (from 80 + 12 to 90 + 7 %, p <.01), SCI (from 85 + 9 to 94 + 6 %, p <.01) and significantly decreased percentage of stage 1 (from 6 + 2 to 3 + 1, p <.001), number of awakenings (from 25 + 11 to 13 + 6, p <.01), number of stage shifts (from 106 + 38 to 69 + 21, p <.05) compared to the baseline night (acute effect). The significant improvement in these sleep parameters in the first night of trazodone administration was also obtained after 7 days of treatment, compared to the baseline condition. Mean PSQI score was reduced.
from 15 + 2.5 to 5 + 1.6 at the end of study (p <.005). The initial score of HDRS was 23.4±3.7 and it was reduced to 12.2± 3 (p <.005) with placebo, to 11.5±4.5 (p <.005) with trazodone treatment. The significant decrease in HDRS with Trazodone and placebo did not differ significantly from each other.

Conclusions: Trazodone was effective in the treatment of antidepressant associated insomnia both on acute and subacute administration.

107.L

Characteristics of the Ideal Hypnotic: A Survey of Primary Care Physicians, Sleep Specialists, and People with Insomnia

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Introduction: Myriad medications are used in the treatment of insomnia. These medications include benzodiazepines, benzodiazepine receptor agonists (BZRs) such as zolpidem (Ambien) and zaleplon (Sonata), sedating antidepressants (e.g., trazodone), and over-the-counter products (e.g., diphenhydramine). Practitioners who recommend these medications to their patients often issue prescriptions on the basis of the efficacy, safety, or other key attributes of a medication. However, there are no data regarding the characteristics of hypnotic medication that practitioners and patients consider important or essential.

Methods: Three groups of eight physicians were interviewed between January 1999 and December 1999 in round table discussions in which they were asked to identify the characteristics of the ideal hypnotic. These discussions resulted in the creation of a list of 35 characteristics that were considered highly valuable attributes of hypnotic medication. This list was mailed to 530 primary care physicians, 530 sleep specialists, and 515 people with insomnia between June 2000 and December 2000. Subjects were asked to rank the importance of each characteristic on a zero - four scale, with zero being "not important" and four being "necessary." Subjects also were given a list of commonly used sleep products, and they were asked to rank these products for 11 key attributes on a one (absolutely false) to five (absolutely true) scale. Subjects returned their completed questionnaires in stamped, addressed envelopes or submitted them to the investigator by fax.

Results: Twenty-one (4%) primary care physicians, 33 (6%) sleep specialists, and 31 (6%) people with insomnia returned completed questionnaires. The 35 items were ranked by computing the sum of the responses from all subjects. The top five ranked items were: (1) Does not produce morning hangover, (2) No kidney or liver toxicity, (3) Decreases the time it takes to fall asleep, (4) No withdrawal symptoms, and (5) No intermediate or long-term adverse effects. Chi-square analyses revealed statistically significant differences between groups on 11 of 35 items. Significant differences were observed on two of the top five ranked items: Primary care physicians rank the absence of morning hangover as less important than do sleep specialists and patients (p < 0.02); and primary care physicians and sleep specialists rank decreasing the time it takes to fall asleep as more important than people with insomnia (p < 0.03). Rankings of therapeutic products indicate that zolpidem (4.9) is ranked most highly on the item "decreases the time it takes to fall asleep," followed by zaleplon (4.7), and temazepam (4.4). Trazodone (3.4) and diphenhydramine (3.7) were ranked similarly. Zaleplon (4.5) was ranked most highly on the item "does not produce morning hangover," followed closely by zolpidem (4.2). Temazepam (2.5), trazodone (2.5), and diphenhydramine (2.3) were ranked similarly low. Temazepam was ranked lowest (2.1) on the item "no withdrawal effects."

Conclusions: The results of this study indicate that there are 35 characteristics of hypnotic medication that are regarded as important by primary care physicians, sleep specialists, and patients. There are significant differences in the rankings of 11 of these items by subject group. Further, the key characteristics of hypnotic products named in this study are ranked differently by practitioners, indicating perceived differences between these products.

108.J

Response of Human Protrudor and Retractor Tongue Muscles to Negative Pressure and Chemical Stimuli

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Introduction: Genioglossus (GG) muscle activity is influenced by both mechanoreceptor and chemoreceptor input and consequently this muscle plays a significant role in maintaining or re-establishing patency of the upper airway in obstructive sleep apnea (OSA). Nevertheless, the maintenance of airway patency likely involves the interaction of other upper airway muscles including the tongue retractor muscles (hyoglossus - HG and styloglossus - SG). Recent studies in rats and humans showed that both the GG, and the HG and SG are activated simultaneously in response to hypoxia and hypercapnia (2,3). Despite these findings, the concurrent response of human protruder and retractor muscles to stimuli normally present in OSA has not been fully examined. Thus, the present investigation was designed to determine whether or not human protruder and retractor muscles are activated concomitantly in response to negative pressure and to examine the impact of hypoxia/hypercapnia and hypocapnia on these responses.

Methods: Fine wire electrodes were inserted in the GG muscle and in the area of interdigitation between the SG and HG muscles in 4 healthy seated subjects who breathed through a sealed facemask that was attached to a pneumotachometer that measured inspiratory and expiratory flow. In addition, mask pressure, end-tidal oxygen and carbon dioxide, heart rate, oxygen saturation and raw and integrated electromyographic (EMG) activity was recorded. The subjects initially completed a series of protruder and retractor isometric maneuvers in order to record a maximal response from these muscles and to ensure that the muscles were properly isolated. All EMG activity recorded was reported as a percentage of the maximal response. After completing these maneuvers, GG, HG and SG responses 100 ms after the presentation of negative pressure pulses (- 25 cmH20) were recorded during normoxia, hypoxia/hypercapnia (10 % oxygen and 7 % carbon dioxide) and hypocapnia induced by voluntary hyperventilation (3 %). The responses were reported as the difference from baseline to account for any changes in tonic activity.

Results: The average results obtained from the 4 subjects are shown in Fig. 1. These preliminary findings show that under all conditions negative pressure caused a simultaneous increase in both protruder and retractor muscle activity. Similarly, a trend, which was more evident in the retractor muscles, suggests that the response to negative pressure may be enhanced by hypoxia/hypercapnia and attenuated in response to hypocapnia. However, the variability as indicated by the error bars suggests that more studies are required before the interaction between mechanoreceptor and chemoreceptor inputs can be fully established.
Figure 1

Response of human protruder and retractor muscles to negative pressure during normoxia, hypoxia/hypercapnia and hypocapnia.

Conclusions: We conclude that the retractor muscles of the tongue are co-activated with protruder muscles in response to pulses of negative pressure. Furthermore, this response may be altered by chemoreceptor stimuli, although further studies are required before the impact of the interaction of mechanoreceptor/chemoreceptor stimuli on the retractor muscles is fully established. These results add further support to the suggestion that the retractor muscles have a role in the maintenance of airway patency in humans.

References:

Research supported by American Heart (Heritage Affiliate - 9951469T) and Lung Associations (RG-048-N) and the VIDDA foundation.

Seroiin at the Hypoglossal Motor Nucleus Augments Genioglosus Muscle Responses to CO2: Implications for Pharyngeal Motor Control in Sleep

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Introduction: A decrease in genioglossus (GG) muscle activity in sleep can predispose to airway narrowing and obstructive sleep apnea. GG activity increases in response to CO2 in wakefulness, but responses are markedly reduced in sleep (1). GG muscle is innervated by the hypoglossal motor nucleus which in turn receives a tonic excitatory drive mediated by serotonin (5-hydroxytryptamine, 5-HT) from raphe neurons (2). Raphe neurons show sleep-state dependent activity, with higher activity in wakefulness and decreased activity in sleep (3). Of importance, this latter study also showed that a subset of raphe neurons show increased activity in response to CO2 in wakefulness but that this response is reduced in sleep (3). Therefore, these observations suggest that 5-HT mechanisms at the hypoglossal motor nucleus may be importantly involved in modulating GG responses to CO2, although this has not been tested. Accordingly, this study tests the hypotheses that application of 5-HT to the hypoglossal motor nucleus will increase GG responses to CO2, and conversely, that antagonism of endogenous 5-HT will decrease GG responses to CO2.

Methods: Eleven urethane-anesthetized, tracheotomized and vagotomized rats were studied. Diaphragm and GG muscle activities, the electroencephalogram and blood pressure were recorded. Microdialysis probes (240 um diameter, 1mm tip), were placed into the hypoglossal motor nucleus for delivery of 5-HT (0, 0.001, 0.01, 0.1, 1, 10, 30 and 50 mM, n=5) or mianserin (5-HT antagonist, 0 and 0.1mM, n=6). All drugs were dissolved in artificial cerebrospinal fluid. Responses to steady-state (>5 min) inspired CO2’s of 0, 5, 7.5 and 10 % were recorded for each dose of mianserin, and responses to 0 and 5% CO2 were recorded for each dose of 5-HT. The different CO2 levels were applied in random order. Microdialysis sites were histologically confirmed with 50 um sections at the end of the experiment. GG activity was quantified as mean tonic activity (i.e., basal activity in expiration), peak inspiratory activity and phasic respiratory activity (i.e., peak inspiratory - tonic activity).

Results: Microdialysis perfusion of 5-HT into the hypoglossal motor nucleus increased tonic GG activity and phasic respiratory GG activity (p<0.002). The threshold 5-HT dose to increase GG activity was 1mM. GG responses to CO2 were also increased by 5-HT delivery to the hypoglossal motor nucleus (p<0.03). Conversely, antagonism of endogenous 5-HT with mianserin caused a decrease in phasic respiratory GG activity (p<0.01) during both air and CO2 breathing (mean decrease = 36.3 and 50.9 % respectively). Responses were specific to GG muscle as diaphragm muscle activity and respiratory rate were unaffected by 5-HT stimulation or antagonism at the hypoglossal motor nucleus (p>0.350).

Conclusions: The results suggest that 5-HT facilitates GG muscle responses to increased CO2, and conversely, that antagonism of endogenous 5-HT reduces GG responses to CO2. Since 5-HT inputs to the hypoglossal motor nucleus are sleep state dependent, with increased 5-HT inputs in wakefulness and decreased 5-HT inputs in sleep, we conclude that 5-HT mechanisms at the hypoglossal motor nucleus may be importantly involved in modulating GG responses to CO2 as a function of sleep-wake state.

References:

Research supported by the Medical Research Council of Canada and the Canada Foundation for Innovation.
Long term Facilitation During NREM Sleep in Patients with Obstructive Sleep Apnea (OSA)

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Medical Service, John F Dingell Veterans Affairs Medical Center, and the Division of Pulmonary/Critical Care Medicine, Department of Medicine, Wayne State University School of Medicine, Detroit, MI

Introduction: Repetitive stimulation of the carotid bodies is followed by persistently elevated VE lasting over a long duration (hours) This phenomenon is referred to as long-term facilitation (LTF), and has been shown (to a variable extent) in dogs, cats, rats, and goats. We have previously shown that LTF is elicited by repetitive hypoxia during sleep only in subjects who snore regularly and who have evidence of inspiratory flow limitation during sleep, LTF manifested as increased VE and amelioration of flow limitation (SLEEP, Vol. 21, No. 7, 1998). We wished to ascertain whether LTF could be activated in OSA patients by episodic hypoxia exposure.

Methods: 11 subjects with OSA (AHI ≥35±21/h) were included. Every subject had a baseline polysomnographic study, on sub optimal CPAP pressure. (Sham night)n=8). The following Measurements was taken: lowest sub optimal CPAP pressure to elicit LTF of the thoracic pump muscle activity. Following repeated apneas/hypopneas.4) CPAP did not alter the inability of OSA patients to elicit LTF of the thoracic pump muscle activity.

Results: In the recovery period there was no change in VE (99±10% of control), despite decreased UR to 58±24% of control (P<0.05).also there was no significant change in VE (P=0.23) nor UR (P=0.53) between N1(pre CPAP use )and N2(after 4 wks. of CPAP use) as shown in table below

<table>
<thead>
<tr>
<th>VE (% OF CONTROL)</th>
<th>UR (% OF CONTROL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>N2</td>
</tr>
<tr>
<td>H1 132±23</td>
<td>143±36</td>
</tr>
<tr>
<td>R 5 87±31</td>
<td>98±16</td>
</tr>
<tr>
<td>R20 100±10</td>
<td>87±10</td>
</tr>
<tr>
<td>R40 94±12</td>
<td>89±11</td>
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</tbody>
</table>

Conclusion: 1) Patients with sleep apnea do not manifest ventilatory LTF following repetitive hypoxic exposure during NREM sleep. 2) Lack of hyperpnea in the recovery period suggests that thoracic pump muscles do not demonstrate LTF 3) Reduced upper airway resistance in the recovery period indicates LTF of upper airway dilators. 4) We speculate that LTF may temporarily stabilize the upper airway in OSA patients following repeated apneas/hypopneas.4) CPAP did not alter the inability of OSA patients to elicit LTF of the thoracic pump muscle activity.

Reference:

Effect of Inspiratory Resistance on Lung Volume in Asthmatics

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(1) Sleep Health Centers at National Jewish, (2) National Jewish Medical and Research Center, (3) University of Colorado Health Sciences Center

Introduction: We have previously demonstrated that sleep is associated with reduced lung volume in asthmatics with nocturnal worsening (1). Changes in inspiratory muscle tone (2) and intrapulmonary blood pooling (3) apparently contribute to this effect of sleep, but we hypothesized that sleep associated upper airway narrowing could also play a role. To assess this, we applied progressively increasing inspiratory resistances to awake, supine asthmatic patients while measuring functional residual capacity (FRC).

Method: Subjects - 15 adults (10 asthmatic patients, 5 healthy controls). Techniques - tight-fitting face mask; esophageal balloon; horizontal body plethysmograph; surface EMG electrodes for diaphragm, intercostals, sternocleidomastoid, rectus abdominus muscles (asthmatics only). Protocol - 3 hr control and progressive inspiratory resistance studies (both supine, random order). Resistance was 9.0 cm H2O/l/s during the first hr of the resistance study, 17.0 cm H2O/l/s during the second hr, and 21.5 cm H2O/l/s during the third hr. FRC, end-expiratory esophageal pressure (EEP), and end-expiratory (“tonic”) EMG activities were measured at 15 min intervals throughout both studies.

Results: In the 10 asthmatics there occurred a progressive increase in FRC during the control study (Mean FRC’s for hr 1 = 4.28 ± 0.41 l, hr 2 = 4.53 ± 0.45 l, hr 3 = 4.83 ± 0.53 l, p < 0.05). However, there occurred a progressive load-dependent decrement in FRC with increasing inspiratory resistance (Mean FRC’s for hr 1 = 4.12 ± 0.38 l, hr 2 = 3.95 ± 0.39 l, hr 3 = 3.78 ± 0.42 l, p < 0.001). In the 5 healthy controls there occurred no significant change in FRC during either study. EEP became increasingly negatively in both asthmatics and controls during both studies. End-expiratory EMG activity of the rectus abdominus (an expiratory muscle) significantly increased after the addition of inspiratory resistance.

Conclusion: 1. The addition of progressive inspiratory resistance causes a load-dependent decrement in FRC in awake, supine asthmatics, but not in healthy controls. 2. This reduction in FRC may result from reduced pulmonary compliance and recruitment of expiratory muscles. 3. These observations suggest a mechanism by which sleep associated narrowing of the upper airway could contribute to the sleep associated decrement in FRC previously observed in asthmatics. 4. This mechanism could contribute to nocturnal asthma, as sleep apnea and snoring (conditions of marked upper airway narrowing) have been linked to the nocturnal worsening of coexistent asthma.

Reference:
Genioglossal Inspiratory Activation: Central Respiratory versus Mechanoreceptive Influences
Malhotra A,1 2 Pillar G,1 2 Fogel RB,1 2 Edwards JK,1 Stanchina M,1 2 Shea SA,1 2 White DP,1 2
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Introduction: Pharyngeal dilator muscles are involved in the maintenance of pharyngeal patency in both normal subjects and patients with obstructive sleep apnea. Both central respiratory pattern generators and local mechanisms are likely important in the control of pharyngeal dilator muscle activity. However, the interaction of these mechanisms has not been carefully assessed to date.

Methods: We studied 16 subjects who were normal based on history and physical exam. In each subject we assessed GGEMG (intramuscular electrodes, as a percent of maximum activity) and airway mechanics (choanal and epiglottic pressures plus airflow, Millar catheters plus pneumotachometer). Each subject underwent recordings during baseline (choanal and epiglottic pressures plus airflow, Millar catheters plus electrodes, as a percent of maximum activity) and airway mechanics (choanal and epiglottic pressures plus airflow, Millar catheters plus pneumotachometer). Each subject underwent recordings during baseline spontaneous breathing, increased central respiratory drive (inspiratory resistive loading; IRL), and decreased respiratory drive (hypocapnic spontaneous breathing, increased central respiratory drive (inspiratory resistive loading; IRL), and decreased respiratory drive (hypocapnic negative pressure passive ventilation in an iron lung). We then assessed the relationship between GGEMG and airway pressures and flows within breathing.

Results: In each condition negative epiglottic pressure (Pepi) was significantly correlated with GGEMG across inspiration (i.e., within breath, R>0.7 for all three conditions). Both passive ventilation and IRL led to significant decreases in the slope of the relationship between GGEMG and Pepi [slope GGEMG vs. Pepi, 1.78±0.4 (spontaneous breathing) vs 1.09±0.3 (passive) vs 0.59±0.1 (IRL), p<0.05 for both compared with spontaneous breathing], but yielded no change in the relationship (correlation) between GGEMG and Pepi (p>0.05 for both). During negative pressure ventilation, pharyngeal resistance increased (0.93±0.3 vs 1.52±0.4 cmH2O/l/sec, p=0.05). Pharyngeal resistance similarly tended to increase during IRL (1.87±0.68, p=0.06).

Figure 1

GG/Pepi Relationships in Individuals during Spontaneous, Passive and Loaded Breathing Conditions

Conclusions: We conclude that both central respiratory neuronal output and local reflex mediated activation are important in controlling the activity of pharyngeal dilator muscles and in maintaining upper airway patency.

Research supported by NIH NHLBI, AHA, Medical Research Council Canada, Sleep Medical Education Research Fdn

SLEEP, Vol. 24, Abstract Supplement 2001

GABA-A Receptor Stimulation at the Hypoglossal Motor Nucleus Potently Inhibits Genioglossus Muscle Activity Even in the Presence of Excitatory Drives Produced by Added CO2.

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Introduction: Suppression of genioglossus (GG) muscle activity in sleep, especially rapid-eye-movement (REM) sleep, predisposes to obstructive apneas but the neural mechanisms mediating such GG suppression are unknown. It is known that inhibitory neural pathways suppress postural lumar motor activity in REM sleep (1). However, although there is evidence for GABA-A receptor mediated inhibition of hypoglossal motoneurons in neonatal tissue slices in-vitro (2), it is controversial whether such inhibition of hypoglossal motor output to GG occurs in-vivo. Accordingly, this study tests the hypothesis that GABA-A receptor stimulation at the hypoglossal motor nucleus suppresses GG activity in-vivo, even in the presence of heightened GG activity produced by stimulation with added CO2.

Methods: Eight urethane-anesthetized, tracheotomized and vagotomized rats were studied. Diaphragm and GG activities, blood pressure and the electroencephalogram were recorded. Microdialysis probes were implanted into the hypoglossal nucleus with sites verified by histology. GG responses to microdialysis perfusion of muscimol (GABA-A receptor agonist: 0, 0.1, 1 & 10 uM in artificial cerebrospinal fluid) were recorded at steady-state inspired CO2’s of 0, 5 and 7.5 % in hyperoxia.

Results: GG activity significantly decreased with application of muscimol (p < 0.0001), with major suppression observed at 1 and 10 uM during air breathing, i.e., 0% CO2 (decreases = 69.1% and 90.3% p < 0.01). GG activity increased with added CO2 (p = 0.002), but activation with 5 and 7.5% CO2 was almost abolished with 1 and 10 uM muscimol (decreases = 70.1 and 93.8 % respectively, p < 0.02). Responses were specific to GG muscle as there were no changes in diaphragm muscle activation, respiratory rate or blood pressure with muscimol (p > 0.144).

Conclusions: The results show that GABA-A receptor stimulation at the hypoglossal motor nucleus potently inhibits GG activity even in the presence of excitatory drives to GG produced by added CO2. It remains to be determined whether such inhibitory GABA mechanisms are recruited in natural REM sleep to explain the major GG suppression also observed in this sleep state.

References:

Research Supported by the Medical Research Council of Canada and Canada Foundation for Innovation.
Genioglossus Versus Diaphragm Muscle Responses to Hypercapnia Across Sleep-wake States in Freely Behaving Rats


Introduction: The effects of sleep on the ventilatory and diaphragm muscle responses to hypercapnia have been well described in animals and humans. In contrast, there are little data on the genioglossus (GG) muscle responses to CO2 across all sleep-wake states. Determining the effects of sleep on GG activity, and the interaction with excitatory respiratory stimuli such as CO2, has important implications for normal respiratory control and understanding the pathogenesis of sleep-disordered breathing events such as obstructive sleep apnea. A recent study in humans showed no significant GG activation in non-rapid-eye-movement (non-REM) sleep with hypercapnia, but GG responses in REM sleep and wakefulness were not specifically studied (1). In rats, GG responses to CO2 have been measured in non-REM and REM sleep (2) but responses across a range of CO2’s and comparisons with respiratory pump (diaphragm) muscle activity were not performed. Therefore, this study aims to determine GG responses to hypercapnic stimuli across all sleep-wake states, and to compare these GG responses to the diaphragm.

Methods: Seven rats were implanted with electroencephalogram and neck muscle electrodes to record sleep-wake states, and GG and diaphragm wires for respiratory muscle recording. The rats were studied 4-13 days after surgery in a chamber flushed with 0, 1, 3, 5, 7 and 9% CO2 in random order. Measurements were made > 6 min after equilibration of ambient CO2 levels. Observing tongue protrusion in response to electrical stimulation (0.9 to 2.0 V) under anesthesia confirmed that electrodes were in GG muscle before and after the experiments.

Results: Diaphragm muscle activity and respiratory rate increased with CO2 (p < 0.001) across all sleep-wake states, with significant increases at 3-5% CO2 (p < 0.05). Phasic respiratory GG activity also increased with CO2 (p < 0.01), but significant increases occurred at 7-9% CO2 (p < 0.05), i.e., a higher threshold than the diaphragm. Moreover, GG activity was significantly reduced in non-REM and REM sleep (p < 0.04), with GG activity almost abolished in REM even with stimulation by 9% CO2 (decrease = 80.4 % vs. wakefulness).

Conclusions: These results show that REM sleep potently suppresses GG activity even with stimulation by CO2. Whether this major GG suppression in REM sleep is explained by disfacilitation and/or inhibition of hypoglossal motor output needs to be determined. Such major suppression of GG activity in REM sleep, even with significant respiratory stimulation (in this case produced by added CO2), may explain why obstructive apneas are more common in this sleep state.

References:

Research Supported by the Medical Research Council of Canada and Canada Foundation for Innovation.
The Relationship between Pharyngeal Pressure and Genioglossal Muscle Activation in Patients with OSA vs. Controls

Fogel RB,1, 2 Malhotra A,1, 2 Pillar G,1, 2 Shea SA,1, 2 Edwards JK,1 White DP1, 2
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Introduction: It has previously been observed that the activity of the pharyngeal dilator muscles, such as the genioglossus (GEMG), is substantially increased during wakefulness in patients with obstructive sleep apnea (OSA) compared to controls. This is thought to represent a neuro-muscular compensatory mechanism for an anatomically deficient upper airway. As previous work from our laboratory has demonstrated a close relationship between GEMG and epiglottic pressure both within and between breaths, we hypothesized that the slope of the GEMG/Pepi relationship would be greater in patients with OSA compared to controls across a range of epiglottic pressures.

Methods: We studied 10 normal controls and 10 patients with OSA (RDI > 20) during wakefulness. Measures included ventilation, ETCO2, airway pressure (Millar catheters) and GEMG (intramuscular electrodes, % of maximum) during basal breathing, increased pharyngeal negative pressure (passive ventilation in an iron-lung negative pressure ventilator) and decreased pharyngeal pressure generation (heliox breathing). Both peak GEMG and the slope of the GEMG/Pepi relationship within a breath were analyzed.

Results: Table 1 shows that during both air and heliox breathing, peak GEMG was higher in patients with OSA than in controls. While this finding was consistent across all conditions, it appeared to be due to both (a) an increased tonic GEMG and (b) increased epiglottic pressure generation, as the slope of the GEMG/Pepi relationship was not different between apneics and controls (Figure 1). In addition, in both groups, the slope of the GEMG/Pepi relationship was constant across conditions (ANOVA, p > 0.7).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>OSA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Phasic GEMG (basal breathing—room air)</td>
<td>5.02 ± 0.92</td>
<td>10.96 ± 1.26</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Tonic GEMG (basal breathing—room air)</td>
<td>3.28 ± 0.55</td>
<td>6.11 ± 1.03</td>
<td>&lt; .026</td>
</tr>
<tr>
<td>Peak Epiglottic Pressure (basal breathing—cm H2O)</td>
<td>1.64 ± 1.1</td>
<td>3.42 ± 0.4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Peak Phasic GEMG (basal breathing—heliox)</td>
<td>5.03 ± 0.87</td>
<td>9.89 ± 1.71</td>
<td>&lt; .041</td>
</tr>
<tr>
<td>Tonic GEMG (basal breathing—heliox)</td>
<td>2.91 ± 0.43</td>
<td>5.95 ± 1.33</td>
<td>&lt; .043</td>
</tr>
<tr>
<td>Peak Epiglottic Pressure (basal breathing—cm H2O)</td>
<td>1.26 ± 0.1</td>
<td>2.90 ± 0.3</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Conclusions: The increased GEMG seen in awake patients with OSA is not due to an increased sensitivity of the relationship between GEMG and pharyngeal negative pressure but rather to an increase in tonic GEMG as well as increased pharyngeal negative pressure.

References:

Research supported by NHLBI HL48531/HL60292/HL1024601, NSF Pickwick Fellowship
Changes in Neuroendocrine Reactivity in Chronically Sleep Restricted Rats

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Introduction: Chronically restricted sleep is an increasing problem in industrialised Western countries. Frequent sleep loss is not only common among young people but the rapid development of a 24h economy affects people at all levels of society. Controlled studies in humans and animals have shown that sleep deprivation strongly affects cognitive performance and emotionality. Whereas subjects generally recover from these effects after subsequent sleep, frequent or chronic sleep loss may induce physiological changes that are not immediately evident but ultimately may have serious consequences for health and well being (1). An activation of the hypothalamus-pituitary-adrenal (HPA) axis due to sleep deprivation has been reported in both human beings and animals (2,3). However, most studies applied short-lasting total sleep deprivation and not restriction of sleep over a longer period of time, as often occurs in human society. Furthermore, while several studies measured alterations in HPA-axis activity due to sleep deprivation, few attempts have been made to examine how sleep loss affects the reactivity of the HPA axis to subsequent new stimuli.

Methods: Adult male Sprague Dawley rats were subjected to a schedule of sleep restriction allowing them 4h of sleep per day. All animals were allowed to sleep in their home cage during the first 4h of the light phase. The other 20h of the day, animals were sleep deprived by putting them in slowly rotating wheels (n=21). Control animals were placed in non-rotating wheels (n=21). The reactivity of the HPA axis was measured after 1 and 9 days of sleep restriction by subjecting the animals to a 30-min restraint stress. Blood samples were taken and analysed for ACTH and corticosterone.

Results: Levels of ACTH and corticosterone were significantly elevated at the end of the daily 20h sleep deprivation session but returned to baseline in the course of the 4h recovery period. Thus, sleep restriction did not result in persistent alterations in basal levels of ACTH and corticosterone. After 1 day of sleep restriction, the ACTH and corticosterone response to restraint stress applied at the end of the 4h recovery period did not differ between control and sleep deprived animals. However, after 9 days of sleep restriction the ACTH response to restraint was significantly reduced whereas the corticosterone response was unaffected. In other words, the reduced ACTH response was accompanied by an increased adrenal sensitivity to ACTH.

Conclusions: These data show that chronic restriction of sleep over an extended period of time gradually results in an altered regulation of the HPA axis. Too little sleep, day after day, changes neuroendocrine reactivity and subsequent responses to stress.

References:

Results supported by NIH grants AG-11412, AG-18200, and HL-59598

Lack of Compensatory Sleep After 7-Day Continuous Cocaine Infusion

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Introduction: Cocaine and other dopamine reuptake blockers are followed by less recovery of NREM sleep than similarly potent doses of other classes of stimulants (Seidel & Edgar, 1998). It thus becomes of interest whether or not sleep loss induced by a continuous infusion of cocaine results in compensatory sleep.

Methods: Adult male Wistar rats were surgically prepared with a cranial implant that permitted chronic EEG and EMG recording, and with a miniature transmitter in the abdomen for monitoring body temperature and locomotor activity. Sleep-wake states were discriminated using SCORE, an on-line sleep-scoring system validated for rodents, which also collected the concurrent telemetry data. Animals entrained to LD 12:12 lived continuously in separate chambers. After a week of baseline recording, an Alzet minipump was implanted via dorsal incision under metaphane anesthesia. Immediately after surgery rats received gentamycin and buprenorphine and were returned to their recording chamber. Each minipump delivered either 40 mg/kg/day cocaine (N=8) or vehicle (N=6) for precisely 7 days. Daily group mean total sleep time was computed for 2 baseline days and for each day after minipump implant. From the daily total sleep means we calculated the “sleep deficit” — that is, the cumulative daily post-treatment change-from-baseline. Analogous computations were made for NREM and REM sleep and locomotor activity.

Table 1

<table>
<thead>
<tr>
<th>Infusion Day</th>
<th>cocaine ±SE</th>
<th>vehicle ±SE</th>
<th>P(t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-236 ±37</td>
<td>-26 ±32</td>
<td>0.0015</td>
</tr>
<tr>
<td>2</td>
<td>-402 ±52</td>
<td>-26 ±52</td>
<td>0.0003</td>
</tr>
<tr>
<td>3</td>
<td>-532 ±65</td>
<td>-32 ±82</td>
<td>0.0004</td>
</tr>
<tr>
<td>4</td>
<td>-641 ±80</td>
<td>-42 ±114</td>
<td>0.0008</td>
</tr>
<tr>
<td>5</td>
<td>-754 ±90</td>
<td>-76 ±145</td>
<td>0.0013</td>
</tr>
<tr>
<td>6</td>
<td>-848 ±101</td>
<td>-61 ±172</td>
<td>0.0013</td>
</tr>
<tr>
<td>7</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Post-infusion

| 8            | -913 ±122   | -47 ±193    | 0.0018   |
| 9            | -1006 ±136  | -61 ±208    | 0.0019   |
| 10           | -1056 ±152  | -87 ±231    | 0.0033   |
| 11           | -1084 ±168  | -99 ±265    | 0.0064   |
| 12           | -1062 ±177  | -127 ±301   | 0.0150   |
| 13           | -1022 ±193  | -148 ±336   | 0.0339   |

* Data incomplete due to time lost removing files from the computer.

Results: Daily average baseline time asleep (NREM+REM) for the active treatment and control groups was 705±21 and 702±20 minutes, respectively. Table 1 shows that during the week of cocaine infusion, the cumulative sleep loss steadily increased to -848±101 minutes by the end of Day 6. During withdrawal, the sleep deficit continued to increase slightly for the first 4 days, then leveled off at a sleep deficit roughly equal to 1.5 days of total sleep loss (approx -1050 minutes) without showing any sign of compensatory sleep. Data for REM sleep and NREM sleep analyzed separately showed a pattern closely similar to total sleep. Cumulative locomotor activity initially dropped for both

A73
Impact of Sleep Length on the 24-h Leptin Profile

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Introduction: Recent human studies strongly suggest that leptin plays a role in regulating hunger and satiety, enabling the maintenance of normal weight by signaling energy balance. Leptin levels show a strong diurnal rhythm with the acrophase occurring during the nocturnal period and the nadir during the morning hours. The present study investigates the effect of sleep length on the 24-h leptin profile.

Methods: The subjects were 11 healthy young male subjects (age: 22 ± 1 years; mean ± SEM), taking no medication and having regular life habits. They spent 16 nights in the Clinical Research Center (CRC) including 3 nights with bedtime from 23 to 07, 6 nights with bedtime limited to a 4-h period (01-05), and 7 nights with bedtime extended to 12 hours (21-09). Sleep was recorded during each of these 16 nights. The subjects spent also the last 60 hours of each of the 3 parts of the study entirely in the CRC. During the 60-h studies at the end of sleep curtailment and sleep extension, the subjects remained recumbent in bed and blood samples were obtained during a 24-h period for the measurement of leptin levels. Identical carbohydrate-rich meals were presented at 5-h intervals. Limitations on amount of blood volume withdrawal did not permit to obtain the 24-h leptin profile during the 8-h bedtime condition. However, 9 of the 11 subjects participated in a separate study with 8-h bedtime which was performed one year later using the same experimental procedures. The mean weight of this subset of subjects did not change significantly over this one year period (+ 0.64 kg).

Results: The figure shows the mean 24-h leptin profiles in the 4-h and in the 12-h bedtime conditions. Mean 24-h leptin levels were markedly decreased in the 4-h bedtime condition (3.6 ± 0.6 vs 4.4 ± 0.8 ng/ml; p<0.005). Consistent with the literature, leptin levels show a diurnal rhythm with a morning nadir and increasing levels throughout the daytime culminating in a nocturnal acrophase. Analysis of the temporal pattern of the 24-h leptin profiles revealed a marked decrease of both the nadir (-29%; p<0.005) and the acrophase (-37%; p<0.001) leading to a 43 % decrease in amplitude during the 4-h bedtime condition as compared to the 12-h bedtime condition (2.1 ± 0.4 vs 3.7 ± 0.7 ng/ml; p<0.01). The rate of increase of leptin levels between 09 and 21, the period during which meals were consumed, was reduced (3.5±0.2 ± 0.8±0.2 vs 4.2±0.2 ± 0.9±0.2 ng/ml/h; p<0.03) and leptin levels stopped increasing earlier in the 4-h bedtime condition (24:30 vs 1:30). Importantly, for each of these measures, the values obtained during the 8-h bedtime study were intermediate between the 4-h and the 12-h bedtime conditions. However, no statistical analysis was performed between the three study conditions since the 8-h bedtime study was conducted one year later.

Conclusions: These results demonstrate that healthy young subjects submitted to nightly sleep curtailment for less than one week present a marked decrease in leptin levels and amplitude of the rhythm. The magnitude of the decreases is similar to that seen in subjects who are underfed by approximately 1000 Kcal per day for three consecutive days (1). Since energy intake and activity levels (i.e. continuous bed rest) were kept constant in all study conditions, differences in energy balance between study conditions were minimal. These results therefore suggest that sleep loss alters the ability of leptin to accurately signal energy balance. The reduced leptin levels during the 4-h bedtime condition may therefore lead to increased food intake when food is available ad libitum. We conclude that chronic sleep loss is likely to promote weight gain.

References:

Research supported by NIH grants RO1 DK-41814, P01 AG-11412 and RR-00055.

Short Sleep: A Risk Factor for Insulin Resistance and Obesity

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Introduction: Encouraged by the view that sleep deprivation impairs vigilance but has no adverse health effects, millions of individuals voluntarily curtail their sleep to the shortest amount tolerable. A recent study of sleep restriction conducted in a clinical environment showed, however, that sleep curtailment to 4 hours in bed per night for 5 days results in a significant impairment of glucose tolerance, which could promote the development of obesity and diabetes under chronic conditions. The present study examines glucose regulation in healthy individuals who chronically curtail their sleep in their normal environment.

Methods: Twenty-seven healthy non-obese adults, 13 chronic short sleepers (mean sleep duration during weekdays < 6.5hrs) and 14 “normal” sleepers (mean sleep duration during weekdays > 7.5hrs and < 8.5 hrs), aged 23-42 years old, were studied in their normal environments. The two groups were carefully matched for gender distribution, ethnic distribution and exercise habits. The subjects were on a wrist activity monitor for 8 consecutive nights (starting on a Friday night) and during the last two nights recorded their sleep at home using the Nightcap, an ambulatory sleep recording system. The correlation between sleep duration estimated by wrist actigraphy and by Nightcap was r=0.9, p=0.0001. On the final day of the study (a Saturday), the subjects were admitted to...
Animals were sleep deprived by the disk-over-water method (2) for 15-16 or 20-21 days. Blood was sampled periodically from indwelling jugular catheters in 3 sleep-deprived and yoked pairs to corroborate a T4 decline in sleep-deprived rats. Food intake and body weight were monitored daily. Regional levels of proTRH and 5’D-II mRNA were determined by in situ hybridization and quantitative autoradiography. Serum T4 was determined by radioimmunoassay. Treatment effects were assessed by one-way ANOVA and Fisher’s PLSD test.

Results: Sleep deprivation resulted in increased food intake, loss of body weight, and hypothyroxinemia as reported in previous studies (1). Total T4 in sleep-deprived, but not yoked, rats decreased dramatically and progressively, reaching a level below the limit of assay detection by 21 days. ProTRH mRNA expression in the PVN showed a significant increase in the sleep-deprived group (P < 0.02), and a similar trend in the yoked group (P < 0.11) vs. sham control, while proTRH mRNA expression in the thalamic reticular nucleus and the lateral hypothalamus did not differ among groups, consistent with preferential upregulation of TRH biosynthesis in the hypophysoptistiotic pathway. Evaluation of individual sleep-deprived animals revealed 3-fold elevations in 3 of 4 animals studied at 20 to 21 days, but not in those studied after a shorter duration (Fig. 1). The time course and magnitude of this response is consistent with that observed in experimental hypothroidism (3). The mean 5’-DII hybridization signal tended to be modestly higher in sleep-deprived animals compared with sham and yoked animals (Fig. 2), also as observed in other clinical studies of low circulating T4 and T3.

Figure 1

![ProTRH mRNA Expression](image1)

Figure 2

![5’-DII mRNA Expression](image2)

Conclusions: Serum TSH is not increased in sleep-deprived rats despite demonstrated increases in proTRH mRNA expression in brain consistent with compensatory TRH biosynthesis. These findings indicate that the central locus of abnormal thyroid hormone regulation resulting from sleep deprivation lies after proTRH transcription, at steps up to and including release of mature TRH peptide.

References:
(2) Bergmann BM, Kushiya CA, Everson CA, Gilliland MA, Oberney-


Research support by the National Institute of Neurological Disorders and Stroke (NS 38733) and the National Heart, Lung, and Blood Institute (HL59271).

122.I

Serotonin and dopamine in the human cortex and limbic system during a 40 h sleep deprivation challenge

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(1) University of California at Los Angeles, Department of Neurology, (2) University of California at Los Angeles, Brain Research Institute, (3) University of California at Los Angeles, Department of Psychiatry and Biobehavioral Sciences, (4) University of California at Los Angeles, Division of Neurosurgery, (5) University of California at Los Angeles, Department of Neurobiology

Introduction: The diffuse neuromodulatory systems that innervate the human cortex, as well as subcortical structures, are likely to be intimately involved in human state regulation. Both the serotonergic raphe nuclei and the dopaminergic ventral tegmental area and substantia nigra have been implicated in the regulation of state, but their exclusivity and precise role are not known. We used a 40 h sleep deprivation protocol in an attempt to determine the circadian and/or homeostatic changes in the concentrations of extracellular dopamine and serotonin in the human limbic system and extra-limbic cortex using in vivo microdialysis.

Methods: To provide diagnostic guidance for surgical resection of epileptogenic tissue in the temporal lobe of patients with intractable complex-partial seizures, patients were implanted with depth electrodes targeted to clinically relevant portions of their brains. Within at least one of the depth electrodes in each patient, was a specially designed microdialysis probe (MW < 12.5 kD) used to collect dialysate. Following collection, dialysate was frozen and later assayed for dopamine and serotonin concentration using reverse phase HPLC with electrochemical detection. Reported are data collected during a 40 h sleep deprivation which was preceded and followed by a night of polysomnographically recorded sleep. Areas thus far examined include the amygdala, supplementary motor area, and parietal cortex.

Results: Dialysate concentration of dopamine recovered from our probes was typically in the 500 – 1000 pM range, while serotonin concentrations were in the range of 100 – 400 pM. As the dialysate samples collected for this analysis were collected 2 – 3 days following implantation, recovery from the initial tissue damage caused by the surgical probe implantation was stabilized. In the few patients studied thus far, we have observed no significant circadian or homeostatic influence on the concentration of dopamine or serotonin in the dialysate recovered from the amygdala, supplementary motor area, or parietal cortex. Rather, the concentration of both serotonin and dopamine both remain fairly steady throughout the enforced sleep deprivation.

Conclusions: Electroencephalographic data has described robust topographically-specific changes present during both sleep deprivation and the recovery sleep that follows. These changes are likely due to an increase in a homeostatic sleep mechanism. Our data indicate that the sleep homeostat is unlikely to be expressed via a local change in either dopaminergic or serotonergic presynaptic mechanisms in the areas thus far examined. Additionally, any independent influence of the human circadian timing system on the release patterns of dopamine or serotonin in the areas thus far examined are either small or not present. As behavioral deficits are observed in a variety of cognitive tasks during a 40 h sleep deprivation challenge, in the areas examined it is unlikely that such deficits are due to significant changes in dopaminergic or serotonergic mechanisms.

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123.I

Cry1/-/- or Cry2/-/- Mice Reveal Circadian Regulation of the Compensatory Sleep Response to Sleep Deprivation

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Introduction: Mice lacking both the Cryptochrome (Cry) 1 and 2 genes (Cry1(-/-)Cry2(-/-)) provide an opportunity to study sleep in an animal that is devoid of circadian rhythmicity without surgical ablation of suprachiasmatic nuclei. Circadian regulatory processes interact with the light/dark cycle to influence the daily timing of sleep in rodents and may influence the timing and magnitude of the compensatory sleep response (CSR; increased non-REM sleep time and non-REM delta power relative to baseline) that occurs after sleep deprivation (SD). In order to characterize the regulatory influence of the circadian clock on the CSR, we examined sleep in (Cry1(-/-)Cry2(-/-)) mice.

Methods: Male (Cry1(-/-)Cry2(-/-)) (age 240 days; weight 24 + 1 g) and wild type (+/+) (age 291 days; 25 days; weight 32 , 1 g) mice were anesthetized with isoflurane and surgically prepared for electroencephalogram (EEG) and electromyogram (EMG) recording. Following two weeks of recovery, mice were isolated in separate compartments of a sound-attenuated stainless steel recording chamber with ad libitum food and water in an LD12:12 cycle. Digitized EEG (bandpass 1-30 Hz, digitization rate 100 Hz), integrated EMG (bandpass 10-100 Hz) and wheel and drink signal (binary variables) were stored in ten second epochs, which were classified by a computerized system (SCORE). SD was implemented by introduction of novel objects into cages and by gentle tapping on the cages when mice exhibited sleep postures. Data were collected for at least 24 h before and after SD, during which time the animals were not disturbed by experimenters.

Results: In contrast to +/- mice, (Cry1(-/-)Cry2(-/-)) mice did not exhibit daily oscillations of non-REM or REM sleep, or of cortical slow wave activity (as measured by EEG delta power) when housed in LD12:12, constant light or constant dark conditions. They thus provided a means for studying homeostatic sleep regulation in the absence of overt circadian modulation. When subjected to 6 h of SD terminating at the daily onset of darkness, both genotypes exhibited increased non-REM delta power but failed to exhibit an increase in non-REM time above baseline levels (Table 1). When subjected to 6 h of SD terminating at the middle of the daily light period, +/- mice exhibited a robust compensatory sleep response, with increased non-REM time above baseline levels, while (Cry1(-/-)Cry2(-/-)) mice failed to exhibit this increase (Table 1). Both genotypes exhibited an increase in NREMdelta power at this time.
**Table 1**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wild Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM</td>
<td>44 ± 3</td>
<td>34 ± 2*</td>
</tr>
<tr>
<td>NREM</td>
<td>138 ± 11</td>
<td>148 ± 10</td>
</tr>
<tr>
<td><strong>Cry1 (-/-) Cry2 (-/-)</strong></td>
<td>19 ± 3</td>
<td>19 ± 4</td>
</tr>
</tbody>
</table>

Values are mean (± SEM); non-REM and REM sleep (minutes per 6 h period) under baseline and post-SD conditions. *p < 0.05, post-SD vs. baseline, repeated measures Student’s T with Bonferroni correction. N=6, all groups. Note that ZTs listed refer to the timing of SD, not the timing of baseline and post-SD recordings, which are from the subsequent 6 hours on baseline and post-SD days.

Conclusions: Sleep homeostasis, manifested by increased non-REM delta power after sleep deprivation, is intact in a genetic model of circadian dysregulation. By contrast, increased non-REM time after SD is genotype and time of day dependent, occurring only in +/- mice and only when SD ended at ZT6. The specificity of the latter response suggests that it is the result of a circadian influence on non-REM sleep expression or an interaction between the circadian clock and light masking in wild type mice. These observations suggest that two components of the CSR (non-REM time vs. delta power), are regulated by distinct physiological determinants. Research was supported in part by HL64243 and MH12244 (JW).

Research was supported in part by HL64243 and MH12244 (JW).

124.I

**Dynamics of Frontal Low EEG-Activity and Subjective Sleepiness under High and Low Sleep Pressure**

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**Introduction:** We have recently obtained data to indicate that the effects of sleep loss on low-frequency components (1-7 Hz) of the EEG during wakefulness and during non-REM sleep in the subsequent recovery night are most pronounced in frontal cortical areas (1,2). Furthermore, increased frontal lobe electrical activity has been reported after sleep deprivation (3). In a constant routine (CR) and nap protocol (Nap), we further investigated the effects of the sleep-wake homeostat and circadian phase on dynamics of subjective sleepiness and frontal low EEG activity during wakefulness.

**Methods:** Following two scheduled days in the laboratory during which subjects slept at their habitual bedtimes, six male and two female subjects (age 21-32 y), underwent a 40-h CR or a 40-h nap protocol in a balanced cross over design (intra-subject comparison). In the NREM protocol, subjects were scheduled to an alternating cycle of 150 min of wakefulness and 75 min of sleep. Subjective sleepiness was assessed every 30 min, and the Karolinska Drowsiness Test (KDT) was performed every hour during wakefulness. Bipolar EEGs were calculated off-line from a continuous 12-referential EEG recording. EEG data collected during the KDT were scored for artifacts and subjected to a fast Fourier transform routine.

**Results:** Subjective sleepiness exhibited a prominent circadian modulation during both the Nap- and the CR protocol. The overall build up of subjective sleepiness was not present in the Nap protocol (see figure, 2-way rANOVA; Cond x Time p < 0.0001). Sleepiness ratings were significantly lower in the Nap protocol starting at around 5 am which coincided with the core body temperature (CBT) minimum. Low EEG activity (%) in the frontal derivation increased across the CR protocol, whereas in the Nap protocol virtually no increase was observed (Cond x Time: p < 0.001). The time course of CBT did not indicate a significant difference between the two conditions (p > 0.7).

**Figure 1**

Conclusions: The present data reveal and confirm that naps, scheduled over the entire circadian cycle, attenuate the homeostatic drive for sleepiness, whereas its circadian modulation remains mostly unaffected. Changes in frontal low EEG-activity during wakefulness seem to accurately represent levels of sleep pressure in either protocol. This provides further evidence that changes in frontal low EEG-activity during wakefulness may be primarily determined by the homeostatic sleep-wake dependent process.

**References:**


Research supported by the Swiss National Science Foundation START Grant # 3130-055385.98.1 to CC.

125.A

**Uncoupling Proteins and Sleep Deprivation**

*Cirelli C, Tononi G*

The Neurosciences Institute, San Diego, CA

**Introduction:** In both humans and rats sleep deprivation (SD) produces increase in food intake and in energy expenditure. Long-term SD rats show loss of body fat, decrease in body weight, decrease in albumin/globulin ratio and “low T3 syndrome”. Humans affected by fatal familial insomnia, a prion disease characterized by an extreme insomnia for several months, also show increase in energy expenditure and decrease in body weight. The increase in energy expenditure during sleep deprivation has been attributed to a primary heat loss, although the
causes of such loss are unclear (Rechtschaffen et al., Sleep 12:68-87, 1982). Uncoupling (UCP) proteins are mitochondrial transporter proteins that create proton leaks across the inner mitochondrial membrane, thus uncoupling oxidative phosphorylation from ATP synthesis. As a result, energy is dissipated in the form of heat. In addition to the well known UCP1 that is expressed only in brown fat tissue, several other UCP proteins have recently been cloned and characterized: UCP2 is ubiquitous, UCP3 is mainly expressed in the muscle, and UCP4 and UCP5 are mainly expressed in the brain. In this study, we examined the expression of several UCP proteins in the brain, liver and muscle after spontaneous sleep and wakefulness and after periods of sleep deprivation ranging from a few hours to several days. We also examined the expression of PGC1, a recently discovered coactivator of nuclear receptors, which stimulates mitochondrial biogenesis.

Methods: Wistar WKY rats were sacrificed after 8 hours of sleep (n=6), spontaneous wakefulness (n=6), sleep deprivation by gentle handling (n=6), or after 5-14 days of long-term total sleep deprivation by the disk-over-water method (n=14). mRNA levels of UCP2 (cerebral cortex, muscle, liver), UCP3 (muscle), UCP5 (cerebral cortex) and PGC1 (cerebral cortex, muscle) were measured with ribonuclease protection assays and real time quantitative PCR.

Results: In the cerebral cortex, no changes in UCPs and PGC1 expression were found between spontaneous sleep and wakefulness. By contrast, relative to sleep, UCP2, UCP5 and PGC1 mRNA levels increased (70%, 50% and 15%, respectively) after short-term SD and slightly decreased (20%, 40% and 10%) after long-term SD. In the muscle, UCP3 mRNA levels showed a 3-fold increase relative to sleep after both short-term and long-term SD, and PGC1 mRNA levels increased (60%) in short-term SD relative to sleep, and UCP2 mRNA levels showed a 3-fold increase in long-term SD rats relative to all other groups. UCP2 mRNA levels in the liver increased 2-fold and 8-fold after short-term and long-term SD, respectively.

Conclusions: During the normal sleep-wake cycle there is no change either in the brain or in peripheral tissues in the level of mitochondrial uncoupling as measured by UCPs expression. An acute upregulation of UCPs and PGC1 occurs in the brain and muscle after a few hours of SD. By contrast, during long-term SD UCPs expression is downregulated in the brain and significantly upregulated in the muscle. The selective upregulation of UCP2 in the muscle suggests a potential mechanism by which heat loss could cause the marked increase in energy expenditure observed after long-term SD.

Supported by Neurosciences Research Foundation.

126.L

Does Behavioral Insomnia Therapy Reduce Health Care Utilization?

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Introduction: Chronic insomnia is a prevalent condition that imparts considerable medical and psychiatric morbidity to those who suffer from this form of sleep difficulty.1 As a result, it is not surprising that insomnia sufferers make significantly more visits to primary and specialty care providers than do those without such sleep problems.2 Moreover, this propensity is shown, not only by those presenting insomnia complicated by comorbid medical or psychiatric conditions, but also by those with uncomplicated, primary forms of insomnia.2 Although various, reasonably effective insomnia treatments are currently available, their effects on insomnia sufferers’ health care utilization patterns has yet to be explored. This study was conducted to assess pre-to-post-treatment changes in insomnia symptoms and health care utilization patterns shown by clinic patients who participated in an outpatient behavioral insomnia therapy program.

Methods: The current case series, clinical effectiveness study was conducted at the Fallon Clinic (Worcester, MA), a multispecialty medical group practice that provides comprehensive health care services to patients enrolled in a northeastern HMO and to other patients. Data for the current report were derived from a cohort of 76 (49 F, 27 M) patients (Mage = 52 years) who participated in the clinic’s 8-session, outpatient insomnia treatment program. All patients were referred to the program by their respective physicians, and they were treated by the first author in groups varying between 8 and 14 members in size. The treatment program consisted of a mixture of cognitive and behavioral interventions, including sleep hygiene, cognitive restructuring, stimulus control, and relaxation training. All patients were asked to maintain sleep diaries prior to and throughout treatment. Also, they were asked to complete the Brief Symptom Inventory (BSI), and the Profile of Mood States (POMS), both prior to beginning treatment, and again upon completing the program. In addition, data were obtained from the HMO computer database to tally the number of visits made by each patient to health care providers during the six months prior to and six months after participating in the treatment program.

Results: Analyses of pre- and post-treatment data uniformly suggested patients appreciated significant improvements as a function of participating in the treatment program. Available sleep diary data showed that patients’ sleep efficiencies, which averaged 73 % prior to treatment, increased significantly (t = 3.29 (54); p < .005) to an average of 86 % by the end of treatment. Patient’s average sleep time also increased significantly (t = 3.79; p < .001) from an average pre-treatment value of 5.45 hours to a post-treatment value of 6.19 hours. Furthermore, MANOVA’s and subsequent univariate ANOVA’s showed that patients reported significant (all p’s < .005) pre-to-post-treatment improvements across all BSI and POMS subscales whereas patient satisfaction data showed that 96 % of those who took part in this program reported they would be highly or extremely likely to recommend the program to a friend. In addition, the 47 patients who completed at least 6 treatment sessions showed significant (t (46) = 6.0; p < .001) pre-to-post-treatment reductions in the total number of outpatient visits they made to HMO providers. Moreover, both primary (t (46) = 2.8, p < .01) and specialty (t (46) = 8.6, p < .001) care visits showed significant pre-to-post-treatment declines. Figure 1 shows the mean changes in these health care utilization patterns.

Conclusions: These findings suggest that the behavioral insomnia treatment strategies, which have proven efficacious in previous studies of highly screened patient samples, are also clinically effective with more ‘real-world’ patients. More importantly, this study provides initial evi-

SLEEP, Vol. 24, Abstract Supplement 2001
dence that behavioral insomnia therapy reduces health care utilization among those who receive an adequate dose of this treatment. Additional controlled clinical effectiveness studies of this nature are warranted.

References:

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127.L

The Distribution of Insomnia: Age, Gender, Type, and Race

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Introduction: Epidemiological studies assessing sleep usually ask respondents to confirm or deny the presence of insomnia, but collect little additional data on sleep pattern. Thus, data on demography and detailed data on sleep characteristics are often unavailable. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diaries to study insomnia sleep patterns.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Volunteers were paid between $15 and $200 (it was more difficult to recruit older adults and they were paid more) for completing 14 sleep diaries. This paper will focus on the sleep diaries.

Results: We have analyzed data from 744 people, and we will have nearly 800 subjects by the meeting. The current sample is 48% men and 52% women, ranging from 20 to 98 years of age. The racial breakdown is 69% White, 29% African American (AA), and 2% Asian and Hispanic. We will report analyses on how insomnia varies by age, gender, type (onset, maintenance, mixed, or combined), and race. Below is a sampling of the results we will report. As suggested in Figure 1, insomnia prevalence, ignoring race, gradually rises across the life span and peaks in the decades 70 and 80, \( \chi^2 (6, N = 737) = 44.79, p < .01 \). Also in Figure 1, it can be seen that insomnia prevalence among AA about doubles that of Whites in the decades beginning 30-50, \( \chi^2 (1, N = 338) = 7.56, p < .01 \). This pattern reverses in the decades 60-80, with Whites showing a higher rate of insomnia, though this does not attain significance, \( \chi^2 (1, N = 289) = 3.34, p = .07 \). To compare types of insomnia (Figure 2), we first tested the whole sample and found that maintenance insomnia was the most common, \( \chi^2 (3, N = 262) = 11.62, p < .01 \). We then compared types within age groupings suggested by the Figure. In the younger age groups, decades beginning 20-50, there was no significant difference in prevalence of types, \( \chi^2 (3, N = 124) = 1.68, p = ns \). In decades beginning 60-80, the prevalence of maintenance insomnia about doubled any other type, \( \chi^2 (3, N = 138) = 19.74, p < .01 \).

Conclusions: Based upon self-reported sleep derived from 14 days of sleep diaries, we conclude that (1) the prevalence of insomnia significantly increases with advancing age, (2) in the middle-aged range, insomnia is significantly more prevalent among AA than Whites, and (3) the several types of insomnia do not significantly differ till about age 60, when maintenance insomnia predominates. Gender analyses will also be presented at the meeting. These data shed new light on insomnia among AA, dispute the common belief that onset insomnia predominates in the middle-aged, and confirm clinical lore that maintenance insomnia escalates in older adults.

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128.L

Predictors of Objective Sleepiness in Insomniacs and Normal Sleepers

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Introduction: Patients with insomnia typically have consistent physiological abnormalities including longer MSLT latencies despite poor nocturnal sleep. The present study examined demographic, subjective sleep, personality, performance, and mood correlates of MSLT scores in subjects reporting insomnia or normal sleep to identify non-EEG sleep predictors of objective sleepiness.

Methods: Subjects in the insomnia group (72 males, 49 females, ages 19-52) reported a sleep problem lasting at least one year with sleep latencies of at least 45 min, or wake after sleep onset (WASO) of at least 60 min, at least four nights per week. Those in the normal group (35
129.L

Daytime Versus Nighttime Self-Administration of Hypnotics


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Introduction: Previous studies have shown insomniacs self-administer hypnotics at high nightly rates. This study assessed whether insomniacs self-administration of hypnotics extends to the daytime. Further, given that studies have reported that insomniacs are “hyperaroused” during the day as reflected by elevated scores on the MSLT, the study also determined whether MSLT scores would be predictive of individual differences in daytime self-administration.

Methods: Forty-four healthy men and women with (n=22) and without (n=22) insomnia, 21-55 yrs, were studied. To qualify insomniacs had complaints for >1 yr, estimated nightly sleep of <6.5 hr, and had a sleep efficiency of <85% without apnea or leg movements, while normals had estimated nightly sleep of >7 hr and sleep efficiency of >85% on diagnostic NPSGs. They were randomized to one of two triazolam dose groups (0.125 or 0.25 mg) and their preference for placebo versus triazolam was assessed at night (2230 h) and day (0900 h). In both night and day phases of the study, subjects received triazolam or placebo in color-coded capsules on two sampling days or nights and then were required to choose their preferred capsule on 5 subsequent days or nights. The order of day and night phases and the placebo and triazolam sampling days was counterbalanced. In the night phase subjects went to bed from 2300 h to 0700 h and in the day phase were tested for level of sleepiness-alertness at 1000, 1200, 1400, and 1600 hr by the Multiple Sleep Latency Test (MSLT) and divided attention performance at 1100 and 1500 hr.

Results: At night more triazolam was chosen than placebo. The preference for triazolam was comparable for the two triazolam doses, both at night and during the day. Insomniacs did not differ in their triazolam preferences between night and day, while normals choose triazolam less frequently during the day. Insomniacs were grouped by their daytime preference. Forty percent choose triazolam on most days and 50% choose placebo on most days. Those with a daytime triazolam preference had greater average daily sleep latencies on the MSLT than those with a placebo preference, on both the screening and placebo sampling days. Despite the higher MSLT scores, the triazolam preference subgroup had poorer divided attention performance than the placebo preference subgroup. Triazolam reduced MSLT latencies to a similar level in both preference groups and impaired the divided attention performance of both subgroups.

Results: MSLT results for the normal and insomnia groups were correlated with 44 demographic, subjective sleep, personality, psychomotor performance, and mood variables. For the normal group, significant correlations were observed between MSLT and two subjective sleep variables (number of nocturnal awakenings and amount of wake time during the night) and number of lines reviewed in a proofreading task (see Table). For the insomnia group, MSLT values were significantly correlated with the POMS Tension/Anxiety Scale, subjective nocturnal sleep latency, habitual level of caffeine consumption, and habitual tobacco use. Stepwise regression reinforced these findings. For normal sleepers, only number of nocturnal awakenings remained significantly related to MSLT with a multiple correlation of $r = .41$. For the insomnia group, MSLT was best predicted by a combination of caffeine use, cigarettes smoked, POMS Tension/Anxiety and a subjective sleepiness scale resulting in a multiple correlation of $r = .41$.

Conclusions: To the extent that the MSLT is a ‘pure’ measure of sleepiness, it would not be related to any non-sleep variable following normal nights of sleep. The current results from normal sleepers broadly support that conclusion except for the fact that the correlation between the subjective wake variables and MSLT was positive - more frequent awakenings and wake time during the night were associated with longer MSLT values on the following day. A different pattern was observed in the insomnia group where caffeine use, tobacco use and tension/anxiety were associated with MSLT latencies. These correlations suggest either increased sensitivity to stimulants (i.e., increasing already elevated arousal), increased use of stimulants, or both. In the current data, the insomnia group smoked significantly more than normals but did not report excessive caffeine intake, substance abuse, clinical depression, or other psychiatric illness, or if laboratory recordings indicated sleep apnea, periodic leg movements, or drug-activated EEGs. Subjects were recorded polysomnographically for two nights and spent the intervening day participating in MSLT, mood, and performance tests. Metabolic rate was measured during the day. For the reported correlation and regression analyses, the mean value for the MSLT across the day was used.

Results: MSLT results for the normal and insomnia groups were correlated with 44 demographic, subjective sleep, personality, psychomotor performance, and mood variables. For the normal group, significant correlations were observed between MSLT and two subjective sleep variables (number of nocturnal awakenings and amount of wake time during the night) and number of lines reviewed in a proofreading task (see Table). For the insomnia group, MSLT values were significantly correlated with the POMS Tension/Anxiety Scale, subjective nocturnal sleep latency, habitual level of caffeine consumption, and habitual tobacco use. Stepwise regression reinforced these findings. For normal sleepers, only number of nocturnal awakenings remained significantly related to MSLT with a multiple correlation of $r = .41$. For the insomnia group, MSLT was best predicted by a combination of caffeine use, cigarettes smoked, POMS Tension/Anxiety and a subjective sleepiness scale resulting in a multiple correlation of $r = .41$.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insomnia</th>
<th>Normal</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subj. awakenings</td>
<td>.06</td>
<td>.32*</td>
<td>.02</td>
</tr>
<tr>
<td>Subj. time awake</td>
<td>.15</td>
<td>.30*</td>
<td>.05</td>
</tr>
<tr>
<td>Subj. latency</td>
<td>.20</td>
<td>.04</td>
<td>.05</td>
</tr>
<tr>
<td>Proofreading</td>
<td>.11</td>
<td>.28*</td>
<td>.06</td>
</tr>
<tr>
<td>POMS tension</td>
<td>.20</td>
<td>.21</td>
<td>.05</td>
</tr>
<tr>
<td>Caffeine</td>
<td>-.23</td>
<td>.00</td>
<td>.02</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>.20</td>
<td>.03</td>
<td>.05</td>
</tr>
</tbody>
</table>

Conclusions: To the extent that the MSLT is a ‘pure’ measure of sleepiness, it would not be related to any non-sleep variable following normal nights of sleep. The current results from normal sleepers broadly support that conclusion except for the fact that the correlation between the subjective wake variables and MSLT was positive - more frequent awakenings and wake time during the night were associated with longer MSLT values on the following day. A different pattern was observed in the insomnia group where caffeine use, tobacco use and tension/anxiety were associated with MSLT latencies. These correlations suggest either increased sensitivity to stimulants (i.e., increasing already elevated arousal), increased use of stimulants, or both. In the current data, the insomnia group smoked significantly more than normals but caffeine use did not differ between groups. Overall, the results suggest that non-sleep sources of arousal consistently influence sleep tendency in subjects reporting insomnia.

Supported by the Dayton Department of Veterans Affairs Medical Center, Wright State University School of Medicine, the National Institute for Occupational Safety and Health, and the Sleep-Wake Disorders Research Institute
Conclusions: This study shows that a majority of insomniacs do not self-administer hypnotics during the daytime. The minority of insomniacs who do self-administer hypnotics during the day are physiologically aroused and triazolam reduces their daytime arousal suggesting that their drug self-administration is therapy seeking behavior and not drug abuse.

Research supported by National Institutes of Health (NIDA) grant No R01 DA05086 awarded to Dr. T Roehrs.

130.R

Quantitative Evaluation of Autonomic Heart Rate Control During Sleep Stages Using Poincare Plots

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Institute Psychophysiology and Rehabilitation

Introduction: Autonomic heart rate (HR) control might be evaluated using HR frequency and HR variability analysis. Pattern of HR variability, as a Poincare plot of RR intervals, have been shown as being visually informative. The goal was an evaluation of HR variability by means of quantification of Poincare plots during all night sleep, and individual sleep stages for healthy subjects and coronary artery disease (CAD) patients.

Methods: One hundred ninety three subjects (32 healthy Ss and 161 CAD pts between of 20 and 79 yr. (average 49.0±0.89 yr.) underwent convenient polysomnography using Alice-4 system. HR variability was analyzed using Poincare plots of RR intervals (RRi+1, ordinate; RRi, abscise) that have been constructed from all night and from individual sleep stages records. Quantification of Poincare plot was performed by calculating: 1) general HR variability as the plot of all square (P, ms2); 2) maximal HR response reflected by diagonal of square (dRRr = RRmax-RRmin); 3) maximal HR variability (dRRt), measured as maximal width between of tangential lines of square, parallel to diagonal. Maximal HR variability might be seen as reflecting tonic HR control level, while maximal HR response - as reflex one. Comparison of the results has been performed with the results obtained from HR power spectrum analysis from the same records of RR intervals.

Results: Stages 1 and 2, as compared with stages 3 and 4, demonstrated low average and minimal HR frequency during sleep followed by the highest its level at maximal HR (RRmin). Due to this reflex and tonic HR control reflecting HR variability were becoming high. Stages 3 and 4 were characterized by the low level of both, tonic and reflex HR control, the latter because of low maximal HR frequency level. Reflex HR control lowering was more expressed than tonic one. REM sleep was characterized by increased HR frequency, especially at its maximal level. Due to that reflex control was much higher than at stages 3 and 4. Despite of significantly different baseline level of HR variability and HR frequency at wakefulness, HR parameters demonstrated principally similar changes during transition from wakefulness through all sleep stages in healthy Ss and CAD pts: increased reflex (dRRt = 569 vs. 984 for healthy Ss and dRRr = 367 vs. 600 ms for CAD pts) and tonic HR control (dRRt = 322 vs. 512 and 137 vs. 196 ms, correspondingly) during stages 1 and 2 with opposite changes at stages 3 and 4 (dRRr = 983 vs. 696 ms for healthy Ss and dRRr = 600 vs. 384 for CAD pts). Thus the pattern of Poincare plot was more related to sleep stage, while HR variability - to the functional state of investigated person. The differences of HR control, reflected by means of Poincare plots, were principally similar to those, demonstrated by HR power spectrum. Poincare plot was less precise in evaluation of sympathetic-parasympathetic components of tonic autonomic HR control, as compared to HR power spectrum analysis, although better for evaluation of reflex HR control.

Table 1

<table>
<thead>
<tr>
<th>W Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRt</td>
<td>1015</td>
<td>1039</td>
<td>1062</td>
<td>1066</td>
</tr>
<tr>
<td>RRh</td>
<td>±11.1</td>
<td>±10.2</td>
<td>±10.7*</td>
<td>±10.8*</td>
</tr>
<tr>
<td>dRRr</td>
<td>46.2</td>
<td>68.4</td>
<td>68.3</td>
<td>66.7</td>
</tr>
<tr>
<td>ms</td>
<td>±1.6</td>
<td>±2.1*</td>
<td>±2.4*</td>
<td>±2.4*</td>
</tr>
<tr>
<td>RRmax</td>
<td>863</td>
<td>824</td>
<td>821</td>
<td>881</td>
</tr>
<tr>
<td>ms</td>
<td>±10.6</td>
<td>±8.9*</td>
<td>±8.8*</td>
<td>±9.0*</td>
</tr>
<tr>
<td>RRmin</td>
<td>1145</td>
<td>1240</td>
<td>1251</td>
<td>1261</td>
</tr>
<tr>
<td>ms</td>
<td>±130±13.6*</td>
<td>±15.3*</td>
<td>±15.0*</td>
<td>±14.6*</td>
</tr>
<tr>
<td>ΔRRt</td>
<td>399</td>
<td>595</td>
<td>663</td>
<td>521</td>
</tr>
<tr>
<td>ms</td>
<td>±13.0</td>
<td>±16.3*</td>
<td>±18.6*</td>
<td>±17.6*</td>
</tr>
<tr>
<td>ΔRRh</td>
<td>167</td>
<td>205</td>
<td>248</td>
<td>223</td>
</tr>
<tr>
<td>ms</td>
<td>±8.2</td>
<td>±9.2*</td>
<td>±11.9*</td>
<td>±10.5*</td>
</tr>
<tr>
<td>P</td>
<td>58030</td>
<td>96137</td>
<td>131613</td>
<td>97337</td>
</tr>
</tbody>
</table>
| ms²       | ±4614±56750*| ±9191*| ±74437*| ±26203*| ±86664*| * p<0.05 from W before sleep;  p<0.05 from previous sleep stage

Conclusions: Autonomic HR control evaluation using Poincare plot and its quantification might be seen as informative method for an analysis of HR control during sleep, particularly for practical medicine.

131.R

REM-related Peripheral Vasoconstriction - Association with Rapid Eye Movement Density

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Introduction: We have previously demonstrated that sympathetic activation in the form of peripheral vasoconstriction is a prominent feature of REM sleep both in normal young adults and in sleep apnea patients. In the present study, using the same non-invasive technique of measuring peripheral arterial tone (PAT) in the finger, we investigated the relationship between the degree of REM-related peripheral vasoconstriction and rapid eye movement density during REM sleep.

Methods: Nine healthy subjects, aged 23-26 participated in this study. Peripheral arterial tone was measured as has been previously described (1). Recordings of the subjects’ PAT signal were conducted simultaneously with conventional polysomnographic measures to determine sleep stages. In each bin the EOG signal was coded for eye movement density on a scale from 0-5, where a score of 0 indicated no movements, scores 1-2 indicated one to four eye movements, scores 3-4 indicated five to ten eye movements, and a score of 5 was equivalent to a minute filled with dense ocular activity. The mean peak-to-peak amplitude (MPA) of the PAT signal was then determined for each bin. The relationship between the EOG score and PAT amplitude was analysed by regression analysis. This was done separately for the first, second, third and fourth REM periods of the night, as well as for all REM periods combined.

Results: A total of 37 REM periods were analyzed with an average of 4.11 (SD=0.78) REM per night. Regression analysis revealed an inverse
relationship between EOG score and PAT amplitude in each REM period during the night. This association strengthened as the night progressed. Whereas the first two REM periods showed only a nonsignificant tendency toward inverse relationship, REM periods 3 and 4 & 5 (combined) showed a significant relationship (p<.005). Analysis across all REM periods confirmed these results by showing a highly significant inverse association between the degree of peripheral vasoconstriction and EOG score (F=11.9, p=.0007, Figure 1). On the average, the change from a “quiescent” minute without eye movement to a minute scored as 5, was a decrease of 50-60% in PAT amplitude.

Conclusions: The present results and previous findings demonstrating blood pressure surges during REM sleep suggest that the sympathetic activation during REM sleep is phasic in nature. This endogenous phasic activation is increased across the night, reaching a peak in the early morning hours. Future research should determine if the early morning peak in REM-related sympathetic activation is related to the early morning circadian peak in cardiovascular events.

References:
(2) Muller JE, Toffler GH, Willich SN, Stone PH: Circadian variation of heart rate and heart rate variability (HRV) during REM sleep, these methods have severe limitations. Obstructive sleep apnea is characterized by strong variations in heart rate, called “cyclical variation of heart rate”. We applied a new method of HRV analysis (DFA). We used constant, linear, and higher order trend removal and compared the results (1). Already linear trend removing gave satisfactory results. The method was applied to inter beat time series obtained from sleep recordings of 12 healthy subjects and 20 patients with moderate sleep apnea. The ECG was digitized at 200 Hz. Only patients with moderate sleep apnea were selected, because patients with severe sleep apnea do not have enough slow-wave sleep. The analysis of HRV in wakefulness, light sleep (stage 1 + 2), deep sleep (stage 3 + 4) and REM sleep were compared.

Results: Correlations gained by DFA showed significant differences between sleep stages. In slow-wave sleep, for time lags below 10 heart beats, correlations were strongest. Using longer time lags than 10 sec, correlations became smaller, indicating a more “random” behavior. In light sleep a similar effect was found, but a loss of correlations occurred at 30 seconds. In REM sleep, correlations remained large, even for longer time lags, at least up to 500 sec. Correlations for long time lags are also large for wakefulness. This indicates the presence of heart rate regulating influences during REM sleep, similar to wakefulness and very different to slow-wave sleep. When comparing healthy subjects with sleep apnea patients, we found that the modulating influence of sleep stages on heart rate variability remained very strong even though obstructive sleep apnea caused additional variations. Differences between sleep stages were larger than differences between normals and sleep apnea subjects.

Conclusions: Our analysis is able to distinguish light sleep, deep sleep and REM sleep based on HRV. REM sleep HRV appears to be similar to wakefulness. Slow wave sleep has a more random heart rate regulation. In addition our results suggest that the typical pattern of cyclical variation of heart rate in patients with obstructive sleep apnea does not affect the underlying sleep stage-dependent heart rate regulation when compared to sleep in normals. The new method of DFA may allow to detect the different regulation of heart rate specific for sleep stages.

References:

133.R

Alteration of Digital Pulse Amplitude Reflects Alpha-adrenoceptor Mediated Constriction of the Digital Vascular Bed

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Introduction: Autonomic activity is readily modified during transition between sleep stages, changes in arousal and after activation of physiological stressors such as hypoxemia and blood pressure elevation which occur during sleep disordered breathing. The present study investigated the utility of the finger pulse wave amplitude (PWA) assessed by means of a fingerplethysmographic device and a PAT-signal device (Ilamar, Caesarea, Israel) to detect autonomic activation. Moreover, modulators of the PWA response were determined after simultaneous assessment of a muscle vascular bed flow response (venous occlusion plethysmography).

Methods: A variety of autonomic stress tests were used to induce autonomic activation. Norepinephrine (alpha-receptor agonist), phentolamine (alpha-receptor antagonist) and isoproterenol (beta 2-agonist) were administered in incrementing dosages by intraarterial infusion. Studies were undertaken in 5 healthy volunteers (age 34.0 (3.3) years, BMI 25.8 (3.1)) and in 10 patients with sleep apnea (age 46.7 (5.1)}
Results: During awake rest, norepinephrine (7.4 – 1421 pmol/dl/min) dose-dependently reduced PWA (peak reduction approx. 90%) in the digital vascular bed. Similar, but less pronounced, vasoconstriction was seen in the forearm vasculature. The constrictive response in both vascular beds after norepinephrine was significantly attenuated by a background infusion with the phentolamine (2 microg/dl/min). Isoproterenol (1-15 ng/dl/min) induced vasodilatation in the forearm but not in the digital vascular bed (factor “methods” p <0.001). Three different autonomic stress tests (Mueller, Valsalva and the Cold Pressor Test) reduced PWA by 40.4 (11.9) to 61.3 (4.8) %, Sleep disordered breathing induced an arousal-related (end of apnea) attenuation of PWA which was attenuated by concomitant phentolamine infusion. Moreover, phenomena like periodic limb movements and sudden arousal from sleep were all associated with considerable attenuation of the PWA.

Conclusions: The digital vascular bed is characterized by a dominant and tonic alpha-receptor mediated control. This selectivity permits a continuous, accurate identification of arousal mediated autonomic activation by the PWA signal. The modulating influence of other vascular control mechanisms in this vascular bed remains to be determined.

Supported by the Swedish Heart and Lung Foundation and the Gothenburg University.

134.D

Deficiencies of Dream Recall: I. Results from Real Dreams

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Introduction: Although few dreams are remembered it is assumed that recall of a whole dream, especially following REMS awakenings, is accurate. Yet memory for stories1 and waking experiences2 is imperfect and subject to change with the passage of time. Since dreams are typically story-like experiences it is possible that their recall is likewise imperfect and also subject to change with the passage of time.

Methods: Seventeen subjects (14 were usable) were each asked to recall a dream into a tape recorder following a REMS awakening then again the next morning, one week later, and one month later. Each transcribed recall was divided into distinct “storyboard” components (91.0 % scorer agreement). Pooling the components from all recalls and eliminating redundancies, yielded a composite dream. (Components in the composite may not have been in the original dream and components in the original dream may be missing from the composite, yet we contend this composite is the closest obtainable approximation to the original.)

Results: Percentages were used when exploring similarities and differences between recalls to diminish the effect of report lengths. Comparison data were subjected to a one-way (time of recall) repeated measures ANOVA followed by 1) Tukey’s HSD test or, when the ANOVA was not significant or not the appropriate test, 2) single sample T-test collapsed across time. Significance (p<.05) indicated by *. The gist of each dream was perfectly recalled every time. The mean recall was 49.9% (± one standard deviation of 11.2%) of the composite (F(3, 39)=2.61; t=-16.205* compared to perfect recall). The REM awakening recalls contained a mean of 55.6% (± 15.3%) of the composite components (t=0.494* compared to perfect recall). A mean of 43.5% (± 24.1%) of the REM awakening recall components were retained in each subsequent recall (F(2,26)=1.532; t=-8.438* compared to perfect recall). (However, this is not a measure of identical components retained throughout the entire month. In many cases when something in the REMS awakening report was forgotten in a later report something else was remembered and vice versa.) The mean composite components not reported in the REMS awakening recall but added in subsequent recalls was 22.2% (± 9.7%) (F(2, 26)=1.270; t=8.304* compared to nothing being added). A mean of 53.7% (± 36.5%) of the added components were retained in subsequent recalls (F(1, 10)=0.189; t=-4.009* compared to perfect retention and t=4.644* compared to no retention).

Conclusions: These results show it is unlikely that most components of dreams are well recalled, even following REMS awakenings. Further, there are also significant changes in the recall of a dream with the passage of time. Finally there is a great deal of individual difference in overall recall accuracy of dream recall.

References:

135.D

The Effect of Ethnicity on the Relationship Between Nightmares and Stress

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Introduction: The cause of nightmares in adults remains unclear. However, previous research suggests that stress almost certainly plays a key role.1 Thus, perhaps the presence of strong emotions during dreaming helps resolve or process the emotional turmoil associated with stressful events. In addition to the general ability of ethnicity to influence sleep-related variables,2 it has also been shown that Asian-Americans have significantly less social support than European-Americans.3 The purpose of this study was to examine the possibility that nightmares serve as a coping mechanism for stress by correlating nightmare intensity with waking coping strategies and examine the possibility that ethnicity mediates this relationship by means of social support.

Methods: A group of 412 introductory psychology students completed three scales among others in a survey packet for course credit. These were the Nightmare Distress Questionnaire (nightmare intensity), the Interpersonal Support Evaluation List (social support) and the Ways of Coping Questionnaire (coping strategies). The WOCQ is a 48-item survey that asks the respondent to describe a specific stressful event and rate how much they used a particular strategy to cope with the event. The items are broken down into eight different coping strategies as followed: confrontive, distancing, self-controlling, seeking social support, accepting responsibility, escape/avoidance, planful problem solving and positive reappraisal. After an initial evaluation of the entire sample, identical correlations were conducted for European-Americans (n = 112) and Asian-Americans only (n = 140). Tukey post-hoc tests were used to evaluate the differences in social support between ethnic groups and all correlations reported are two-tailed with p <.05.

Results: Disregarding ethnicity, nightmare intensity correlated positively with six of the eight subscales of the WOCQ (see Table 1 for all correlations). As has been previously found, Asian-American students had significantly lower levels of perceived social support when compared with European-Americans (p <.05). This was reflected in the differences between the same set of correlations using European-Americans and Asian-Americans only. While only two subscales were significant for
European-Americans, six were significant for Asian-Americans. Moreover, the single subscale that was only significant for European-Americans was Self-controlling. This particular finding fits very well with the idea that the positive correlation of nightmares with coping strategies indicates a continuity of coping throughout the sleep-wake cycle because this coping strategy might still be useful despite high levels of social support.

Table 1

<table>
<thead>
<tr>
<th>Nightmare Intensity and the Ways of Coping Questionnaire subscales (correlations and sample sizes)</th>
<th>Entire Sample</th>
<th>European-Americans</th>
<th>Asian-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confomitive</td>
<td>.13*</td>
<td>.80</td>
<td>.24*</td>
</tr>
<tr>
<td>.372</td>
<td>.102</td>
<td>.126</td>
<td></td>
</tr>
<tr>
<td>Distancing</td>
<td>.08</td>
<td>.16</td>
<td>.12</td>
</tr>
<tr>
<td>.376</td>
<td>.104</td>
<td>.128</td>
<td></td>
</tr>
<tr>
<td>Self-controlling</td>
<td>.09</td>
<td>.20*</td>
<td>.09</td>
</tr>
<tr>
<td>.376</td>
<td>.104</td>
<td>.128</td>
<td></td>
</tr>
<tr>
<td>Seeking Social Support</td>
<td>.11*</td>
<td>.12</td>
<td>.19*</td>
</tr>
<tr>
<td>.376</td>
<td>.104</td>
<td>.128</td>
<td></td>
</tr>
<tr>
<td>Accepting Responsibility</td>
<td>.19*</td>
<td>.25*</td>
<td>.27*</td>
</tr>
<tr>
<td>.373</td>
<td>.104</td>
<td>.128</td>
<td></td>
</tr>
<tr>
<td>Escape/Avoidance</td>
<td>.21*</td>
<td>.10</td>
<td>.33*</td>
</tr>
<tr>
<td>.371</td>
<td>.101</td>
<td>.127</td>
<td></td>
</tr>
<tr>
<td>Planned Problem Solving</td>
<td>.12*</td>
<td>.07</td>
<td>.10*</td>
</tr>
<tr>
<td>.373</td>
<td>.104</td>
<td>.126</td>
<td></td>
</tr>
<tr>
<td>Positive Reappraisal</td>
<td>.14*</td>
<td>.07</td>
<td>.23*</td>
</tr>
<tr>
<td>.375</td>
<td>.104</td>
<td>.127</td>
<td></td>
</tr>
</tbody>
</table>

*p < .05 (two-tailed)

Conclusions: The propensity for nightmares to correlate with coping strategies mainly in situations where social support is low provides evidence for not only the meaningful role of nightmares in the response to stress, but in the process of overcoming stress. In addition, these data indicate the need for a clinician to consider ethnicity when presented with a patient who is complaining of nightmares.

References:

(1) Tan VL & Hicks RA: Type A-B behavior and nightmare types among college students. Perceptual and Motor Skills, 1995; 81, 15-19.


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136.D

Remote Memories in Dreams: Are Certain Components Privileged?

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Introduction: Grenier et al. (2000) examined temporal references in REM dreams of young and older women and found, for both groups, a very high proportion of elements (characters, objects, settings, events, activities) that refer to recent experiences (i.e., day residues). As for the older women, they observed a resurgence of elements that refer to more remote experiences that took place over 40 to 60 years ago (corresponding to adolescence and early adulthood). It was discussed that this cubic-like distribution of temporal references is consistent with the temporal distribution of autobiographical memories proposed by Rubin, Wetzler & Nebes (1985), thus supporting their hypothesis of continuity between the retrieval of mnemonic elements in dreaming and in autobiographical memory. In this study, we further explored the remotesness of elements identified in dreams in order to determine if any given element (characters, objects, settings, events, activities) was particularly more remote than others. Based on Rubin, Rahal & Poon’s (1998) study that memories for events and activities that took place in adolescence and early adulthood are most often recalled, we hypothesised that amongst the elements identified in dreams, events and activities would be the ones most often relating to more remote life experiences.

Methods: Twenty-eight undergraduate women (M age = 22) and thirty retired teachers/nurses (M age = 65) each spent one night in the laboratory and were awakened in all REM periods. During the week prior to the night in the laboratory, all participants kept a home dream diary. In the morning, participants were asked to identify temporal references for five dream elements (characters, objects, settings, events, activities). Only temporal references that were reportedly non accessed by conscious awareness since time of original experience were categorized using a 16 category temporal reference scale ranging from “last evening” to “60 to 69 yrs ago”.

Results: For REM dreams, the young participants identified 661 temporal references (out of 80 dreams) and the older participants 474 (out of 68 dreams). For home dreams, young women identified 743 temporal references (out of 82 dreams) and the older women 970 (out of 91 dreams). Two independent 2 (age groups) x 5 (elements) ANOVAs were conducted using most remote elements in each categories (characters, objects, settings, events, activities). For laboratory dreams, we observed a main effect of age (F(1,33)=15.50, p<0.01) and a main effect of elements (F(4, 132)=3.61, p<0.01). Elements combined, older participants identified significantly more remote references than the young. Age groups combined, the order from the most to the least remote element is activities (M=8.48), events (M=7.78), objects (M=7.69), characters (M=7.13) and settings (M=6.2). Post-hoc analyses revealed that activities were significantly more remote than settings. As for home dreams, we observed a main effect of age group (F(1,48)=15.72, p<0.01) and a main effect of elements (F(4, 192)=5.48, p<0.01). Elements combined, older women identified significantly more remote references than young. Age groups combined, the order from the most to the least remote element is activities (M=9.48), objects (M=8.69), events (M=8.25), settings (M=7.62) and characters (M=7.56). Post-hoc analyses revealed that activities are significantly more remote than settings (p<0.01) and characters (p<0.01).

Conclusions: In REM and home dreams, activities seemed to be the element most often referring to a more remote past while events were the second element most often referring to a more remote past in REM dreams only. In light of Rubin, Rahal & Poon’s (1998) comments, we suggest that in terms of remoteness, memories for activities seem to be most often retrieved by dream mechanisms. This finding supports the notion of continuity between waking and dreaming cognitive processes. The possibility that the classification of element (i.e., characters, objects, settings, events, activities) may be a key variable influencing the retrieval of mnemonic elements by dream production mechanisms needs further investigation.

References:


Research supported by National Science and Engineering Research Council of Canada.
The Immediate Effects of Expressively Writing about Dreams Following Loss or Trauma

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Introduction: Expressive writing has been used to alleviate distress associated with personal crises\(^1\). The purpose of this study was to assess the immediate effects of expressively writing about dreams related to loss or trauma.

Methods: Fifty university students who reported a significant and recent loss or trauma recorded a related impactful dream. They wrote about their experience before, during, and after that dream in one of three ways: Objective Narrative (writing as an objective observer); Emotional Narrative (writing with full attention to related feelings); or Expressive Narrative (writing while focusing on feelings that emerged during writing). Then, participants completed a questionnaire assessing (a) writing-induced changes in mood, specifically, agitated anxiety (anger, anxiety, vitality) and depression (sadness, fatigue);\(^2\) (b) perceived responsibility for events related to their loss or trauma; and (c) their outlook on the future.

Results: Expressively writing about impactful dream experiences accented the extent to which agitated anxiety was associated with the acceptance of blame. A Writing Condition by Agitated Anxiety interaction (Wilk’s Lambda=2.146; df=6,84; p<.056, eta squared=.133) indicated condition-specific levels of association between agitated anxiety and acceptance of blame. The correlations between agitated anxiety and acceptance of blame were: Objective Narrative, .363; Emotional Narrative, .323; Expressive Narrative, .567. Similarly, expressively writing accentuated the extent to which agitated anxiety was associated with self-perceived causal responsibility. A Writing Condition by Agitated Anxiety interaction (Wilk’s Lambda=3.845; df=6,84; p<.002, eta squared=.215) indicated condition-specific levels of association between agitated anxiety and causal responsibility. The correlations between responsibility and agitated anxiety were: Objective Narrative, .290; Emotional Narrative, .341; Expressive Narrative, .640. In contrast, independently of writing condition, depression predicted participants’ thoughts about counterfactual choices that “might have” alleviated distress associated with their loss or trauma (Wilk’s Lambda=4.266; df=3,42; p=.010, eta squared=.234). The correlation between depression and counterfactual thought was .440. Also, independently of writing condition, depression predicted responses reflective of future-oriented purposiveness (Wilk’s Lambda=5.092; df=3,42; p<.004, eta squared=.267). The correlation between depression and future-oriented purposiveness was -.457. Thus, depression predicted thinking about the future, specifically, about the loss of purposiveness.

Conclusions: Since agitated anxiety was associated with trauma (r = .478, p<.001), whereas depression while writing was characteristic of both loss and trauma, this study suggests that writing about dreams, especially in the exploratory style of the Expressive Narrative Condition, may accentuate self-attributed blame and responsibility among people who have recently experienced trauma.\(^3\)

References:

Research supported by programme grant #53-10128 from the Social Sciences and Humanities Research Council of Canada.
Results: Rather than being free of masking effects from the imposed 11-h sleep/wake/light/dark schedule, the melatonin of all three subjects showed a cycle-by-cycle modulation in phase similar to that observed in 20-h FD experiments. This modulation makes it impossible to infer the initial or final phases of the bright light stimulus (open box), so that the resultant phase shift cannot be assessed.

Conclusions: These data suggest that plasma melatonin is much more sensitive to masking effects of an upright:supine/wake/wake/light/dark cycle than previously recognized, even under dim light (10-20 lux) conditions. The relative impact of the changes in posture, sleep-wake state, and light level on the observed melatonin rhythm requires further study since it cannot be assessed from this study. However, it is clear that plasma melatonin data collected in these types of protocols is inappropriate for measuring circadian phase shifts in response to bright light due to significant masking effects.

References:

Research supported by NIMH grant RO1-MH45130; NIA grant PO1-AG09975; NIH GCRC grant MO1-RR02635; NASA-NSBRI cooperative agreements NCC9-58 to MEJ and CAC.

139.E

Reduced Responsiveness to Light in the Aging Circadian Clock

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Introduction: In older adults the timing of habitual wake, hormonal rhythms, and the endogenous temperature nadir occur at an earlier clock hour, suggesting an advance of the circadian clock. Two mechanisms might explain this advance, a shortening of the circadian period or altered entrainment to the light/dark cycle. It was recently reported that the free running period of elderly subjects is not different from young subjects when measured in a forced desynchrony protocol1. In the present experiment we tested the alternative hypothesis that age decreases the phase shifting response of the human circadian clock to light.

Methods: Twelve young (7 M, 5 F, 29.3 ± 1.4 years) and 15 elderly (8 M, 7 F, 67.0 ± 1.5 years) subjects were admitted for 4 night/3 day stays in the Clinical Research Center. All subjects had normal cognition and normal ophthalmologic exams. Studies were conducted in a dim light/dark cycle (< 20 lux) with 8 h sleep at the usual time. On night 3 subjects were exposed to light (3 - 4,000 lux for 3 h) centered 2.5 h before the baseline core body temperature minimum (Tmin young: 4.86 ± 0.52 h; Tmin elderly: 3.85 ± 0.57 h). Seven of the young subjects also received dim-light treatment (crossover). Blood samples collected from 7:30 pm to 9:30 am on the nights before and after light exposure were analyzed by radioimmunoassay for melatonin. Treatment-induced shifts in the rising and declining phases of the melatonin rhythm (onset: 20% of peak, synoff: 75% of peak, offset: 20% of peak) were compared by ANOVA with repeated measures.

Results: In young subjects exposed to dim light there was a tendency for the melatonin rhythm to delay (onset: -0.36 ± 0.38 h, synoff: -0.20 ± 0.37 h, offset: -0.80 ± 0.25 h, p = 0.06). In contrast, young subjects exposed to bright light exhibited robust delays in the rising and declining phases of the melatonin profile (Fig. A, onset: -1.30 ± 0.15 h, synoff: -1.20 ± 0.36 h, offset: -1.25 ± 0.20 h, p < 0.001), that were greater than in the control condition (p < 0.05). Melatonin levels in 4 of the 15 elderly subjects were near detectable limits for this radioimmunoassay (2.5 pg) and phase could not be determined. The 11 remaining elderly subjects exhibited light-induced phase delays in the melatonin rhythm (Fig. B, onset: -0.80 ± 0.25 h, synoff: -0.50 ± 0.20 h, offset: -1.00 ± 0.26 h, p < 0.001) of a smaller magnitude than those observed in the young subjects (p < 0.05).

Figure 1

Conclusions: Single exposure to light (3 - 4000 lux for 3 h) induced reliable shifts in the timing of the circadian clock in both young and elderly subjects studied under a dim light/dark cycle. However, the magnitude of the phase shifting response of the circadian clock to light was reduced in the elderly subjects. This reduction in the responsiveness of the aging circadian clock to light is likely to contribute to the alterations in circadian phase commonly observed in older adults.

References:

Supported in part by USPHS grants NCCR-00048, R01 AG11412, K01 AG00810 and R25 RR15404-01.

140.E

Nocturnal Exercise Phase-Delays the Circadian Rhythms of Older Adults

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Introduction: Nocturnal exercise of sufficient intensity and duration can
Methods: This was a within-subjects, repeated measures design testing the phase-shifting effects of exercise versus a control condition. Subjects completed the 2 conditions in counterbalanced order at the Clinical Research Center of Northwestern Memorial Hospital. There were 8 healthy older adult subjects (5 women, 3 men) aged 64.8 ± 6.1 years (mean ± SD), and 8 healthy young subjects (4 women, 4 men) aged 27.1 ± 4.3 years. Subjects were required to keep a fixed, 8-h sleep schedule (based on habitual sleep times) for 2 weeks prior to each admission. Upon admission, subjects commenced constant conditions in dim light (< 50 lux), received a catheter for intravenous blood sampling, and received 200-250 calorie snacks at 2-h intervals during waking hours. On the first (adaptation night) and third nights of each admission, subjects slept for 8-h at their habitual time. On the second night of the exercise condition, subjects exercised at 40 and 60% of peak VO2 on a stationary cycle ergometer for 3 hours, beginning ½ hour after habitual bedtime. On the second night of the control condition, subjects did not exercise. On this night subjects in both groups went to bed 4-h after habitual sleep onset and slept for 6-h. Blood was sampled at 20-60 min intervals (20 min intervals when melatonin was expected to rise). Samples were analyzed for melatonin using RIA. The melatonin onset was defined as the time of the first plasma level > 20% of the peak value for each day. The phase shift was the difference between the onset of the nocturnal rise of melatonin on day 3 compared to day 2 (the melatonin onset on day 2 occurred before the exercise started). In the exercise condition, the peak value for day 1 was used in place of the peak value on day 2, because peak melatonin levels on day 2 were elevated as a result of the acute effects of exercise.

Results: The figure shows average plasma melatonin phase shifts for the young and older subjects in the control and the exercise conditions. ANOVA revealed a statistically significant main effect of exercise (F(1, 12) = 10.39, p < .01), and no effect of age. Older adult subjects did not shift any more or less than young subjects. With both age groups combined, the phase delay was -0.07 ± 0.58 h in the control condition and -0.73 ± 0.79 h in the exercise condition.

Conclusions: Results of this study indicate that healthy aging does not alter the response of the circadian clock to the phase shifting effects of exercise. Therefore, physical activity may be a useful intervention for phase-shifting or synchronization of circadian rhythms and sleep in older people.

Research supported by N.I.H. grant # I P01AG 11412-03 to P.C.Z., N.I.H. grant # RR-00048 to the CRC, and Glenn/AFAR scholarship to E.K.B.

141E

Afternoon Siesta Naps in the Elderly: Effects on Sleep, Circadian Rhythms, Alertness and Performance

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Methods: Nine healthy elderly subjects (4m, 5f, age range 74y - 87y) each experienced both nap and no-nap conditions in two studies each lasting 17 days (14 at home, 3 in the laboratory). In the nap condition a 90 minute nap was enforced between 13:30 and 15:00 every day, in the no nap condition daytime napping was prohibited, and activity encouraged in the 13:30 - 15:00 interval. The order of the two conditions was counterbalanced. Diary measures, pencil and paper alertness tests and wrist actigraphy were used at home. In the 72h laboratory studies, these measures were augmented by polysomnographic sleep recording, continuous rectal temperature measurement, a daily evening single Multiple Sleep Latency Test (MSLT), and computerized tests of mood, activation and performance efficiency.

Results: By the second week in the “at home” study, an average of 58 minutes of sleep was reported per siesta nap; in the laboratory, polysomnography confirmed an average of 57 minutes of sleep per nap. When nap and no nap conditions were compared, mixed effects on nocturnal sleep were observed. Diary and actigraphic measures indicated only a slight decrease in nocturnal sleep duration, but a significant increase in 24h Total Sleep Time (TST) from 397 mins. to 435 mins. (p<0.025) when nocturnal sleeps and naps were added together. The laboratory study revealed a decrease of 2.4% in nocturnal sleep efficiency in the nap condition (p<0.025), a reduction of nocturnal Total Sleep Time (TST) by 48 mins. in the nap condition (p<0.001) which was produced by significantly earlier waketimes (p<0.002); but no reliable effects on Wake After Sleep Onset (WASO) or percent Stages 1 & 2. Unlike the diary study, the laboratory study yielded no significant overall increase in 24h TST consequent upon the siesta nap regimen. The only measure of evening alertness or performance to show an improvement was sleep latency in a single-trial evening MSLT (nap: 14.9 mins., no nap: 11.1 mins., p<0.02). No change in circadian rhythm parameters was observed.

Conclusions: Effects of taking a <90 minute siesta nap appear to be modest in the healthy elderly. Thus, there is probably no need to counsel healthy seniors against planned daytime napping, although the same may not be true for seniors with significant sleep complaints.
Circadian Adjustment to Night Shift Work with a Bright Light Intervention Regimen in the Workplace

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Introduction: Laboratory simulations and field studies have revealed that phototherapy may be a powerful approach in helping the shiftworker adjust to an inverted sleep/wake schedule (1,2). The present combined field and laboratory investigation aims to accurately assess the effects of an intervention regimen on the adjustment of the endogenous circadian system of night shift workers.

Methods: A total of 15 nurses (6 male, 9 female; mean age ± SD: 40.8 ± 8.4 years) working regular night shifts (≥ 8 shifts/15 days) were recruited from area hospitals. Following a vacation period including ≥ 10 days on a daytime schedule, workers were admitted to the laboratory for a 36-hour constant routine procedure (CR). Workers then returned to their regular night shift work schedule for an average of 12 shifts, under one of two experimental conditions: treatment or control. Workers assigned to the treatment condition were exposed to bright light (2000-8000 lux) during the first 6 hours of each night shift, and wore dark goggles on the commute home. Control group workers were observed in their habitual lighting conditions. Subjects maintained regular 8-hour day sleep/dark periods beginning 2 hours after the end of their night shifts. At the end of the ambulatory period, workers were readmitted to the laboratory for a final 36-hour CR. Endogenous circadian phase was determined from CR temperature data via a dual-harmonic regression model without serial correlated noise.

Results: At the start of the study, both groups were adjusted to a day-oriented schedule and no between-group differences were observed (F(1,34)=0.39, p=0.54). Mean initial circadian phase of the treatment and control groups were (± SEM) 5:54 ± 1:09 and 4:40 ± 0:37, respectively. Following the period of night shifts, mean circadian phase (± SEM) was assessed at 16:14 ± 1:10 and 9:49 ± 2:14 hours for the treatment and control groups, respectively. An ANOVA for repeated measures revealed that these final values differed significantly between groups (F(1,34)=10.56, p=0.003).

Conclusions: In the treatment group, the shift in endogenous phase was one that allowed the maintenance of a harmonious relationship between the circadian pacemaker and the inverted sleep schedule. These results suggest that judicious control of exposure to bright light and darkness can hasten the adjustment to night shift work in the field. Further, the partial adjustment of the endogenous circadian pacemaker as observed in the control group may be the result of the strong resetting effects exerted in low levels of light (3), and in the maintenance of a regular schedule of sleep/darkness.

References:
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143.E

Adolescent Sleep Spindle Regulation: Circadian and Homeostatic Contributions to Morphology

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Introduction: Comparisons of sleep EEGs between young and older adults reveal differences in sleep spindle expression, including decreased frequency and increased overall number, amplitude, and duration of sleep spindles in young adults. Young adults displayed robust circadian variations of spindle amplitude, frequency, duration, and count, while in older adults only spindle frequency varied significantly with circadian phase. The present study examines these phenomena in adolescents using a 28h “forced desynchrony” (FD) protocol.

Methods: C3-A2 sleep EEG data were analyzed from eight healthy children (ages 13-15 years; Tanner stage 3-5; 4F) who completed a 20-day, 28h FD protocol. After maintaining a regular 24h sleep-wake home schedule, participants came to the laboratory, where they were shielded from obvious time cues and light brighter than 20 lux. Following an adaptation night, 36h constant routine, and recovery night, subjects underwent 12 cycles of 28h FD consisting of an 11h40m sleep opportunity and 16h20m wake episode per cycle. FD sleep recordings were assessed with Nicolet Ultrasom pattern recognition software to detect spindles and derive four measures averaged across 30 second epochs: amplitude (0.5-75.0 microvolts), frequency (12.5-15.0 Hz), duration (0.5-3.0 seconds), and count (i.e., number of spindles). An independent circadian effect was assessed from data averaged by 60-degree bins using estimates of intrinsic period obtained from dim-light salivary melatonin (0-degrees=melatonin onset). For each measure, an independent sleep-dependent effect was assessed from data averaged in 2h bins from sleep onset. We determined circadian, sleep-dependent, and interaction effects using repeated measures ANOVA.

Results: For spindle frequency, duration, and count, we found significant sleep-dependent effects (all p<0.001), circadian effects (all p<0.001), and significant interactions (all p<0.05). Spindle amplitude showed no significant sleep-dependent effect, but did show a significant circadian effect and an interaction effect (both p<0.001). Figure 1 displays the circadian results. The nadir of spindle frequency and the peaks of spindle amplitude, duration, and count occurred around the time of melatonin onset. Figure 2 displays the sleep-dependent results. Duration and count were lowest at the start of sleep, then rose sharply to a plateau.
approximately midway into the sleep episode.

**Conclusions:** As reported in young adults, spindle measures in adolescents were modulated by both circadian and sleep-dependent (homeostatic) factors. When comparing the overall values for each measure with those from young adults, adolescents exhibited higher sleep spindle amplitude, lower frequency, longer duration, and slightly lower spindle count per 30 seconds. These differences likely represent a developmental component to sleep spindle generation and morphology. Circadian relationships across spindle features were similar in adolescents and young adults, with the frequency peak occurring 180 degrees out of phase with the peaks of the other measures. Adolescent sleep spindle count and duration also showed similar sleep dependent patterns to those observed in young adults. These findings indicate the retention of circadian and sleep-dependent influences on sleep spindles from adolescence into young adulthood.

**References:**

Research supported by MH52415 and MH01358.

**Growth Hormone Secretion During Entrained and Non-Entrained Conditions in Humans**

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**Introduction:** The 24-h pattern of Growth Hormone (GH) secretion is primarily controlled by the sleep-wake cycle. The major secretory episode occurs systematically just after sleep onset, and when the sleep period is abruptly shifted, the GH profile is similarly shifted. Furthermore, extensive evidence indicates a consistent relationship between slow wave sleep and GH release. However, although weak influences from the endogenous circadian system have been reported (1), whether the 24-h pattern GH secretion results from an interaction between sleep and circadian processes remains unclear.

**Methods:** We studied 11 healthy young subjects (11 males, 1 female; 20-41 yrs) for 55 days in an environment free of time cues. After six adaptation days and a 40-h constant routine, subjects were scheduled for 25 days to a dim light/dark cycle (< 1.5-25 lux at angle of gaze). Blood was sampled for melatonin, and during two windows (day 6, day 30), blood was sampled for GH at 10-min intervals. Dim light melatonin onset was used as the marker of circadian phase. Subjects were categorized as “entrained” if the period of the sleep-wake cycle was included in the 95% confidence interval of the observed period of the circadian pacemaker or “non-entrained” otherwise. GH secretory rates were estimated using a deconvolution procedure. ANOVAs for repeated measured were used. Data are given as mean±SE.

**Results:** Four subjects were categorized as “entrained”, and 7 subjects as “non-entrained”. In entrained conditions, both during day 6 and day 30, GH displayed the well known pattern (Figure 1, top) with the majority of its secretion at the beginning of the sleep period (66% of the 24-h secretion occurred during the first half of the sleep episode on day 30). In non-entrained subjects (Figure 1, bottom), the habitual GH profile was observed on day 6 (when still entrained), whereas the profile was altered when subjects were not entrained (only 37% of the 24-h secre-
tion occurred during the first half of the sleep episode on day 30). The amount of GH secreted over the first half of the sleep episode was significantly reduced in non-entrained subjects (42% decrease from day 6 to day 30, p<0.005), however, the amount secreted over the 24 hours was not significantly different (527±88 mg vs. 482±27mg).

Conclusions: This study demonstrates that the activity of the somatotropic axis, although strongly sleep-related, is influenced by circadian processes. When sleep occurs at an inappropriate phase angle with the circadian pacemaker, the 24-h pattern of GH is modified. GH release is significantly reduced at the beginning of the night; however, we did not detect a significant difference in the amount secreted over the 24 hours in this small sample. As recently hypothesized (2,3), these data suggest that a compensatory mechanism may occur during the daytime to counteract the reduction of the nocturnal secretion. The physiological impact of an abnormal GH secretion is unknown, but might be of particular importance under conditions in which circadian misalignment is expected, such as in night work or in long term space missions.

References:

Research supported by NASA Cooperative agreement NCC 9-58 with the National Space Biomedical Research Institute.

145.E

Circadian and Sleep-Wake Dependant Control of Urine Volume Output on a 28-h Forced Desynchrony

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Introduction: Under normal sleep-wake schedules individuals have low urine volume output during sleep and high output during the middle of the waking day (1) whereas, constant routine studies have reported the circadian variation in urine volume output to be lowest near to habitual bedtime and peak shortly after habitual wake time (1-2). We used a 28-h forced desynchrony protocol to examine the degree to which the previously described daily pattern of urine volume output is determined by circadian and wake dependent processes.

Methods: Healthy subjects, 12 males and 2 female ages 20-41, were studied as part of a 55-day inpatient protocol on circadian entrainment. Following the entrainment protocol (3), subjects were scheduled to a 28-hr day for 12 consecutive days, 18.66 hr awake and 9.33 hr asleep. Fluid intake was similar across days. Urine volume (ml/min) was calculated by dividing the total volume of each sample by the time since last void. Urine volume output was transformed into deviation from the mean and averaged into 15 degree (1hr) bins with the temperature minimum assigned to 0 degrees for the circadian component and averaged in 1 hr bins across the 28-h day. Significance of circadian and wake dependent components was analyzed with repeated measure ANOVA techniques.

Results: Urine volume output (see Figure) showed significant main effects for circadian phase and time of day (p< 0.0001). Urine volume was above the mean between ~15 and 210 degrees (~0700 to 2000 hr) and was lowest near 300 degrees (~0200 hr) prior to the temperature minimum. For the time of day component, urine volume levels increased across the waking day. Superimposed on the daily pattern were evoked increases related to meals. Urine output decreased across the first half of scheduled sleep and remained below the 28-hr mean until the last 12 hr of the day. The magnitude of circadian and wake dependent variation in urine output was similar with the exception of the evoked peak related with dinner.

Conclusions: We found urine volume output to vary as function of circadian phase and time awake consistent with an opponent process model. That is, the circadian system promotes urine output during the first half of the habitual waking day whereas the time of day component promotes urine output towards the second half of the waking day resulting in low urine output during sleep. These results suggest that the circadian and time of day processes interact to regulate urine production such that sleep is minimally disrupted by the need to void.

References:

Research Supported by NASA Cooperative Agreement NCC 9-58 with the National Space Biomedical Research Institute. KPW was supported in part by the Medical Foundation and Harold Whitworth Pierce Charitable Trust.
Do Indices of Autonomic Arousal Predict Sleepiness Better than Standard Polysomnographic (PSG) Measures?

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Introduction: Neither ASDA arousal index (AI) nor respiratory disturbance index (RDI) correlate well with subjective or objective sleepiness,1 suggesting that they may be unsatisfactory measures of sleep fragmentation. The Peripheral Arterial Tonometer (PAT) is a finger-mounted optic sensor that measures the digital arterial pulse volume. Arterial vasoconstriction, a marker of sympathetic nervous system (SNS) activity, induces signal attenuation.2 Autonomic arousals with SNS activation may cause daytime sleepiness without full ASDA arousals.3 We hypothesized that PAT derived sleep fragmentation indices may better predict daytime sleepiness than RDI or AI.

Methods: We prospectively studied (n=8 to date) subjects both with and without sleep apnea. For one week prior to the PSG, all subjects spent at least 8 hours in bed (verified with actigraphy) to eliminate the confounding effect of acute on chronic sleep deprivation. After an in-laboratory PSG with PAT, we administered the Epworth sleepiness scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), the Maintenance of Wakefulness Test (MWT), and the Psychomotor Vigilance Task (PVT). An autonomic arousal index (AAI) was determined from the PAT signal (AA=either a reduction in signal to 50% of baseline or 35% of baseline with a 10% elevation in heart rate). The weighted AAI (WAAI) was computed by multiplying AAI with the mean duration of the PAT attenuations. AI was determined using ASDA definitions and RDI using Chicago criteria.

Results: The table illustrates the Spearman correlation co-efficients (top) and p values (bottom) between sleep fragmentation indices and outcome measures (index with the highest correlation is bold-faced). The data show that: 1) WAAI was the best predictor of FOSQ, Epworth sleepiness score, and PVT measures; 2) RDI was the best predictor of MWT; and 3) Weighting AAI improved the predictive value of AAI for all outcomes.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>AAI</th>
<th>WAAI</th>
<th>AI</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MWT</td>
<td>0.762</td>
<td>-0.643</td>
<td>-0.539</td>
<td>-0.69</td>
</tr>
<tr>
<td>(mins)</td>
<td>0.021</td>
<td>0.857</td>
<td>0.755</td>
<td>0.619</td>
</tr>
<tr>
<td>PVT</td>
<td>0.714</td>
<td>0.057</td>
<td>0.695</td>
<td>0.548</td>
</tr>
<tr>
<td>(mean)(ms)</td>
<td>0.037</td>
<td>0.0212</td>
<td>0.047</td>
<td>0.139</td>
</tr>
<tr>
<td>PVT</td>
<td>0.714</td>
<td>0.057</td>
<td>0.695</td>
<td>0.548</td>
</tr>
<tr>
<td>(slowest 10%)</td>
<td>0.037</td>
<td>0.0212</td>
<td>0.047</td>
<td>0.139</td>
</tr>
<tr>
<td>FOSQ</td>
<td>-0.643</td>
<td>-0.762</td>
<td>-0.587</td>
<td>-0.5</td>
</tr>
<tr>
<td>-0.07</td>
<td>0.02</td>
<td>0.10</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>ESS</td>
<td>0.756</td>
<td>0.903</td>
<td>0.724</td>
<td>0.610</td>
</tr>
<tr>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Our data suggest that indices of autonomic arousal may be better in predicting subjective sleepiness, quality of life, and decrements in performance than standard PSG variables. Also, when study design controls for sleep deprivation, standard measures of sleep fragmentation (AI and RDI) are reasonable predictors of waking hypsomnolence.

References:

Research supported by Itamar Medical Ltd.

Association of Excessive Daytime Sleepiness with Sleep Disordered Breathing: The Influence of Age and BMI

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Introduction: It has been demonstrated that excessive daytime sleepiness (EDS) is associated with the severity of sleep disordered breathing (SDB) in an older cohort [1]. It is unclear whether this association changes with age. The purpose of this study was to assess the effects of age on the relationship between the presence of SDB and EDS when controlling for BMI in a large general random sample of adult men and women.

Methods: We examined this question in a cohort based on a two-stage general randomized sample of men and women. In the first phase, 4,364 men and 12,219 women were interviewed ranging in age from 20-100 years. In the second phase of this study, 741 men and 1,000 women who participated in the first phase were evaluated for one night in the sleep laboratory. The complaint of EDS (moderate or severe) was evaluated on the initial interview. The definition of SDB used in this study was obstructive apnea + hypopnea index ³15. The respective association of EDS with SDB, age and BMI and their inter-relationships were assessed using Logistic Regression.

Results: In the multiple logistic regression analysis using the laboratory data, EDS was shown to have a decreasing association with age and a strong association with BMI (OR=0.7(0.5, 0.9) for every decade increase of age); OR=10.3 (3.2,33.3) for every increase of log(BMI)). The association between SDB and EDS was significant (OR =4.0(1.2,13.3) for the mean age and the mean log(BMI)). Finally, in terms of the relative contribution to the complaint of EDS, the strongest risk factor was BMI, then age and then SDB (standardized effect sizes were 3.9, -3.1, 2.3, respectively).

Conclusions: These data indicate that SDB makes an independent contribution to the complaint of EDS even after controlling for age and BMI. These results suggest that EDS is strongly associated with BMI. This association may in part account for the difference in the proportion of those with SDB who are obese in clinic and epidemiologic samples because EDS is a major symptom leading to a sleep disorders clinic evaluation. Further, the risk of EDS in those with SDB decreases with age. This finding is similar to the negative relationship between age and the severity of SDB [2] as well as the moderating effect of age on the association between SDB and hypertension [3]. These findings add further support to the position that studies of the clinical significance of sleep apnea based on samples of older individuals should be interpreted cautiously.

References:
(1) Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD,


Supported in part by R01 HL 40916 and R01 HL51931.

148.J

Diagnosis and CPAP Titration for Sleep Apnea Using a Split-Night Protocol
Sleep Disorders Center, Beijing Chaoyang Hospital

Introduction: In order to demonstrate the accuracy of diagnosis and CPAP titration with split-night protocol.

Methods: 288 patients with obstructive sleep apnea confirmed with full night polysomnograms (PSGs) were enrolled to evaluate the split-night protocol for diagnosis and continuous positive airway pressure (CPAP) titration. Patients spent two consecutive nights in our sleep lab with PSG studies. Full night CPAP titration was performed throughout the first titration. On the second night, we applied a split-night protocol; the first half (22:00-02:00) was used to make diagnosis (Split-night diagnosis), and the second half (02:00-06:00) was applied for CPAP titration (Split-night CPAP).

Results: With the results of full-night diagnosis, all patients met the diagnosis criteria. 176 patients (group A) with AHI of 41.3-120.1, 69 (group B) with 20.7-39.6 and 43 (group C) range 5.3 to 19.8. The mean AHI of group C was higher than that of split-night diagnosis, although there were no statistics differences between full- and split-night diagnosis studies in group A and B. 273 patients successfully underwent CPAP titration both in split- and full-night treatment. 15 patients with AHI between 5.5-22.1 discontinued CPAP therapy during the full-night study, 6/15 were failed to undergo split-night CPAP study. 98/299 patients did not appear slow wave sleep and 86/288 did not show REM sleep during split-night diagnosis. The split- and full-night CPAP both reveal a significant reduction in arousal index (p<0.001), percent total sleep time below 90% SaO2 (p<0.001). There were no statistical differences in final CPAP pressure between the split-night and full-night study (11.7±5.4 vs. 12.2±4.8 bpi, p>0.05). The final CPAP pressure was different only in the group C with AHI>20 (p<0.05). Most of patients (268/288) felt much better after both two nights' treatment.

Conclusions: We demonstrated that a diagnosis of OSAS can be reliably made on the basis of partial night evaluation. Minimizing the time required to establish the diagnosis of OSAS offers the potential opportunity to initiate a trial of CPAP titration during the same night. The improvements during the split-night CPAP are significant even though this time period includes the gradual increase of CPAP pressure. If successful treatment can be established in this manner, it can reduce the costs of sleep laboratories and the clinical need for correct assessment of the severity of disease. This difference may be due to the relatively small number of patients in the groups with 20<AHI<40. There is night-to-night-variability in apnea and this variability may lead to a false-negative study if patients have a low AHI. However, the distribution of final CPAP pressure shows that: this difference, however, was small, and when the patients were divided into three groups, significant differences were found only in the group with AHI>20. We also found significant differences in the final pressure of CPAP in patients with AHI<20, this may be due to variability in AHI. Careful follow-up may be necessary to confirm the diagnosis and the effectiveness of treatment. We believe that a split-night protocol was effective in reducing arousals, apneas, and hypopneas, and improving oxygenation even in patients with AHI<20. Conclusion A split-night protocol may be sufficient to obtain an effective and reliable CPAP pressure for most patients with obstructive sleep apnea, especially with AHI>20. For patients with AHI<20, if symptoms are not improving, reevaluation may be necessary to confirm the effectiveness of treatment. A split-night protocol may be sufficient to diagnosis patients with OSAS and determine the effective CPAP pressure, especially in patients with AHI>20.

149.J

Predictors of Improvement in Health-Related Quality of Life (HRQL) in Obstructive Sleep Apnea (OSA)
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Introduction: Treatment of OSA with nasal continuous positive airway pressure (CPAP) has been reported to result in significant improvement in daytime sleepiness and HRQL. Some studies have suggested that the magnitude of improvement can be predicted by baseline severity of disease and adherence to CPAP treatment. However, the study populations have been relatively small and the strength of the correlation is inconsistent between studies. We wish to examine this issue in a larger group of subjects seen in our sleep laboratory.

Methods: In a group of 223 consecutive subjects, we conducted prospective surveys of HRQL (SF36) at the time of the diagnostic Level I polysomnograph and again 3 months afterwards. 145 (64.0%) of these subjects had clinical diagnosis of OSA and were treated with nasal CPAP after a CPAP titration test in the laboratory (either a split-night protocol or a separate PSG for CPAP titration). The mean CPAP compliance rate was 87% at 3 months (as objectively measured by a monitoring chip in the CPAP device and defined as average nightly use of ³ 3.5 hours). Using linear regression analyses, we analyzed the relationship of the magnitude of the changes in the emotional and physical domains of SF36 questionnaire with CPAP compliance and other individual parameters (age, BMI, mean SaO2, during sleep and apnea-hypopnea index).

Results: (presented as mean ± SD): There were 145 (65.0%) males and 78 (35.0%) females, with age 49.9 ± 12.9 years, BMI 33.6 ± 8.4, AHI 31.8 ± 33.4 events per hour and mean SaO2 during sleep 92.3 ± 3.3%. For the OSA group (AHI > 20) the EMOTIONAL DOMAIN score at baseline was 56.7 ± 24.3 and at 3 months was 68.3 ± 23.0. The PHYSICAL DOMAIN score at baseline was 55.5 ± 24.4 and at 3 months was 61.9 ± 24.0. For the non-OSA group (AHI < 20) the EMOTIONAL DOMAIN score at baseline was 57.1 ± 21.5 and at 3 months was 60.2 ± 21.6. The PHYSICAL DOMAIN score at baseline was 54.8 ± 24.2 and at 3 months was 56.8 ± 25.9. Improvements in general emotional domain scores over 3 months were positively associated with baseline AHI (b-coefficient 3.0 ± 1.2) and CPAP compliance (b-coefficient 2.6 ± 1.1) and negatively associated with baseline SaO2 (b-coefficient -1.2 ± 0.5). [see graphs below] On the other hand, improvements in general physical domain were not associated with AHI, mean SaO2 during sleep, CPAP compliance or any other variables measured (i.e. BMI, age, gender, sleep efficiency).
Conclusions: 1) We conclude that a positive clinical response to CPAP treatment is correlated to the baseline severity of OSA as indicated by AHI and mean SaO\textsubscript{2} during sleep. The magnitude of improvement is also correlated to the adherence to CPAP therapy (hours of use/day). 2) Our findings support the contention that CPAP use is beneficial to symptomatic OSA patients and suggest that optimizing compliance with CPAP can improve HRQL.

**Sleep Disorders in Chronically Sleepy Drivers**

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**Introduction:** In a recent study we found that >3% of a randomly selected group of drivers were chronically sleepy while driving (ie. feared falling asleep while driving at least one in three times they drove)(1). These drivers reported a >10 fold higher automobile crash rate and performed poorer on a driving simulator than matched controls. We now ask the question: Do these chronically sleepy drivers have identifiable sleep disorders?

**Methods:** From a random sample of drivers, we studied 87 chronically sleepy drivers and 44 age and gender control drivers who were not chronically sleepy while driving. Each of these subjects had a clinical evaluation, an extensive sleep questionnaire, and a full night polysomnogram. Unfortunately, we were not able to perform multiple sleep latency testing, so we could not exclude narcolepsy in our drivers.

**Results:** A higher percentage of chronically sleepy drivers had an identifiable sleep disorder (86% vs 26%, P<0.01). Compared to controls, chronically sleepy drivers had a significantly higher prevalence of: 1) breathing disorders during sleep and 2) sleep deprivation (including shift work).

**Table 1**

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>Sleepy Drivers</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing disorders during sleep</td>
<td>55%</td>
<td>14% *</td>
</tr>
<tr>
<td>Sleep deprivation</td>
<td>23%</td>
<td>5% *</td>
</tr>
<tr>
<td>Periodic limb movements</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Chronic insomnia</td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*P<0.001

**Conclusions:** The large majority of chronically sleepy drivers have an identifiable sleep disorder. Breathing disorders during sleep and sleep deprivation (including shift work) are more common among chronically sleepy drivers than controls. Since these sleep disorders can be successfully treated, the increased number of auto crashes in chronically sleepy drivers may be prevented.

**References:**


**Research supported by Government of Spain**

151.J

**The Frequency of Gastroesophageal Reflux Disease in Obstructive Sleep Apnea Syndrome Patients**

*Kim H, Vorona RD, Fishback NF, Winn MP, Ware JC*  
Eastern Virginia Medical School, Norfolk, VA

**Introduction:** Five percent of the U.S. population has Gastroesophageal Reflux Disease (GERD). GERD appears to be increased in Obstructive Sleep Apnea Syndrome (OSAS) population. Studies have shown conflicting results concerning a positive correlation between GERD and OSAS (Graf et al., 1995, Ing et al., 2000). Many of the studies assessing the relationship between GERD and OSAS have been limited by a small number of subjects.

**Methods:** We prospectively administered a GERD questionnaire (Shaw et al. in press) to 294 of the planned 1000 new patients age 18 and over (mean age = 50 ± 13 years, BMI = 34.5 ± 8.2 kg/m\textsuperscript{2}) referred to Sentara Norfolk Sleep Disorders Center. Those with a score of 15.5 or greater were determined to have GERD. The presence and the severity of OSAS were determined by polysomnography. A patient with a respiratory disturbance index (RDI) of 10 or greater was considered to have OSAS. We also collected data on sex, age and BMI.

**Results:** The frequency of GERD in all patients referred to the Sleep Disorders Center was 23%. There was no relationship between the presence of GERD and OSAS (Table 1). Logistic regression indicated that sex and BMI were predictive of GERD. Females (p < 0.05) and patients with higher BMI (p < 0.05) were more likely to have GERD. Age and RDI were not related to GERD. Sex, age and BMI were predictive of the presence of OSAS (p <0.001).
Table 1

<table>
<thead>
<tr>
<th>Relationship between Apnea Frequency and GERD</th>
<th>Apnea Severity (RDI)</th>
<th>All Apnea patients</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>&lt;20</td>
<td>≥40</td>
</tr>
<tr>
<td>N</td>
<td>85</td>
<td>50</td>
<td>66</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>% with GERD</td>
<td>31</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>% women c GERD</td>
<td>24</td>
<td>24</td>
<td>87</td>
</tr>
<tr>
<td>% men c GERD</td>
<td>23</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>% on GERD Rx</td>
<td>66</td>
<td>72</td>
<td>73</td>
</tr>
</tbody>
</table>

Conclusions: We found no relationship between GERD and OSAS, i.e., the frequency of GERD was not related to the presence of apnea or its severity. The high frequency of GERD in all patients who were referred to the Sleep Disorders Center may suggest that these patients’ GERD symptoms were misinterpreted as OSAS symptoms. The finding that females were more likely to have higher GERD scores than males is contrary to the accepted knowledge that males are equal to or more likely to have GERD. This may be due to the fact that female patients are more likely to express having symptoms of GERD while male patients are more likely to deny having such symptoms. Another possibility is that GERD in patients with sleep disturbance is different in pathophysiology than GERD in the general population. We are now beginning to examine the change in GERD symptoms as the OSAS patients are treated with CPAP.

References:

Research supported by Sleep Academic Award HL 03652-01A1 Eastern Virginia Medical School Student Summer Research Scholarship

152, J

Evaluation and Comparison of Two Autotitrating CPAP Machines
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Introduction: Autotitrating continuous positive airway pressure (auto-CPAP) devices automatically adjust the pressure they deliver based on need. The third generation auto-CPAP machines use airflow restriction measured at the nasal mask to determine presence of airway instability. This determines whether the pressure increases or decreases. The purpose of this study was to determine the effectiveness of two such auto-CPAP machines, the Respironics Tranquility and the ResMed AutoSet T, and how they compared with each other.

Methods: Patients with obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS) were randomly assigned to undergo attended auto-CPAP titration with either the Respironics Tranquility or ResMed AutoSet T machine. Criteria for aborting autotitration and switching to manual titration were established as 10 apneas or hypopneas without a response from the auto-CPAP machine or recurrent arousals from frequent pressure changes. For each patient, the auto-CPAP machine was given a performance score between 0-9 (with 9 signifying no problems with autotitrating). A score of 3 or lower indicated that autotitration had to be discontinued and manual titration attempted.

Results: Sixty patients were studied with one of the auto-CPAP machines; 35 with the Respironics Tranquility and 25 with the ResMed AutoSet T. The mean age of the whole group was 55.4 years (range 25-80), whereas the mean body mass index (BMI) was 32.7 (range 19.2-49.8). The mean RDI was 37.5 (range 1-111), and the mean arousal index prior to use of auto-CPAP was 41.4 (range 6.7-145.9). The two treatments groups were comparable in terms of age, BMI, RDI and arousal index. The mean performance scores for the Respironics Tranquility and ResMed AutoSet T machines were 6.4 and 5.2, respectively. These were not statistically different. Autotitration with the Respironics Tranquility machine had to be discontinued (performance score less than or equal to 3) in 10/35 (29%) patients, whereas with the ResMed AutoSet T, autotitration was discontinued in 11/25 (44%) patients. There were no remarkable differences in the mean age, BMI, RDI or arousal index between patients in whom autotitration was successful and those in whom it was not. However, due to small subgroup sizes, statistical analyses could not be performed.

Conclusions: Despite advances in auto-CPAP machines, there remains a large minority of patients with OSA and UARS in whom these machines do not accomplish treatment goals. Of the two machines compared, the Respironics Tranquility was successful slightly more often than the ResMed AutoSet T. This study does not address tolerability and compliance with the different auto-CPAP machines.

153, J

Adherence with CPAP: Weighing the Pros and the Cons
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Introduction: The effectiveness of nasal CPAP therapy is limited by low patient adherence. Previous studies examining the predictors of adherence to CPAP have restricted the variables studied to patient-related, disease-related, and treatment-related variables, with no reliable predictors found (Collard et al, 1997). The current study investigated the relationship between the Decisional Balance Index (DBI) as adapted from the Transtheoretical Model (Prochaska et al, 1997) and objectively measured CPAP adherence.

Methods: Invitations requesting study participation were sent out to 201 Albuquerque VA patients who had been diagnosed with sleep apnea, issued a CPAP machine, and followed in the Pulmonary Clinic. Data were collected on 58 participants. All CPAP machines were outfitted with an internal clock counter that recorded objective usage information. Adherence was defined as the number of hours of CPAP use per night. The DBI is a relative weighting of the individual’s pros and cons of using CPAP. Hierarchical regression analysis was performed between CPAP adherence and DBI, with CPAP pressure and side effects as covariates. The 21-item side effect questionnaire from Kribbs et al. (1993) was used. CPAP pressure was chosen as a covariate because it has been shown that it is a function of body mass index and AH1.

Results: Background information on the sample can be found in Table
1. Regression analyses results are shown in Table 2. At step one, $R^2 = .325$, adjusted $R^2 = .295$ (p < .001). At step two, $R^2 = .522$, adjusted $R^2 = .490$ (p < .001). The change in $R^2$ was .197 (p < .001), meaning that DBI accounted for a statistically significant amount of variance in objective CPAP adherence.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7</td>
<td>10.1</td>
<td>37 – 80</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>32.6</td>
<td>5.3</td>
<td>22 – 46</td>
</tr>
<tr>
<td>Apnea-Hypopnea Index</td>
<td>61.5</td>
<td>36.3</td>
<td>2.0 – 155</td>
</tr>
<tr>
<td>CPAP pressure</td>
<td>9.7</td>
<td>2.8</td>
<td>4 – 18</td>
</tr>
<tr>
<td>Side Effects</td>
<td>8.9</td>
<td>8.0</td>
<td>0 – 30</td>
</tr>
<tr>
<td>Adherence (hrs/night)</td>
<td>3.3</td>
<td>2.9</td>
<td>0.2 – 8.7</td>
</tr>
<tr>
<td>CPAP period of use (days)</td>
<td>750.9</td>
<td>574</td>
<td>179 - 3296</td>
</tr>
</tbody>
</table>

Conclusions: Twenty percent of the variance in CPAP adherence was associated with scores on the Decisional Balance Index, over and beyond the variance accounted for by CPAP pressure (and thereby BMI and AHI) and side effects. These results are encouraging because they provide us with a new direction for research in order to better understand the factors associated with CPAP adherence. The advantage to studying a variable such as DBI is that it is modifiable and can help provide the basis for an intervention to increase CPAP adherence.

References:

Research supported by Biomedical Research Institute of New Mexico.

154.K

Morphology of Hypocretin Neurons in Human Narcolepsy

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Introduction: In previous work, we reported that human narcoleptics have an 85%-95% reduction in the number of hypocretin (Hcrt) (orexin) neurons in the hypothalamus (Thannickal et al., 2000). We wanted to further examine the remaining hypocretin neurons in narcoleptics to see if some particular cell type or other subset of the cells was being selectively eliminated, and to see if the surviving cells had a normal morphology.

Methods: The hypothalamic areas of four narcoleptic and four normal individuals were used. Sections were cut at 40 microns and pretreated with 10 mM sodium citrate at 80 degrees C for antigen retrieval (Jiao et al., 1999). Sections were immunostained for Hcrt-1 or Hcrt-2. A total of 748 cells from 20 sections were measured. All areas of each section were examined, and cells were systematically sampled so that approximately 25-35 cells were analyzed from each section. Analysis was performed by tracing the outlines of the cells at a magnification of 400x using the Neurolucida program produced by Microbrightfield Corp. The areas and roundness parameters of each of the cells were calculated using the same program.

Results: In the normal individuals, two distinct areas were identified on the basis of cell density. A cell dense area that corresponded to the perifornical nucleus was observed. A larger area that included the dorsal, dorsomedial and the lateral hypothalamus was identified in which the Hcrt cells were widely scattered. In the perifornical area, the cells were smaller (mean area 352 sq. microns), rounder (roundness index .38) and generally gave rise to a single dendrite or were spindle shaped. In the rest of the hypothalamus the cells were larger (mean area 512 sq. microns with a roundness index of .30), and were generally multipolar.

In the narcoleptics, the cells in the perifornical area were not significantly different in size (mean area of 355 sq. microns, t=99, df 46, N.S.) or morphology. Cells in the dorsal and lateral areas in the narcoleptics were also not significantly different in size (mean area 693 sq. microns, t=.03, df 23, N.S.) or morphology from controls.

Conclusions: On the basis of the morphological parameters examined, it appears that no particular subset of cells is being selectively eliminated in narcoleptics. Surviving hypocretin cells showed no evidence of shrinkage or significant hypertrophy relative to normals.

References:

Research supported by NS14610 and the Medical Research Service of the Department of Veterans Affairs.

155.K

Diagnostic Value of Low CSF Hypocretin/Orexin Levels in Human Narcolepsy


(1) Stanford University Center for Narcolepsy, (2) Leiden University, (3) Charles University

Introduction: The diagnosis of narcolepsy is primarily based on clinical impression, assisted by sleep recordings and HLA typing. These tests lack specificity and/or sensitivity. Although the onset of narcolepsy generally occurs during adolescence, diagnosis is usually made years after onset (up to 10 years) [1]. Recently, it was found that genetic alterations in the preprohypocretin or hypocretin receptor 2 genes induce narcolepsy in animals. Although an involvement of hypocretin-related genes is rare in human narcolepsy [2], a series of studies measuring hypocretin content in CSF and brain suggests that a deficit in hypocretin neurotransmission is involved in most cases [2, 3]. Since an absence of hypocretin in the CSF is likely to reflect the major pathophysiology of the disease in humans, CSF hypocretin measurement may be useful in diagnosing narcolepsy. We therefore evaluated the clinical assay condi-
tions of CSF hypocretin measurement and assessed the diagnostic value of CSF hypocretin (i.e. sensitivity and specificity) in human narcolepsy.

Methods: CSF hypocretin was examined in 38 narcolepsy-cataplexy cases (36 HLA-DQB1*0602 positive). Clinical data and narcolepsy questionnaires were reviewed blind to hypocretin and HLA typing data, and only subjects with an established diagnosis of narcolepsy-cataplexy were included. Fifteen healthy volunteers and nineteen additional controls with various neurological symptoms were included as neurological controls. CSF was collected between 9:30 a.m. and 5:30 p.m. CSF samples were frozen immediately at -80°C (range of storage period: 0 - 60 days). Hypocretins were measured using a 125I radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals). CSF was extracted with a reverse phase column (C-18 Sep-Columns). Intra-assay variability was 3.8% and the detection limit was 50 pg/ml. All samples were measured in duplicate.

Results: Hypocretin-1 and hypocretin-2 were undetectable in plasma, regardless of collection time or volume (up to 20 ml, <2.5 pg/ml). Hypocretin-2 was undetectable in CSF samples (<5 pg/ml, measured from 10 ml of control CSF). Hypocretin-1 was consistently detectable in as little as 1 ml of control CSF. Levels were unaffected by repeated freezing/thawing or prolonged storage (up to 10 years) and did not display any CSF concentration gradient (up to 12 ml of the collection). Although hypocretin-1 was measurable in all healthy (280±33 pg/ml) and neurological (260±37 pg/ml) controls, regardless of age, time or season of the lumbar tap, the levels were dramatically decreased or absent (<50 pg/ml for 31 subjects, and 75 pg/ml for 1 subject) in 32 of 38 patients (all HLA positive). Four patients, 2 of which were HLA negative, had normal levels. Two HLA positive patients, including a proband of a familial case, had high levels (609 and 637 pg/ml). Low hypocretin levels in narcoleptic subjects were observed regardless of medication, duration of illness, age (as early as 13 years old and 3 years after the disease onset) or time and season of the lumbar taps.

Conclusions: The results of the current study indicate that a majority of narcolepsy-cataplexy subjects (84.2%) have low CSF hypocretin-1 levels (<100 pg/ml), while the level was detectable and within a narrow range in all control subjects (169-376 pg/ml). This most likely reflects a complete loss of hypocretin peptides in the brains of narcoleptic patients [2]. Of the 6 narcoleptic subjects with detectable levels, 2 were HLA negative. Two HLA positive subjects, including the proband of a multiplex family, had abnormally high hypocretin levels (>500 pg/ml). Thus, overall sensitivity for abnormal hypocretin levels (either low or high) in HLA positive subjects was 95.4%. We conclude that measuring CSF hypocretin levels can be used as a diagnostic tool for narcolepsy. Our results also suggest that multiple etiologies exist in human narcolepsy-cataplexy, with a majority of patients lacking hypocretin ligands. Supplementing hypocretin transmission may therefore be a promising approach to treat narcolepsy. Measuring CSF hypocretin levels may also, in time, be helpful in predicting treatment response.

References:
This work was supported by: NS 27710, NS23724, NS 33797, MH40041 and MH01600

156.K
Effect of Systemic and Central Administration of Hypocretin-1 in Narcoleptic (Hcrtr 2 mutated) and Control Dogs
Fujiki N, Yoshida Y, Ripley B, Mignot E, Nishino S
Center for Narcolepsy, Stanford Sleep Center, Stanford University School of Medicine

Introduction: Ninety-five percent of narcolepsy patients currently receive pharmacological treatments: excessive daytime sleepiness (EDS) is treated with amphetamine-like stimulants and cataplexy and other REM sleep-related symptoms are treated with antidepressants. These treatments are still not ideal due to drug tolerance and side effects. Recent progress in narcolepsy research in animals and humans revealed that a deficit in hypocretin neurotransmission is the major pathophysiology in narcolepsy. Mutations in either hypocretin receptor-2 (Hcrtr 2) (in Dobermans and Labradors) or the hypocretin ligands produce narcolepsy in animals. Hypocretin-related gene mutations are rare in humans (Peyron et al), but a deficit in production of hypocretin ligands is involved in a majority of human narcolepsy cases (Nishino et al). Thus, supplements of hypocretin ligands and/or analogs could be a promising new choice for the pharmacological treatment of human narcolepsy, as it has been successful for neuroendocrine diseases. Preclinical trials should be carefully done since hypocretins may have an effect on the autonomic nervous system or other endocrine systems. The canine model may be ideal for the preclinical evaluation since this model has been established for pharmacological experiments for both EDS and cataplexy and since both sporadic (impairment of ligand production) and familial cases (receptor mutation) exist. In order to establish the standard assay protocol, we have assessed the effect of hypocretin administration on cataplexy and sleep using genetically narcoleptic Dobermans.

Methods: Both 1) systemic (i.v.) and 2) central administration (ICV) were employed. 1) Six genetically narcoleptic Doberman pinchers were used (2 - 5 years in age, 3 male and 3 female). Hypocretin-1 (Neurocrine Biosciences and American Peptide Company) was dissolved into physiological saline and was administered through the cephalic vein. Cataplexy in dogs was objectively quantified using the Food Elicited Catalexy Test (FECT). FECT testing was performed 30 min and 10 min before injection, and 5 min, 1 hr, 2 hrs, 3hrs and 4 hrs after injection. 2) One control and one genetically narcoleptic Doberman pincher implanted with electrodes for EEG recording and guide cannulae for ICV injection were used for this study. A sterilized ICV injection needle with tube was inserted into the lateral ventricle through the guide cannulae. After confirming spontaneous CSF outflow with a 50 μl Hamilton syringe, artificial CSF (aCSF) or Hypocretin-1 in aCSF (10, 30 nmol) was administered into the lateral ventricle, and effect on sleep was monitored over 6 hrs by polygraph recordings. In a separate session, we also performed an FECT test after hypocretin-1 ICV injection in a narcoleptic dog (30, 60, 120 nmol).

Results: 1) IV injection study: Acute hypocretin-1 injections (1 to 4 μg/kg) showed no effect on number or duration of cataplexy attacks in all Hcrtr 2-mutated dogs tested. Any change in heart rate, blood pressure and rectal temperature were noted. IV sessions for sleep recordings and chronic drug administration studies on cataplexy are now in progress. 2) ICV injection study: ICV injection of 10 and 30 nmol of hypocretin-1 dose-dependently increased wakefulness in a control animal. In some sessions, a significant increase in drinking was also observed. However, we did not observe any effect on sleep after ICV administration of hypocretin-1 (up to 30 nmol) in a Hcrtr 2-mutated narcoleptic dog. We also found no effect on cataplexy in the Hcrtr 2-mutated narcoleptic dog with all doses (30, 60, 120 nmol) of hypocretin-1.

Conclusions: In contrast to a previous report (John et al.), we did not
observe any effect on cataplexy, either by systemic or central administration of hypocretin-1, in Hcrt 2-mutated narcoleptic dogs. Considering the fact that the highest dose used for the ICV study (120 nmol/dog) is a far larger amount than the dose which produces significant wakefulness in a control animal, and is much greater than the systemic dose used by John et al and us (30 nmol/dog), we believe that supplement of hypocretin ligands is ineffective for Hcrt 2-mutated narcoleptic dogs. These narcoleptic dogs, however, may be an ideal reference to compare the efficacies of hypocretin ligands on sporadic narcoleptic dogs when they are available for pharmacological experiments.

References:

This work was supported by: NS 27710, NS23724, and MH01600

157.K

Dose Response Effects of Modafinil in Narcolepsy

(1) Integris Sleep Disorders Center of Oklahoma, Oklahoma City, OK,
(2) Palms of Pasadena Hospital, St. Petersburg, FL,
(3) Sleep Medicine Institute, Presbyterian Hospital of Dallas, Dallas, TX,
(4) Cephalon, Inc., West Chester, PA,
(5) Sleep Disorders Center of South Carolina, Baptist Medical Center, Columbia, SC

Introduction: Modafinil 200 mg and 400 mg, taken either once daily (in the morning) or as a split dose (morning and lunch), have been shown to significantly improve daytime wakefulness on both objective (MWT, MSLT) and subjective (ESS) measures in narcolepsy patients (1-3). While in these studies there were trends for both wakefulness and overall clinical improvement to be better in the higher dose groups (400 mg QD, 200 mg BID), statistical significance was not achieved. However, neither of these studies assessed sleepiness beyond late afternoon when higher doses of modafinil may better sustain wakefulness. The present study used an extended Maintenance of Wakefulness Test (MWT) testing period to compare the effects of higher doses of modafinil (400 mg QD, 200 mg BID) with the 200 mg QD dose throughout the entire day.

Methods: 32 narcolepsy patients with late afternoon and evening sleepiness despite treatment with modafinil were evaluated in this 13-week, double-blind, randomized, crossover study. All subjects underwent a one to two week washout period before the trial. Subjects were tested in three consecutive 3-week treatment periods that were each preceded by a one-week single-blind placebo washout. The three treatment conditions were: 1) 200 mg QD (7 AM), 2) 400 mg QD (7 AM), and 3) 200 mg BID (7 AM and 12 PM). Treatment sequence was counterbalanced according to a partial Latin Square design. Objective sleepiness was assessed prior to and at the end of each treatment period using the extended MWT. For each treatment, overall clinical effect was assessed using the Clinical Global Impression of Change (CGI-C) scale. Adverse experiences (AEs) were recorded throughout the study.

Results: All 32 patients completed the study. A significant treatment-by-period interaction was observed in the MWT and CGI data. Therefore, per protocol, efficacy data were evaluated for treatment period 1 only. Mean MWT sleep latencies for tests 1-6 were analyzed using ANOVA. All three modafinil dosing regimens significantly improved the mean MWT sleep latency compared to placebo baseline (P<0.01; Figure 1). The mean MWT sleep latencies in both 400 mg groups were significantly longer than the 200 mg QD (P<0.01 Figure 1). While all dose regimens significantly improved CGI-C scores, CGI-C scores were significantly better in both 400 mg conditions compared to 200 mg QD (P<0.05; Figure 2). The percentages of patients rated as much or very much improved on the CGI-C scale were: 27% (200 mg QD), 82% (400 mg QD), and 80% (200 mg BID). The incidence rates of AEs were low (<7% in any group). The most common AEs were headache, nausea, pain, and vomiting, all of which were mild to moderate in severity.

Conclusions: All doses of modafinil significantly improved daytime wakefulness and overall clinical condition. The 400 mg dose of modafinil, given either once or twice daily, was significantly better than the 200 mg dose on both the objective measure of wakefulness and subjective clinical improvement. These data suggest that patients with excessive daytime sleepiness associated with narcolepsy may benefit from higher doses of modafinil, given either once or twice daily.

References:

Supported by Cephalon, Inc. West Chester, PA
Epidemiology of Narcolepsy in Olmsted County, Minnesota: A Population-Based Study

Silber MH, Krahn LH, Olson EJ, Pankratz V
(1) Mayo Sleep Disorder Center, (2) Department of Health Sciences Research, Mayo Clinic, Rochester, MN

Introduction: The incidence and prevalence of narcolepsy is uncertain. The disorder is said to be extremely common in Japan and very rare in Israel. A 1994 Finnish twin study suggested a prevalence of 26 per 100,000 [1]. Two American studies utilized newspaper advertisements, responses to a TV broadcast and interviews to estimate the prevalence as between 50 per 100,000 and 67 per 100,000 [2,3]. Advances in knowledge about the pathogenesis of narcolepsy make it imperative that accurate statistics on the epidemiology of the disease be obtained.

Methods: We used the records-linkage system of the Rochester Epidemiology Project to ascertain all patients in Olmsted County, Minnesota with a diagnosis of narcolepsy. All health care providers in the county participate in the project, which codes essentially all medical information on the local population. Records were reviewed, data abstracted, and cases classified. Incidence cases were detected between 1960 and 1989. January 1, 1985 was selected as the prevalence date. Dates of onset of symptoms, and residence in Olmsted County at onset or on January 1, 1985 were verified. All cases were reviewed by at least one diplomate of the American Board of Sleep Medicine. Cases were classified into Group A (Definite Narcolepsy): sleepiness, cataplexy, mean initial sleep latency on MSLT < 8 minutes, 2 or more SOREMS, and AHI < 10; Group B (Probable Narcolepsy-Laboratory Confirmation): same criteria as Group A, but < 2 SOREMS on MSLT (Subgroup B1) or no cataplexy (Subgroup B2). Group C (Probable Narcolepsy-Clinical): sleepiness and cataplexy, but no sleep studies performed. We showed that this classification has an interrater reliability of 0.98. Cases were also classified by the criteria of the International Classification of Sleep Disorders (ICSD). U.S. census data were used to calculate the incidence rate and prevalence.

Results: See Table.

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalence per 100,000 (number of cases)</th>
<th>Incidence Rate 1960-1989 per 100,000 persons per year (number of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases (A, B1, B2, C)</td>
<td>56.3 (55)</td>
<td>1.34 (35)*</td>
</tr>
<tr>
<td>Cases with Cataplexy (A, B1, C)</td>
<td>35.8 (35)</td>
<td>0.74 (19)</td>
</tr>
<tr>
<td>Cases without Cataplexy (B2)</td>
<td>20.5 (20)</td>
<td>0.63 (16)</td>
</tr>
<tr>
<td>Cases according to ICSD Classification</td>
<td>46.1 (45)</td>
<td>1.09 (28)</td>
</tr>
</tbody>
</table>

*Males 1.72, females 1.05; incidence rate highest in second decade

Conclusions: To our knowledge, this represents the first population-based epidemiological study of narcolepsy in the United States. We conclude that narcolepsy is far from a rare disorder. The prevalence of narcolepsy in Olmsted County diagnosed by our research criteria is 56 per 100,000 (1 patient for every 1,786 people). Narcolepsy diagnosed by ICSD criteria (slightly more stringent than ours) showed a prevalence of 46 per 100,000. The incidence rate for narcolepsy from 1970 through 1989 was 1.3 per year per 100,000 population. Sixty four percent of prevalence cases had cataplexy, making the prevalence of cataplexy positive cases 36 per 100,000 and cataplexy negative cases 20 per 100,000. Thus a large number of sleepy patients with sleep onset REM sleep and no other cause do not experience cataplexy.

References:

Research supported by Mayo Foundation (Piscopo Fund)

Pharmacokinetic Interactions of Zolpidem and Protriptyline with Sodium Oxybate Oral Solution in Healthy Human Subjects

Borgen LA, Okerholm RA, Lai A
(1) Orphan Medical, Inc., Minnetonka, MN, (2) Okerholm Associates, Palm City, FL, (3) CPKD Solutions, Research Triangle Park, NC

Introduction: Previous clinical trials have demonstrated the efficacy and safety of gamma-hydroxybutyrate in the treatment of narcolepsy [1,2]. Xyrem(R) is a 500 mg/ml oral solution of sodium oxybate (sodium gamma-hydroxybutyrate) presently in clinical development as a treatment for narcolepsy, particularly the symptom of cataplexy. The present studies examine the kinetic interactions between sodium oxybate and two drugs commonly prescribed for the treatment of narcolepsy symptoms, namely protriptyline HCl (Vivactil) and zolpidem tartrate (Ambien).

Methods: Two clinical trials were conducted in healthy adult volunteers. Both trials used a unit-dose, randomized, 3-way crossover design. In the zolpidem interaction study, 15 healthy fasted subjects were each given single doses of sodium oxybate (3g) or zolpidem (5mg) alone or in combination 1 week apart. Plasma samples were collected at 17 time points up to 24 hours after dosing and frozen for later analysis. Plasma concentrations of oxybate and zolpidem were determined using validated LC/MS/MS and LC/FD assays, respectively. In the protriptyline interaction study, 12 healthy fasted volunteers were administered 4.5g sodium oxybate (2.25g x 2 given 4 hr. apart), protriptyline (10 mg), or the combination with each treatment given 3 weeks apart. Plasma samples were collected at selected time points up to 312 hours after dosing and frozen for subsequent analysis. Plasma levels of oxybate were measured as above while protriptyline concentrations were measured using a validated LC/FD assay. Pharmacokinetic evaluation included the determination of peak concentration (Cmax), corresponding peak times (Tmax), area under the curve (AUCinf), and elimination half-life (T1/2).

Results: The primary pharmacokinetic results of the two studies are presented in Tables 1 and 2. Statistical analyses by ANOVA indicated that the co-administration of either zolpidem or protriptyline with sodium oxybate had no significant effect upon the pharmacokinetics of oxybate (p>0.05). Conversely, sodium oxybate co-administration did not significantly alter the kinetics of either zolpidem or protriptyline (p>0.05). No serious or unexpected adverse effects or clinically significant changes in vital signs were recorded in either study. The most common treatment-related adverse events seen were headache, nausea and dizziness. All untoward events were mild in severity and resolved without intervention.
Conclusions: The pharmacokinetics of sodium oxybate were not significantly changed by the co-administration of either zolpidem or protriptyline. Conversely, sodium oxybate co-administration did not significantly alter the plasma kinetics of either drug. No serious or unexpected adverse events were associated with either drug combination.

References:

Research supported by Orphan Medical, Inc.

160.K

Increased Body-Mass-Index (BMI), Appetite and Food Intake in Human Narcolepsy, but not in HLA-DR2 Positive Controls

Schuld A, Beiting P, Dalal M, Haack M, Pollmacher T
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Introduction: Recently, a defect hypocretin-receptor gene has been found in canine narcolepsy. Additionally, mice lacking the prepro-hypocretin gene display narcolepsy-like behavior. Moreover, in the cerebrospinal fluid and in the hypothalamus of the brains of narcoleptic patients hypocretins were found to be reduced (1). These findings support the hypothesis that hypocretin-deficiency plays an important role in the pathophysiology of narcolepsy. Because hypocretins stimulate appetite and food-intake, narcoleptic patients therefore should be lean compared to controls. However, we found an increased body-mass-index (BMI) in narcoleptic patients (2). We wanted to know whether this increased weight is associated with the HLA-DR2 antigen and therefore possibly may be apparent already before disease onset, or whether alterations in food intake, appetite and weight goes along with the symptomatology of narcolepsy.

Table 1
Pharmacokinetics of Sodium Oxybate Alone and When Given With Zolpidem or Protriptyline (Mean ± SD)

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Tmax (hr.)</th>
<th>Cmax (µg/mL)</th>
<th>T½ (hr.)</th>
<th>AUC-inf (µg/mL-hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxybate Alone</td>
<td>0.62 ± 0.28</td>
<td>83.8 ± 1.77</td>
<td>0.74 ± 0.22</td>
<td>136 ± 15.9</td>
</tr>
<tr>
<td>Zolpidem Alone</td>
<td>0.70 ± 0.27</td>
<td>93.5 ± 1.77</td>
<td>0.73 ± 0.22</td>
<td>143 ± 2.1</td>
</tr>
<tr>
<td>Oxybate + Zolpidem</td>
<td>0.69 ± 0.33</td>
<td>64.6 ± 1.77</td>
<td>0.57 ± 0.19</td>
<td>177.8 ± 2.1</td>
</tr>
<tr>
<td>Protriptyline Alone</td>
<td>0.81 ± 0.36</td>
<td>58.3 ± 1.77</td>
<td>0.57 ± 0.18</td>
<td>183.1 ± 1.9</td>
</tr>
</tbody>
</table>

Table 2
Pharmacokinetics of Zolpidem and Protriptyline Given Alone or With Sodium Oxybate (Mean ± SD)

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Tmax (hr.)</th>
<th>Cmax (µg/mL)</th>
<th>T½ (hr.)</th>
<th>AUC-inf (µg/mL-hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem Alone</td>
<td>1.08 ± 0.71</td>
<td>107 ± 1.77</td>
<td>3.35 ± 1.88</td>
<td>419.9 ± 21.8</td>
</tr>
<tr>
<td>Zolpidem + Oxybate</td>
<td>1.15 ± 1.22</td>
<td>96.3 ± 1.77</td>
<td>3.34 ± 1.59</td>
<td>424.2 ± 23.0</td>
</tr>
<tr>
<td>Protriptyline Alone</td>
<td>0.84 ± 0.71</td>
<td>4.7 ± 1.4</td>
<td>72.1 ± 3.82</td>
<td>452.4 ± 30.4</td>
</tr>
<tr>
<td>Protriptyline + Oxybate</td>
<td>0.42 ± 1.37</td>
<td>5.0 ± 1.37</td>
<td>68.2 ± 3.62</td>
<td>463.0 ± 31.0</td>
</tr>
</tbody>
</table>

Conclusions: An increased BMI as it has been found in narcolepsy (2) is not apparent in HLA-DR2 positive healthy young subjects. Therefore it obviously is not linked to the HLA-DR2 antigen which most of narcoleptic patients display, but possibly with the narcolepsy itself. Moreover, also increased appetite and food intake seem to be closely related to the onset of narcoleptic symptomatology. Both findings suggest that increased BMI in narcolepsy might not be a premorbid trait, but may be acquired at the disease onset. These changes cannot easily be explained by the changes in eating behavior due to the recently observed alterations in the hypocretin neuromodulatory system (1), which should cause reduced appetite rather than increased. However, it may be due to an additionally disturbed peripheral feedback to hypothalamic appetite-controlling centers because a substantial reduction in systemic leptin levels were found in narcoleptic patients (3).

References:

161.N

The Dopaminergic System and Sleep, and Sleep-Related Involuntary Movements

Amity N, Okura M, Fujiki N, Ripley B, Picchioni D, Mignot E, Nishino S
Stanford University Center for Narcolepsy

Introduction: Using the canine model of narcolepsy (hypocretin receptor 2-mutated), we have demonstrated that the midbrain dopaminergic (DA) system, especially the D2/3 autoreceptor system, is critically involved in the regulation of sleep and cataplexy [1]. Furthermore, presynaptic enhancement of DA transmission at DA terminals is likely to be one of the most important mechanisms for the pharmacological control of vigilance [1]. Since narcoleptic dogs are very sensitive to dopaminergic D2/3 agonists, which induce increased behavioral sleep when compared to control dogs, DA/hypocretin interaction is likely to be underlying in the pathophysiology of canine narcolepsy. Narcolepsy is often associated with periodic leg movements during sleep (PLMS)
Involvement of the DA system in PLMS is well-established, and dopaminergic agonists have been widely used for treatment of PLMS in humans. Interestingly, we recently reported PLMS-like “leg movements” during sleep in our narcoleptic dogs [3]. In this study, we (1) further characterize PLMS-like movement of our dogs, and (2) examine whether DA compounds used for the treatment of PLMS in humans modify the symptoms of narcoleptic dogs and PLMS-like movements.

Methods: Four narcoleptic (2.9 ± 1.33 years) and one control Doberman (5 years), chronically implanted with electrodes for EEG, EOG and EMG, were used for polygraphic recordings to evaluate involuntary movement during sleep. Dogs were freely moving in a lighted recording room (3 x 3 m) and were observed from an adjoining room with a video camera. EMG recordings using surface electrodes for the anterior tibialis muscles or quadriceps femoris muscles were also carried out in some sessions. Involuntary movements during sleep were assessed by reviewing the video recordings and EMG traces. Six narcoleptic Doberman pinschers were used for cataplexy testing. Compounds used for cataplexy testing included pramipexole (up to 0.25 mg/dog p.o.), ropinirole (up to 2.0 mg/dog p.o.), and pergolide (up to 0.125 mg/dog p.o.). The effects of pramipexole and ropinirole on sleep and involuntary movement during sleep were also assessed in narcoleptic and control dogs.

Results: Our narcoleptic dogs exhibited 3 types of involuntary movement during sleep. (1) Shivering occurs during the light and deep sleep stages, and is usually accompanied by large movements around the shoulder and neck (high amplitude EMG activity, 0.2 - 1.0 sec). (2) Muscle twitching during REM sleep is quick and occurs in any part of the body, often accompanying other phasic REM sleep phenomena, such as rapid eye movements. In addition, we also observed (3) jerky, unilateral or bilateral slow leg movements during quiet wake, drowsy stage and light sleep. These movements are characterized by repetitive dorsiflexions of the ankle with occasional flexion of the knee and hip. One such movement lasts 0.5-1.5 seconds and occurs repeatedly (4 to 20 times) within regular intervals of 5-20 seconds. Thus, these slow, rhythmic limb movements exhibit considerable similarities to PLMS in humans. We are currently assessing whether control animals also show a similar degree of leg movements. We found that pramipexole, ropinirole and pergolide—compounds currently used for the treatment of human PLMS—significantly aggravated cataplexy and induced drowsy states in narcoleptic dogs, while little effect on sleep or behavioral sedation was observed in a control animal.

Conclusions: We observed that genetically narcoleptic Dobermans display PLMS-like involuntary leg movements. Cataplexy and drowsy state are significantly aggravated by D2/D3 agonists currently used for the treatment of human PLMS. Since D2/D3 mechanisms are involved in the control of muscle tone during cataplexy [1], these D2/D3 mechanisms may also be responsible for the pathophysiology of PLMS. Dysregulation of the dopaminergic system may exist in canine narcolepsy, and this may be specifically involved in sleep-related motor inhibition (i.e. cataplexy) and activation (i.e. PLMS) and abnormal sleep tendency. Our canines may therefore be an invaluable resource for research on PLMS and other dopamine-related sleep/movement disorders, such as Parkinson’s disease.

References:
(1) Nishino S., et.al., 2000, Sleep Medicine Reviews, 4:57-99
(2) Wittig R., et.al., 1983, Clinical Electroencephalography, 14:130-134
(3) Okura M., et.al., Abstract Book for the 25th Congress of the Japanese Sleep Research Society, Shinyokohama, p. 106

This work was supported by: NS 27710, NS23724, and MH01600.
underlie PLMS. Additional studies will need to be done to confirm this finding and elucidate the exact mechanism of the circadian rhythm.

References:

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163.N

Severity of Disease and Circadian Patterns of Periodic Limb Movement Activity in Restless Legs Syndrome: Preliminary Report

De la Llave Y, Garcia-Borroguero D, Barrio S, Larrosa O, Granizo JJ, Allen R

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Introduction: The presence of periodic limb movements during sleep (PLMS) is considered to be the main objective feature of Restless Legs Syndrome (RLS). In addition, RLS patients also exhibit Periodic Limb Movements during Wakefulness (PLMW). Although both PLMS and PLMW seem to be modulated by a circadian oscillator (showing maximal movements during wakefulness), it is not known to what extent circadian activity reflects the severity of the disease. The main objective of this study was to investigate the relationship between circadian variation of periodic leg movement activity and severity of disease in patients with Restless Legs Syndrome.

Methods: 10 untreated patients diagnosed with RLS according to the criteria of the IRLSSG were included in the study. Diagnostic procedures included medical history, physical exam, laboratory analysis, and polysomnography. All patients underwent between 22:30-24:00 and 7:00-9:00 a 45-60 minute Suggested Immobilization Test (SIT). Patients were asked to lay down in bed and only to move if they experienced symptoms. The following parameters were calculated for each patient based on the PSG, SIT and IRLS rating scale: PLMS-index, PLMW-index (Nicolas et al., 1999), circadian index (CI) on PSG for both PLMW and PLMS (difference of PLM-index between the first and last two hours of PSG), CI on SIT (difference in PLMW between night and morning SIT), IRLS (self-rating score). Statistical analysis was performed by means of Spearman’s correlations.

Results: Preliminary results on 10 patients (mean age ± S.D.: 52y ±13) of this on-going study are shown on the attached Table.a) A significant correlation was found between the indexes of PLMW and PLMS (p<0.01). b) There was a significant association between circadian index on SIT and PSG: CI-SIT with CI-PLMS (p=0.01). c) No association was found between either PLMW or PLMS and circadian indexes (on either SIT or PSG).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>PLMW</th>
<th>PLMS</th>
<th>CI-PLMW</th>
<th>CI-PLMS</th>
<th>CI-SIT</th>
<th>IRLS-Scale (self-rating)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLMS</td>
<td>0.87</td>
<td></td>
<td></td>
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<tr>
<td>CI-PLMW1</td>
<td>-0.15</td>
<td>0.04</td>
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<tr>
<td>CI-PLMW2</td>
<td>-0.26</td>
<td>-0.26</td>
<td>0.68</td>
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<tr>
<td>CI-SIT</td>
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<td>-0.34</td>
<td>0.51</td>
<td>-0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRLS-Scale</td>
<td>0.51</td>
<td>0.46</td>
<td>-0.35</td>
<td>0.05</td>
<td>-0.20</td>
<td></td>
</tr>
<tr>
<td>Time of Onset</td>
<td>0.37</td>
<td>0.34</td>
<td>0.50</td>
<td>0.13</td>
<td>0.40</td>
<td>0.03</td>
</tr>
</tbody>
</table>

All values are given as Spearman’s rho correlation coefficients
(*) p<0.001; (**) p<0.01; (*) p<0.05
1CI-PLMW: PLMW during first 2 hrs of PSG/PLMS during last 2 hrs of PSG
2CI-PLMS: PLMW during first 2 hrs of PSG/PLMS during last 2 hrs of PSG
3CI-SIT: PLMW during SIT at night/PLMW during SIT in the morning

Conclusions: A significant association was found between all-night indexes of PLMW and PLMS, supporting the view that both share a common mechanism. However, no association was found between all-night indexes of PLMS or PLMW and indexes of circadian variation, supporting the view that severity of disease and circadian variation of symptoms might be caused by separate mechanisms, and represent two different dimensions in the assessment of RLS. Our data do not provide external validation of the IRLS severity scale (p=0.133), although, given the small sample size, a definite statement awaits ongoing data collection.

References:

164.N

A Structural Polymorphism in the Tyrosine Hydroxylase Gene is Not Associated with Restless Legs Syndrome

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Introduction: Restless legs syndrome (RLS) is a common disorder that may afflict more than 5% of the population. Although its etiology remains unknown, several lines of evidence suggest that the dopaminergic system is involved in the pathophysiology of RLS. This makes the genes involved in the metabolism of dopamine interesting candidates for investigating in RLS. Since tyrosine hydroxylase (TH) has a crucial role in the metabolism of dopamine, being the rate-limiting enzyme that catalyzes the first step in the biosynthesis of catecholamine, we investigated a possible association between a coding TH polymorphism and RLS.

Methods: A total of 161 unrelated control subjects and 87 patients were genotyped for a point mutation located in the second exon of the TH gene, which results in an amino acid change of Val81Met. Only subjects

SLEEP, Vol. 24, Abstract Supplement 2001
of French-Canadian origin were included in the study. All patients presented clinically definite RLS according to the International Restless Legs Syndrome Study Group criteria. Polysomnographic recordings were carried out on all affected subjects. The nucleotide variants were genotyped by PCR-restriction fragment length polymorphism (RFLP) method. The Val to Met substitution leads to the creation of a NlaIII restriction site; the enzyme is assumed to cleave the mutated type but not the wild type. The digested fragments were separated on 2% agarose gel and subsequently visualized by ethidium bromide staining and ultraviolet transillumination. Patients were categorized into three groups on the basis of their TH genotypes. The association of TH polymorphisms with different parameter scores [namely, periodic leg movements during sleep (PLMS) index, sleep latency and leg movements during the suggested immobilization test (SIT)], was estimated using Kruskall-Wallis analysis of variance. The chi-square test was used to compare patients with controls and to compare subgroups of patients.

Results: Genotype distribution among patients and controls did not deviate from the Hardy-Weinberg equilibrium (Chi-square = 0.049; df= 2; P= 0.975 and Chi-square= 0.861; df= 2; P= .650, respectively). There were no associations with respect to genotype count (Chi-square= 1.990; df= 2; P= 0.370) or allele frequency between patient and controls (Chi-square = 0.156; df= 1; P= 0.693). Moreover, PLMS index, sleep latency and leg movements during the SIT were not significantly different across the TH genotype groups (K-W= 3.238; df= 2; P= 0.198, K-W= 0.773; df= 2; P= 0.680 and K-W= 1.167; df= 2; P= 0.558, respectively) even when possible stratification of the sample according to gender, presence of PLMS or positive family history were included in the model.

Conclusions: This is the first study to investigate mutations in the tyrosine hydroxylase gene and in the context of RLS. The genotyping of the Val181Met variant in a group of RLS patients and controls does not provide evidence toward the involvement of TH in conferring susceptibility to RLS. However, a number of other polymorphisms in TH have also been identified and we cannot exclude the possibility that these are of importance in the etiology of RLS.

This work was financially supported in part by MRC and NIH grants to GAR and JM. AD is supported by MRC studentship.

Segregation Analysis of Families with Restless Legs Syndrome Provides Evidence for a Single Gene and Autosomal-dominant Mode of Inheritance

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Introduction: Investigations in different populations of idiopathic Restless Legs Syndrome (RLS) patients showed the genetic contribution of the disease with a heridity in up to 60% of the cases. Investigations for a gene failed so far. One reason may be the lack of any definitely known genetic model. The likely mode of inheritance has never been investigated. The aim of this study was to clarify the mode of inheritance of RLS in a population of 239 RLS patients and their first-degree relatives.

Methods: We contacted all patients who presented between 1/1996 and 3/1999 who were diagnosed RLS according to the definition criteria. They were encouraged to contact as many first-degree relatives as possible to participate in the Study. All participants were contacted by phone and were questioned by a computer assisted interview about the diagnostic criteria for RLS. They were classified in RLS affected or non-affected subjects. Complex segregation analysis was performed using pedigree analysis package (PAP) and POINTER.

Results: 239 of 397 agreed to participate. 196 of 239 patients, 537 of their first-degree relatives and 132 spouses were interviewed. 89/196 (45.1%) showed definitive hereditary RLS, 43/196 (21.8%) showed hereditary RLS by history and in 64/196 (32.9%) the family history was negative. In further 42 of 239 patients only the index patients could be interviewed;16/42 (38%) showed hereditary RLS by history. The best fitting model for the inheritance was a common allele acting in an autosomal dominant fashion (akaike information criteria (AIC) 2546.9). Multifactorial (p < 0.0001), baseline random (p < 0.0001), recessive (AIC 2547.1) and intermediate models (AIC 2547.8) were less likely. Parameter estimates were 0.11 for the allele frequency, 0.90 for the penetrance and 6.4%, for the phenocopy rate. A test of goodness-of-fit showed that this model was not only the best fitting model, but also explained the family structures, leaving no room for a significant addition to the model.

Conclusions: The segregation pattern found in our families argue for a common autosomal allele acting dominantly, as well as a high phenocopy rate delineating a prerequisite for future linkage studies and offering an explanation for the failure of recent linkage studies in RLS.

Poster Symposia

166.R

A Transformation Function can Equate Readings of Wrist-worn Light Measuring Devices to Those of Hand-held Light Monitors

Brown EL,1 Barger LK,2 May CD,2 Jewett ME2 (1) Allegheny College, Pennsylvania, (2) Brigham and Women’s Hospital/Harvard Medical School

Introduction: We have developed a mathematical model of the effects of light on the human circadian pacemaker that requires an individual’s eye-level light exposure from a hand-held IL-1400 meter (International Light, Newburyport, MA) as an input. However, in field studies wrist-worn light measuring devices such as the Actiwatch-L (AW-L, Minimitter, Sun River, Oregon) are often used. To use AW-L readings in our light model, they must be equivalent to IL-1400 readings. If not, a transformation function must be developed to equate the readings.

Methods: Six AW-Ls and three IL-1400 light meters were tested at nine light levels ranging from very dim (~ 1 lux) to very bright (~10,000 lux). At each level, light intensity was recorded with the IL-1400 meters at each different position on a template with specifically-labeled positions or IL-1400s. There were significant differences between the AW-Ls at many light levels, with the AW-Ls and IL-1400s being placed on the template. At each light level, AW-Ls recorded light exposure continuously and IL-1400s recorded at the beginning, middle and end of a ten-minute period. One-way ANOVAs were conducted for each light level with the factors: template position; IL-1400 meter; and AW-L. Two statistically-identical populations of AW-Ls and IL1400s were established, compared with the Student’s t-test at each light level, and plotted on a log-log scale. A linear regression was fit through the data points, the slope and intercept of which were used to derive a transformation function.

Results: At all light levels, there were no significant differences between template positions or IL-1400s. There were significant differences between the AW-Ls at many light levels, with AW-L3 a clear outlier at low levels (Figure 1, panels a-c) and AW-L 10 a clear outlier at higher levels (panels c-e,g,j). The remaining four AW-Ls were not significantly different from one another at any light level. Therefore, data from AW-
Ls 3 and 10 were removed from all further analyses. Across all light levels AW-L and IL-1400 readings were significantly different (p<0.001) with AW-L recordings consistently lower. The log-log relationship between the AW-Ls and the IL-1400s was linear (Figure 2, solid line, R² = 0.997, p<0.0001). The following transformation function was required to equate the AW-L readings to the IL-1400’s: $\text{adjAWL} = 10^{\log_{10}(\text{AW-L})/0.98+0.35}$. The adjusted AW-L readings (adjAW-L) were not significantly different from the IL-1400’s and fell along the dashed line of identity (Figure 2, circles).

**Figure 1**

![Comparison of AW-L and IL-1400 recordings](image1.png)

**Figure 2**

![Log-log relationship between AW-L and IL-1400 recordings](image2.png)

**Conclusions:** Once inconsistently-calibrated AW-Ls have been identified and removed from consideration, a transformation function accurately adjusts AW-L readings to be approximately equivalent to IL-1400 readings across a wide range of light levels. Our findings from this study, along with another ongoing study comparing light levels at the wrist to readings across a wide range of light levels, will allow us to directly input light values recorded on the wrist-worn AW-L into our light model to predict circadian phase and amplitude.

**References:**

Supported by funding through the auspices of NASA Wyle Laboratories and ARO grant DAAD19-99-1-0241; NASA-NSBRI cooperative agreement NCC9-58; NASA cooperative agreement NCC2-1167; and NHLBI grant 5T32-HL07901 (LKB).

**Circadian Performance Simulation Software (CPSS) Provides a Tool for Validation of Circadian and Neurobehavioral Mathematical Models**

**Dean II DA, Jewett ME**
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**Introduction:** Over the past several decades, mathematical models have been developed and refined that predict the effects of light on the human circadian pacemaker and the joint effects of the pacemaker and a sleep/wake homeostat on human neurobehavioral function. These include mathematical models that predict the effects of even very brief exposure to light on circadian phase1 and of scheduled sleep and light exposure on cognitive throughput and subjective alertness2. We present here a user-friendly, graphical-interface program called the Circadian Performance Simulation Software (CPSS) as a tool for the validation of these models.

**Methods:** The CPSS allows a user to input scheduled sleep/wake and light exposure conditions and to receive Light Model, Subjective Alertness Model, or Cognitive Throughput Model predictions in both graphical and textual form. The CPSS consists of a front end (Microsoft Visual Basic) that handles user inputs and displays simulation outputs, and a back end (Microsoft C++) that uses a fourth-order Runge Kutta procedure to integrate the differential equations defined in each of the models. The CPSS contains a setup utility that installs the CPSS application, sample protocols and an extensive User’s Manual on Windows 98 machines. The software guides the user through the following four-step process of running a simulation: 1) inputting the light exposure and sleep/wake schedule, 2) selecting the model and model parameters (Figure 1), 3) running the simulation, and 4) displaying the output. To demonstrate, the following sample protocol was simulated using the Cognitive Throughput Model: two baseline days (8 h sleep in 150 lux; 16 h wake at 0 lux), followed by 56 h of wake in 10 lux, an 8 h recovery sleep episode in 0 lux, and 16 h of wake at an abnormal circadian phase in 150 lux.

**Results:** The CPSS provides a prediction of cognitive throughput performance throughout the sample protocol for an average healthy young (18-30 yrs) subject, with 1.0 representing the subject’s best possible performance on a standard cognitive throughput task, and 0.0 representing the subject’s worst possible performance (Figure 2). Cognitive throughput predictions during scheduled sleep episodes represent the expected performance if the subject were to awaken at that given moment (at which time s/he would experience sleep inertia)2. The CPSS predicts only minor circadian variations in cognitive throughput during the baseline days when the subject is well-rested, but as the subject becomes sleep-deprived the predicted circadian variation becomes more pronounced. Lower levels of performance are predicted for the final wake episode.
Figures 1 and 2

Conclusions: The CPSS can be used to simulate experimental results, plan new protocols, and as an educational tool. Since the CPSS is released into the public domain, it enables the sleep/circadian research community to use and validate current models and to test the performance efficacy of different work schedules.

References:

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168.U

Analysis of the First Night Effect on Evening and Morning Waking Quantified EEG

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Introduction: The detrimental effect of having to sleep for a first night in a laboratory is a well-known phenomenon. The aim of the present study was to verify whether the first-night effect had an impact on waking quantified EEG measures taken in the morning.

Methods: Eight healthy participants (4 men, 4 women, aged 26.9 ± 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 recordings were obtained in the evening (between 22h00 and 23h00) and in the morning (between 07h00 and 08h00). Subjects were recorded for five minutes with eyes closed. Fifteen 4-second artefact free epochs from the C3 electrode (referred to linked earlobes) were selected and submitted to Fast Fourier Transform with a resolution of 0.25 Hz and a cosine window smoothing. Absolute power amplitude was extracted (µV/Hz, 0.75Hz to 19.75Hz) and six frequency bands were created: Delta (0.75-3.75 Hz), Theta (4.00-7.75 Hz), Alpha 1 (8.00-10.00 Hz), Alpha 2 (10.25-12.75Hz), Sigma (12.00-14.00) and Beta (13.00-19.75 Hz). Data is expressed as means ± SE.M. Statistical comparisons were made using a 2 x 2 ANOVA.

Results: Sleep architecture showed a typical first night effect (see Table 1). EEG spectral analysis however did not reveal any significant differences (see Figure 1).

Table 1

<table>
<thead>
<tr>
<th>First night effect on sleep parameters</th>
<th>Night 1</th>
<th>Night 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset latency</td>
<td>17.5 ± 3.5</td>
<td>12.6 ± 2.2</td>
<td>.08</td>
</tr>
<tr>
<td>SWS latency</td>
<td>29.0 ± 6.8</td>
<td>13.9 ± 2.6</td>
<td>.06</td>
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<tr>
<td>REM sleep latency</td>
<td>124.0 ± 18.6</td>
<td>114.8 ± 16.9</td>
<td>ns</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>15.2 ± 2.2</td>
<td>15.2 ± 2.0</td>
<td>.06</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>57.1 ± 2.8</td>
<td>51.7 ± 2.5</td>
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<tr>
<td>% Stage 3</td>
<td>6.4 ± 0.6</td>
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<td>.01</td>
</tr>
<tr>
<td>% Stage 4</td>
<td>7.0 ± 1.5</td>
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<tr>
<td>% REM sleep</td>
<td>14.3 ± 1.4</td>
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</tr>
<tr>
<td>REM period</td>
<td>4.3 ± 0.3</td>
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<tr>
<td>Wake (min)</td>
<td>36.1 ± 9.7</td>
<td>20.8 ± 14.1</td>
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</tr>
<tr>
<td>% Sleep efficiency</td>
<td>92.1 ± 2.1</td>
<td>15.8 ± 0.8</td>
<td>ns</td>
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<tr>
<td>Total sleep time</td>
<td>444.5 ± 13.7</td>
<td>472.6 ± 5.2</td>
<td>.05</td>
</tr>
</tbody>
</table>

Figures 1 and 2

Conclusions: These results show that the minimal sleep disturbances associated with the first-night effect in young healthy participants has no impact on the following morning waking EEG activity in recorded with central electrodes. We have reported comparable results in a different set of subjects using quantified EEG measures obtained during REM sleep (1). The fact that frontal and temporal electrodes show an overnight effect on waking EEG activity following a normal night of sleep suggests that different neural networks have different sensitivity to the effect of sleep (2).

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(3) Supported by the “Fonds de la recherche en santé du Québec”

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Fatigue or Sleepiness? Evaluation of Pichot-Brun and Epworth Sleepiness Scales

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Introduction: Fatigue and Sleepiness are often hardly differentiated in patients complaints. Nevertheless, there are important social implications and medical consequences in this distinction. If sleepiness may be reliably measured by subjective and objective tools, fatigue is a wooly symptom. We used 2 validated scales to compare subjective sleepiness complaints and fatigue complaints among patients suffering from sleep disorders.

Methods: 583 patients from the Bordeaux Sleep University Clinic were screened with Pichot-Brun (PIC) and Epworth Sleepiness Scales (EPW) self reports. Their scores were compared according to : (1) General data ; (2) The ICSD Diagnosis; (3) Nocturnal Polysomnography recorded at the Sleep Clinic (n=360) and MSLT (n=222; (4) Psychometrics : Hamilton scales for depression (HD) and for anxiety (HA) and Minnesota Multiple Personality Inventory (MMPI).

Groups are compared : (Gr1) EPW £ 15 and PIC £ 20 (318 patients); (Gr2) £ 15 and PIC >20 (92 patients); (Gr3) EPW >15 and PIC £ 20 (96 patients); (Gr4) EPW >15 and PIC > 20 (74 patients). Statistics with Chi square ad ANOVA

Results: 1- General data : all patients were between 18 and 70 years old, with a comparable distribution in the 4 groups (mean age 47±15). There were 239 women and 344 men, the sex-ratio W/M was higher in Gr2 and Gr4 (50 and 51,35) than in Gr1 and Gr3 (38,36 and 34,38). BMI was the same in the 4 groups. There are strong positive correlations, respectively, between Morningness and Sleepiness (EPW) and between Eveningness and Fatigue (PIC). 2- ICSD Diagnosis: In 453 patients the distributions are different in the 4 groups : low PIC in primary Hypersomnies and Respiratory Disorders, high PIC in Secondary Hypersomnies (neurological or psychiatric), in Insomnies and in Fibrositis. 3- Polysomnographic records : MSLT data exhibit, with high levels of EPW, increased sleep propensity and REM propensity, which are greater in Gr 3 than in Gr 4. Night sleep exhibits some differences between the 4 Groups : increased Sleep latency in Gr2, decreased REM latency in Gr 3, REM Time increased in Gr3 and Gr4, Wake Time increased in Gr2. 4 - Psychometric data : An important relation appears between high PIC scores, high levels of anxiety (HA) and psychopathological dimensions of the MMPI as Depression, Psychasthenia, Hypochondria, Hysteria and Schizophrenia items (Gr2 and Gr4).

Conclusions: In patients with sleep disorders, Epworth and Pichot self-evaluation scales are related to different objective physiological and psychological variables such as Eveningness preference, daytime sleepiness, night sleep organization. Among a population of sleepy subjects, fatigue scores can help discriminating clinically sleep disorders.


Usefulness of a Modified MSLT in the Diagnosis of Disorders of Excessive Sleepiness

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The Sleep Disorders Center, New York-Presbyterian Hospital, Columbia Presbyterian Medical Center

Introduction: The Multiple Sleep Latency Test (MSLT) is the standard tool to assess excessive daytime sleepiness (EDS) and to definitively diagnose narcolepsy. Typically, patients keep a sleep log for one to two weeks prior to the MSLT to document sleep wake schedules. Following polysomnography, which typically limits patients to 7-8 hours of time in bed, a MSLT is performed with the first nap conducted 1.5-2.0 hours following morning awakening. Diagnostic confusion may occur in long sleepers and patients with CNS hypersomnolence whose daytime symptoms may have resulted from their attempting to adhere to a limited sleep schedule. In these patients interpretation of the MSLT is confounded by the forced awakening, which truncates sleep and starts the day of the MSLT with some undetermined degree of sleep deprivation. Therefore, abnormally short sleep onset latencies and the presence of REM naps on the MSLT may be a reflection of sleep deprivation. We report data on a modified protocol, which minimizes the effects of sleep deprivation on the MSLT and helps distinguish narcolepsy from long sleepers and CNS hypersomnolence.

Methods: This is a retrospective report on eight patients whose charts were reviewed on the basis of two criteria: 1) each had a previous diagnosis of narcolepsy based on the original MSLT protocol and 2) each were seeking reevaluation. All patients were restudied on a modified PSG/MSLT protocol. The protocol asks patients to allow a minimum of 8 hours for sleep each night for a week before testing. On the PSG patients are allowed to sleep until they awaken spontaneously. Nap opportunities begin 1.5-2.0 hours after the terminal awakening. The timing of the naps is adjusted so as to allow 1-4 naps over the balance of the day.

Results: The modified MSLT protocol divided patients into two distinct groups. Four patients awoke spontaneously after about 7 hours of sleep (Group A); four patients awoke spontaneously after about 12 hours of sleep. Table 1 shows the sleep data (means) for all patients studied on the original protocol. Table 2 shows how the data from the 8 patients fell into 2 distinct groupings with the modified protocol. The A Group retained the short sleep onset and REM latencies on the naps. The results for Group B were changed dramatically by the protocol for all parameters. The long nocturnal sleep times decreased the patients’ excessive daytime sleepiness and decreased the incidence of REM naps. Patients had 0-4 naps opportunities on the modified protocol depending on their total sleep time; one patient had no nap opportunities, as his terminal awakening occurred after 17 hours of sleep, at 6:45 p.m. Group A, we...
feel, includes the truly narcoleptic subjects. Group B subjects may be more accurately diagnosed with "other disorder of sleepiness". Also noteworthy, Group A patients were positive for cataplexy, while Group B patients were not.

**Conclusions**: This review suggests that the modified MSLT protocol may be a useful diagnostic tool for distinguishing narcolepsy from other disorders of excessive daytime sleepiness.

171.R

**A Comparison Between Measurements of Sleep Efficiency and Sleep Latency Measured By Polysomnography and Wrist Actigraphy**

Pilsworth SN, King MA, Shneerson JM, Smith IE
RSCC, Papworth Hospital, Cambridge, UK

**Introduction**: Some new actigraphy software reports sleep-wake data as it is conventionally recorded by polysomnography (PSG). Actigraphy may have practical and cost advantages and because of this practice parameters have been proposed by ASDA (1). These recommendations and other work (2 and 3) suggest uncertainty in the use of actigraphy for describing sleep periods. Although the relationship between PSG and actigraphy sleep parameters in normals appears acceptable, comparisons in patients with sleep disorders have been poorly conducted. This study compares the 2 techniques to measure sleep latency (SL) and sleep efficiency (SE) and uses standard data analysis techniques.

**Methods**: PSG (Alice3, Healthdyne) and Actigraphy (Cambridge Neurotechnology) were recorded on fifty consecutive patients in the Papworth Sleep Laboratory. Actigraphs were worn on the non-dominant wrist and a standard PSG recording montage for sleep was used. The PSG records were manually scored using standard Recheshtaffen and Kales criteria. Actigraphy data were scored using an evaluated sleep-wake algorithm (3) after each record had been corrected for time in bed. Bland Altman analysis techniques were used.

**Results**: The study group was characterised by a PSG SE range 23.8-99.1% and SL range of 2 –98.0 min. The data shows significant positive correlation between PSG and actigraphy for SL and SE (rho = 0.316 and 0.356 respectively at p<0.05). Bland-Altman analysis indicates that while most of the data lies within 2sd of the mean difference this range is not clinically acceptable. The data shows divergence from the mean difference with worsening SE and SL as below.

**Conclusions**: The disparity between PSG and actigraphy results does not exclude independent clinical use of actigraphy which has been reported as an accurate and reliable tool in normals (1). In patients with an abnormal SL or SE actigraphy may be unreliable. Change in terminology is perhaps indicated. It is clear that PSG using EEG is measuring sleep and so conventional terminology is preserved. Actigraphy does not directly measure sleep but reflects changes in activity levels and therefore cannot measure sleep latency but more accurately a termination of activity, and sleep efficiency could be termed more accurately as %inactivity of TIB.

**References**: (1 ) Practice Parameters for the use of Actigraphy in the Clinical Assessment of Sleep Disorders. American Sleep Disorders Association, Sleep, 1995 May;18(4):285-7
(3) L Babin, S Lee, AC Boudreau, CFP George. Determining Sleep-Wake Activity using Acitwatch;Sleep(197) Vol 2, 355

172.R

**Arousal Components Which Differentiate the MWT From the MSLT**

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(1) Dayton Department of Veterans Affairs Medical Center, (2) Wright State University, (3) Kettering Medical Center

**Introduction**: It is well-known that sleep latency on the MWT is longer than sleep latency on the MSLT. The purpose of this study was to determine the relative contribution of the instruction to maintain wakefulness.

**Table 1 - Sleep parameters for all patients studied on the standard protocol.**

<table>
<thead>
<tr>
<th>Dx: Narcolepsy</th>
<th>TST</th>
<th>SE</th>
<th>ROL</th>
<th># of patients with at least 2 REM naps</th>
<th>Mean SOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLT Standard</td>
<td>403</td>
<td>87%</td>
<td>75</td>
<td>8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

**Table 2 - Sleep parameters for Groups A and B on modified MSLT protocol.**

<table>
<thead>
<tr>
<th>Group</th>
<th>TST</th>
<th>SE</th>
<th>ROL</th>
<th># of patients with at least 2 REM naps</th>
<th>Mean SOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>765</td>
<td>93%</td>
<td>93</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>765</td>
<td>93%</td>
<td>93</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

**Figure 1**

**Figure 2**

**Table 3 - Sleep parameters for Groups A and B on modified MSLT protocol.**

<table>
<thead>
<tr>
<th>Dx: Narcolepsy</th>
<th>TST</th>
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<th>ROL</th>
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<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>
versus posture change as major arousal components determining sleep latency in the MWT as compared to the MSLT.

**Methods:** After adaptation, 14 normal subjects spent 3 nights and the following days in the laboratory. On each day, Ss had eight sleep latency measurements including four sleep latency tests from two of the following conditions: Lay down and sleep (MSLT); Lay down and stay awake (LayWake); Sit up and sleep (Sit-Sleep); Sit up and stay awake (Sit-Wake); and sit in a chair in front of a computer and stay awake (Computer).

**Results:** Sleep latency data for the five conditions are plotted in Figure 1. A significant main effect was found for nap condition ($F_{(4,220s)} = 31.11$, $p < .001$). Newman-Keuls pairwise comparisons indicated that mean latencies in all of the nap conditions differed significantly from all others with the exception of the difference between the Sit-Wake Condition and the Computer Condition. The mean heart periods for the conditions are plotted in Figure 2. Again, a significant effect for Condition ($F_{(4,369s)} = 25.67$, $p < .0001$) was found. Heart rate was significantly higher when Ss sat in front of the computer than in all other conditions, and higher in the Sit-Wake condition as compared to all remaining conditions.

**Conclusions:** The MWT differs from the MSLT by taking advantage of the arousal system (motivation, light, and posture) to maintain alertness (i.e., increase sleep latency). Hartse et al (1982) compared a traditional MSLT with a -condition where Ss lay in bed in the dark with their eyes closed and stayed awake. That manipulation increased sleep latencies by 4.5 minutes. In the present study, sleep latencies were increased by 10.6 min compared to the MSLT when subjects were asked to lay in bed and stay awake (dim light with eyes open). The 6-minute difference is probably due to the increased arousal associated with open eyes and dim room light. Sifting up increased latencies by 7 minutes whether Ss were trying to fall asleep or stay awake. The effect of these arousal components was additive: Lay-Wake increased latency by 11 minutes; the request to Sit added 7 minutes to the standard MSLT. In the Sit-Wake Condition, Ss took 18 minutes longer to fall asleep (111 min. for staying awake and light plus 7 min. for sitting). MSLT and MWT results may not correlate well because the MWT measures the combined effects of the sleep and arousal systems. These data attest to the importance of environmental control during testing - even subtle changes in MSLT or MWT environment may provide additional stimuli which prolong wakefulness. At another level, the impact of individual stimuli upon the ability to maintain wakefulness is important in the design of industrial or educational environments. Use of specific arousal components can help increase alertness during sedentary activities.

**Supported by the Dayton Department of Veterans Affairs Medical Center, Wright State University School of Medicine, and the Sleep-Wake Disorders Research Institute**

**173.R**

The Epworth Sleepiness Scale: Widely Used and Often Misinterpreted?

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**Introduction:** The Epworth Sleepiness Scale (ESS) was designed to give a subjective report of objective sleep propensity in daily life (Johns, 2000). It is widely used but its wording may be ambiguous. Some of our patients interpret the “chance of falling asleep” as meaning “feeling sleepy”, without actually falling asleep, whilst others interpret it literally. The aim of this study was to explore this dichotomous interpretation by changing the precise wording of the questionnaire.

**Methods:** Two alternative versions of the ESS were devised. Where the ESS asks, “How likely are you to fall asleep” the terms ‘Do you feel sleepy’ and ‘Do you actually fall asleep’ were inserted. They were named the “Feeling Sleepy Scale” (FSS) and “Falling Asleep Scale” (FAS) respectively. 75 patients who had presented to the Papworth Hospital Sleep Centre with various sleep disorders and 25 healthy volunteers were recruited (N = 100, median age of 48.5 yrs, range 20 to 74; male/female ratio 62:38). All subjects completed the ESS first, followed by the other two versions in random order. The scoring system was the same for all versions.

**Results:** The median scores for the ESS, FSS and FAS were 9 (range 0 to 24), 11 (0 to 24), and 9 (0 to 22) respectively. The Friedman test revealed that the three versions differed significantly ($\chi^2 = 90.920$, df = 3, $p < 0.0005$). Wilcoxon Signed Ranks tests showed that the FSS and the FAS were significantly different from each other ($z = 6.225$, N - ties = 62, $p < 0.0005$) but the FAS was not significantly different from the ESS ($z = 0.974$, N - ties = 67, $p = 0.330$). This suggests that most subjects interpreted the ESS literally. However, 18 per cent of subjects had an ESS score closer to the score for the FSS than to the one for the FAS. Moreover, examining the difference scores for the ESS and the FSS confirmed the dichotomous interpretation proposed, the most frequent value being 0 (see Figure).
Conclusions: This study shows that changing the precise wording of the Epworth Sleepiness Scale may result in different scores. Most subjects interpreted the “chance of falling asleep” as “actually falling asleep”. However, an important proportion had difficulty in differentiating “chance of falling asleep” from “feeling sleepy”. This makes it likely that the ESS may not always reflect objective sleep propensity as previously proposed.

References:
(1) Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. Journal of Sleep Research 2000; 9:5-11

174.R

Pupillometry In Clinically Sleepy Patients

Hauri PJ, McLaren JW, Lin SC
Mayo Clinic Rochester and Mayo Clinic Jacksonville

Introduction: The following is a re-analysis of some data originally reported in 1992, but using new parameters (7 of the variables developed by McLaren et al [1992], and 11 of those suggested by Lüdtke et al [1998]). There is no doubt that pupillometric variables correlate with sleepiness; but we wondered whether on a clinical level pupillometry could actually replace the more cumbersome multiple sleep latency test (MSLT).

Methods: Subjects were 49 not yet diagnosed but clinically sleepy patients undergoing a standard diagnostic MSLT at Mayo Clinic. All patients were then separated into 3 groups: severely sleepy (N=23, MSLT sleep latency <5 min.); moderate sleepiness (N=18; SL 5-10 min.); and mild sleepiness (N=8, SL >10 min.).

Results: Multiple regression analysis indicated that McLaren et al’s variable of Sum of Squares (SS) (0.01, 0.04) was the best predictor of MSLT sleep latency. (SS [0.01, 0.04] is a measure of pupillary fatigue waves, filtering the data with a digital band path filter with cutoffs at 0.01 Hertz and 0.04 Hertz). Adding any of the other 17 variables to the multiple regression analysis did not improve the relationship. However, attempting to predict MSLT groups (severe, moderate, mild) from SS (0.01, 0.04), and using the best empirical cutoff scores, could only classify 45% of the patients correctly (see figure 1). Figure 1 suggests some possible clinical usefulness for pupillometry. If replicated, our data suggest that high SS (0.01, 0.04) scores are predictive of short MSLT sleep latencies. Low SS scores do not predict any scores on the MSLT. Thus, one might run a 15-minute pupillometry session just before starting with the all day MSLT. If the patient has high SS scores (say, above 4), he is documented to be excessively somnolent and does not need an MSLT. If scores are lower than the cutoff, the usual all day MSLT needs to be done. In our sample, this would have meant that about 40% of the patients would not have to undergo an MSLT.

Conclusions: Pupillometry might be useful in selecting clinically sleepy patients who do not need an MSLT.

References:

This investigation was supported by a grant from Mr. and Mrs. J. A. Piscopo, Oakbrook, Illinois.

175.R

Epworth and Daytime Sleepiness Scales: Psychometric Comparison in a Community-based Sample

Johnson EO, Breslau N, Roehrs T, Chase G, Drake C, Roth T
Henry Ford Health Sciences Center, Detroit, MI

Introduction: The Epworth Sleepiness Scale (ESS) assesses excessive daytime sleepiness (EDS) by asking respondents to rate how likely they are to fall asleep during daytime activities. The Daytime Sleepiness Scale (DSS) assesses EDS by asking respondents how often they have fallen asleep or got drowsy during daytime activities over the past two weeks. A psychometric evaluation of the ESS has not been made in a community-based sample and the relative merits of the ESS and DSS have not been compared. In this study, we examine the factor structure, reliability, and construct validity of each of these scales.

Methods: These preliminary data come from the Epidemiology of Daytime Sleepiness Study. To date this study has collected information from a representative sample of 833 people 18-65 years of age in the Detroit primary metropolitan statistical area. The survey used random digit dialing and computer-assisted telephone interviewing techniques. Analyses of factor structure and internal consistency were conducted with split-half samples to assess replicability of the results.

Results: For each split-half sample very similar results were found. A
two-factor model appeared to best account for the variation among the items of the DSS, accounting for 52% of the variance. Factor one was a measure of falling asleep during daytime activities while factor two was a measure of daytime drowsiness. These factors were correlated at \( r = 0.36 \). A two-factor model also appeared to best account for the variation among the items of the ESS, accounting for 53% of the variance. The two factors appeared to measure probability of falling asleep in public versus private, between factor correlation equal 0.43. Factor based scales showed good internal consistency for scales with so few items (three to four items per factor scale): \( \alpha = 0.60 - 0.67 \) (mean correlations = 0.30-0.34). All scales were inversely correlated with total sleep time \( (r = -0.2, p < 0.05) \) and positively correlated with frequency of snoring and number of days of reduced productivity due to sleep problems \( (r = 0.15 - 0.2, p < 0.05) \). In a subset of subjects \( (n=105) \) for whom Multiple Sleep Latencies were available, the ESS total scale score was not associated with pathological sleepiness \( (\text{MSLT} < 5), p = 0.15 \). For the DSS total scale score each one point increase was estimated to increase risk of pathological sleepiness by 14% \( (p = 0.03) \). When factors were examined separately, factor 1 of the DSS (falling asleep during daytime activities) and factor 2 of the ESS (falling asleep in private during daytime activities) were significantly associated with an MSLT of less than five minutes \( (p = 0.02, p = 0.05) \); each one point increase there was an estimated 31% and 25% percent increased probability of being pathologically sleepy, respectively.

Conclusions: The DSS and the ESS showed good psychometric properties and were associated in expected ways with self-reported total sleep time, snoring, and sleep related disability. However, it is suggested that only a subset of items from the DSS and ESS are significantly associated with the MSLT.

Research supported by MH59338

176.R

Autonomic Activation Index (AAI) - A New Marker of Sleep Disruption.

Pillar G,1 Shlitner A,2 Lavie P1
(1) Sleep Laboratory, Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa., (2) Itamar Medical Ltd., Cesarea, Israel

Introduction: Sleep fragmentation in the form of frequent “brief arousals” or “microarousals” have been implicated in daytime impairment of cognitive and psychomotor performance, particularly in breathing disorders in sleep. Large interscorer’s variability in scoring microarousals and poor correlations with daytime measures of sleepiness have led to the suggestion that autonomic markers of arousal may be more reliable predictors of daytime sleepiness than EEG-defined arousal. The term “autonomic arousal” is used to denote transient changes during sleep in autonomic parameters such as in heart rate and blood pressure, which are not necessarily associated with any visible alpha or beta activity in the EEG. This has led several authors to suggest that markers of autonomic activation (e.g. continuous blood pressure monitoring or pulse transit time) should be included in routine sleep studies to assess the true extent of sleep fragmentation. Finger plethysmography is a simple technique that allows measurements of hemodynamic variations in the tip of the finger. Previously we used a novel peripheral arterial tonometer (PAT), which is a modification of finger plethysmography, and showed that it can accurately detect apneic events during sleep. Here, we enlarged upon these findings and report that this technique allows the construction of an index of autonomic arousal during sleep, which is highly correlated with ASDA-defined microarousals.

Methods: Twenty-four subjects (19 men and 5 women, 19 patients referred to the sleep lab with suspected OSA plus 5 healthy volunteers, age 45.6±12.0 years, BMI 30.3±8.4 Kg/m2 , RDI=35.5±32.1) underwent all-night polysomnography with simultaneous recordings of peripheral arterial tonometry. The recordings were blindly analyzed for arousals based on ASDA criteria, and for autonomic arousals based on attenuations of at least 33% in PAT signal associated with 10% increase in heart rate.

Results: There was a significant correlation between ASDA and PAT arousals \( (R=0.95, p<0.01) \). PAT arousals also correlated significantly with RDI \( (R=0.8, p<0.05) \). Fig 1 demonstrates the Bland-Altman analysis between arousals as determined by ASDA criteria and by PAT. As can be seen, except for a few exceptions, there was a good agreement between ASDA and PAT based arousals, across a wide range of values.

Conclusions: We conclude that this modified finger-plethysmographic technique can detect phasic sympathetic activations during sleep, which are associated with microarousals from sleep. This technique can be very valuable for an automatic screening of autonomic arousals during sleep.
Introduction: Sleep disorders are highly prevalent, albeit under-recognized and under-diagnosed by most health care providers. Lack of adequate sleep medicine education, cultural beliefs about, and perjorative attitudes toward sleep, have all been cited as contributing factors to the failure of knowledge transfer in practicing physicians. The NIH-funded Sleep Disorders are highly prevalent, albeit under-recognized and under-diagnosed by most health care providers. Lack of adequate sleep medicine education, cultural beliefs about, and perjorative attitudes toward sleep, have all been cited as contributing factors to the failure of knowledge transfer in practicing physicians. The NIH-funded Sleep Academic Award (SAA) program was developed to provide and promote model educational programs and sleep training curricula broadly. A survey instrument ("MEDSleep") was developed by members of the SAA program to specifically assess knowledge, beliefs/attitudes and behavior regarding sleep and sleep disorders in undergraduate medical students and other health professionals. We present here the initial stages of instrument development and validation.

Methods: The survey consisted of 50 questions delivered via an Internet web site (www2.umdnj.edu/medsleep). Thirty questions on sleep knowledge were derived from a previously reported instrument ("ASKME Survey"). Twenty questions on behavior and attitudes regarding sleep were based on a pre-existing survey developed by Boehlecke et al. The purpose was to provide additional validation for the ASKME Survey and to further query undergraduate and graduate medical students regarding their current sleep-wake behavior (10 q’s) and attitudes towards sleep (10 q’s). Pilot testing of the instrument was conducted with students enrolled at accredited United States medical schools participating in the SAA program. Immediate feedback for correct responses was given for the thirty required knowledge questions. Item analysis was conducted on all knowledge questions. The results were analyzed for the percentage of correct responses given for the knowledge questions, with a further analysis according to question category and the student’s current level of training (e.g., M1-M4). Mean scale scores and frequency data were derived for questions on sleep-wake behavior and beliefs/attitudes towards sleep. Factor analysis and inter-item correlations were performed to further validate and refine the scales.

Results: Preliminary analyses were based on a total of 466 respondents. An approximately equal distribution of M1-M4 students accounted for 79% of the sample. Point biserial correlation for sleep knowledge questions was 0.83 (KR 20), which indicated a high degree of internal consistency among items. The mean percentage for correct responses in sleep knowledge for the entire group was 58.6%±18.8%. Differences across time were statistically significant (F=5.4; p<.001), but no trend indicating inflation was observed. Differences across time were statistically significant (F=5.4; p<.001), but no trend indicating inflation was observed. Mean percent scores on the sleep apnea station were statistically significant between groups (18.7 vs 16.0; F=23.0; p<.001). Students who received the lecture on sleep apnea scored significantly higher on the station than did students who did not. Scores on this station from one administration to the next ranged from a low mean of 15.1 (0.7) to a high of 18.5 (0.8). Differences across time were statistically significant (F=5.4; p<.001), but no trend indicating inflation was observed.

Table 1

<table>
<thead>
<tr>
<th>Group of Students</th>
<th>Mean (Std Err)</th>
<th>Lecture</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>List five symptoms</td>
<td>7.4 (0.3)</td>
<td>6.1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Name clinical syndrome</td>
<td>2.0 (0.1)</td>
<td>1.7 (0.1)</td>
<td></td>
</tr>
<tr>
<td>List fundamental problem</td>
<td>2.2 (0.1)</td>
<td>2.1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of this disorder</td>
<td>1.4 (0.1)</td>
<td>1.3 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases associated with the disorder</td>
<td>5.7 (0.2)</td>
<td>4.8 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Overall Mean Score**</td>
<td>18.7 (0.4)</td>
<td>16.0 (0.4)</td>
<td></td>
</tr>
</tbody>
</table>

**F=23.0; p<.001

Conclusion: The MEDSleep Survey is a relatively brief and easy to administer instrument that measures sleep knowledge, attitudes and behavior. This instrument is designed to provide pre- and post-test measures in conjunction with an educational intervention for sleep medicine. Further studies are planned to assess the construct validity and sensitivity to change of this instrument.

References:

Research supported by K07 HL03635 to RR; K07 HL03637 to BP; K07 HL03897 to BR; K07 HL03645 to AA; K07 HL03647 to DD; K07 HL03891 to PZ.

178.S

An Intervention Can Improve Medical Students’ Recognition of Sleep Apnea

Papp KK, Strohl KP
Department of Medicine, Case Western Reserve University and the Louis Stokes Cleveland VA Medical Center, Cleveland OH

Introduction: We report the effects of introducing formal curricula on the topic of obstructive sleep apnea hypopnea syndrome in the third-year internal medicine clerkship, using a novel station format.

Methods: Six consecutive student groups in the 3rd year internal medicine clerkship from January 1999 through July 2000 (n=259) participated in the study. Half (n=130) received a one hour lecture on obstructive sleep apnea hypopnea syndrome; half (n=129) did not. All completed an Objective Structured Clinical Examination (OSCE) in partial fulfillment of the requirements of the clerkship. The OSCE consists of 17-23 stations; on one station, students observed unlabeled videotape of a person exhibiting several obstructive sleep apneas. The students were asked to diagnose the condition and list clinically relevant facts. The station was scored using a uniform behavioral checklist. Students received full-, partial-, or no credit for each item, which were summed across items and across stations for overall OSCE scores.

Results: Mean percent scores on the sleep apnea station were statistically significant between groups (18.7 vs 16.0; F=23.0; p<0.001). Students who received the lecture on sleep apnea scored significantly higher on the station than did students who did not. Scores on this station from one administration to the next ranged from a low mean of 15.1 (0.7) to a high of 18.5 (0.8). Differences across time were statistically significant (F=5.4; p<0.001), but no trend indicating inflation was observed.
Conclusions: Students who received the curricula on obstructive sleep hypopnea syndrome exhibited better performance on an OSCE station testing their ability to observe and recognize obstructive sleep apnea.

References:

Research supported by NHLBI HL-03650 Sleep Academic Award, a VA GRECC Award, and the VA Research Service

179S

Knowledge about Sleep and Driving In Australian Adolescents

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Introduction: Road statistics in Australia suggest that 18% of all fatal accidents and 30% of fatal accidents in rural areas are attributable to driver fatigue. (1) Driver fatigue and sleepiness is a major problem at all driving ages but particularly in young drivers (2). The driver is often alone, and is especially likely to be young and male (2). A recent NIH workshop (3) identified the lack of data on sleep knowledge in adolescents that would be needed to design and target sleep health promotion strategies. As part of a larger study involving measuring resiliency characteristics and health behaviours in adolescents we asked 5 questions related to sleep knowledge and driving.

Methods: The study group consisted all students involved in a prospective confidential survey of the influence of the Rock Eisteddfod Challenge (REC) on health behaviours. 1387 students from 17 schools in years 8, 9, 10 and 11 completed the survey. The age of the students ranged between 13 and 17 with a mean age of 14.85 (SD=0.92). 31.6 % of participants were male and 63.9 % were female. The preponderance of female participants reflected the higher female participation rate in the REC. The 5 sleep knowledge statements are listed below. 1. Raising the volume of your radio will help you stay awake whilst driving.2. Younger people (aged 17-25) need less sleep than older people3. Most young adults can get by on 4 or 5 hours sleep per night.4. In young drivers, lack of sleep increases the effect of 2-3 glasses of beer (or other alcohol) on driving alone, and is especially likely to be young and male (2). A recent NIH workshop (3) identified the lack of data on sleep knowledge in adolescents that would be needed to design and target sleep health promotion strategies. As part of a larger study involving measuring resiliency characteristics and health behaviours in adolescents we asked 5 questions related to sleep knowledge and driving.

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Results: Incorrect, don’t know or correct responses to statements were respectively -
1. 31%, 26%, 43% 
2. 19%, 23%, 58% 
3. 15%, 20%, 65% 
4. 8%, 36%, 57% 
5. 20%, 51%, 29%

Females generally answered more correctly (p<.01). In females, but not males, the proportion with correct responses increased with age. Lack of knowledge on sleep and driving was correlated with low scores on adolescent resiliency, a measure of individual ability to resist peer and other social pressures towards inappropriate health behaviours.

Conclusions: Sleep and driving knowledge in adolescents is poor. Only 7% of the sample answered all 5 questions correctly. Answers to questions revealed a misperception as to the relative risk of younger versus older drivers. Males had more incorrect scores than females and failed to improve scores as they approached the age of eligibility for driver licenses. High school health promotion and young driver education programs need to focus on the risks of falling asleep while driving, particularly in young drivers.

References:

Research supported by Rock Eisteddfod Challenge and NSW Department of Health

180S

A Tool to Assess Sleep Apnea Knowledge and Attitudes Among Physicians

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Introduction: Despite the high prevalence and clinical significance of obstructive sleep apnea (OSA), primary care physicians are not always skilled at identifying the disorder (1,2). Several recent studies have suggested that educational interventions are necessary to improve the identification and treatment of patients with OSA (1-3). However, in order to target educational strategies for physicians, it is useful to ascertain their baseline familiarity with OSA.

Methods: To this end, we developed a questionnaire to assess knowledge regarding OSA among physicians. The Obstructive Sleep Apnea Knowledge Assessment (OSAKA) consists of 20 true-false statements about OSA; “don’t know” is a third response choice, scored as an incorrect response. Respondents are then asked to rate their level of agreement with 4 statements regarding the importance of OSA and their ability to identify and manage patients with OSA using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). In addition, information regarding demographic data is also collected.

Results: The OSAKA was piloted among a group of physicians associated with the Washington University Physician Network. Nine men and eleven women returned completed questionnaires (45% of those surveyed). Respondents’ mean age was 38.2 years (range = 28-57 years) and the mean number of years in practice was 6.9 years (range = 0.25-29 years). The percentage of correct answers ranged from 60-95% (mean ± standard deviation [M ± SD] = 79.4 ± 11.5). Respondents tended to agree with the statements about the importance of OSA as a clinical disorder (M ± SD = 4.4 ± 0.5) and the importance of identifying patients with OSA (M ± SD = 4.4 ± 0.5). Greater variance was observed in their self-reported confidence in identifying patients at risk for OSA (M ± SD = 3.6 ± 0.8) and in managing patients with OSA (M ± SD = 3.2 ± 1.0).

Conclusions: The OSAKA appears to be a useful instrument to measure physicians’ knowledge about OSA, their views on the importance of OSA as a clinical disorder, and their confidence in identifying and managing patients with OSA. We intend to use this questionnaire in a needs
Exposure to Electromagnetic Fields Emitted by Mobile Phones Affect Human Sleep EEG

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Introduction: The extensive use of mobile phones has given rise to a public debate about possible adverse effects on human health. There are increasing numbers of studies investigating the biological effect of exposure to radio frequency electromagnetic fields (EMF) of the type GSM (Global System for Mobile communications) on cell cultures, animals and humans. Recently, we reported that EMF exposure during sleep (Borbély et al., 1999) and exposure during waking prior to sleep (Huber et al., 2000) resulted in comparable effects on the sleep EEG. The aim of the present abstract is to compare our two previous studies and to expand the analysis of the experiments.

Methods: In a first study 24 subjects were exposed during sleep to an intermittent EMF (900 MHz; modulated with 2, 8, 217, 1736 Hz; spatial peak specific absorption rate 1 W/kg). In a second study subjects (n=16) were exposed for 30 min to an EMF (same field) during the waking period preceding sleep. Either the left or right hemisphere or none of the hemispheres was exposed. Both studies were carried out with healthy young male subjects (age 20-25 years) and a double-blind cross-over design was applied. Simulation of the distribution of the specific absorption rate (SAR) within the brain was performed based on the magnetic resonance imaging data set of the head of a healthy female subject.

Results: In both experiments spectral power in the 9-14 Hz frequency range of the EEG in non-REM (NREM) sleep was initially increased compared to sham exposure (see Figure 1). No topographical differences of the EMF effect were observed. Furthermore, unilateral EMF exposure during waking induced no hemispheric asymmetry of EEG power during NREM sleep. The simulation of SAR revealed a homogenous SAR distribution in the cortex when subjects were EMF exposed during sleep whereas an asymmetrical SAR distribution emerged when subject were unilaterally exposed prior to sleep. In both experiments high SAR values were present in deeper brain structures. In addition to our main EEG finding, exposure during sleep reduced waking after sleep onset and affected heart rate variability during sleep, whereas exposure prior to sleep reduced the heart rate during waking.

Conclusions: The results indicate that EMF emitted by mobile phones affect brain physiology. For the first time, EMF effects on sleep were confirmed in two successive experiments. Furthermore it has been shown that the effects of EMF outlast the exposure period. Interestingly, no asymmetrical EEG effect was present after unilateral EMF exposure. Two explanations may be considered: 1) The attenuated field reaching the non-exposed hemisphere is sufficient to affect the EEG. 2) Subcortical regions may contain the most sensitive structures to EMF (e.g. thalamus) and their bilateral cortical projection may explain the absence of a hemispheric asymmetry. The high simulated SAR values in deeper brain regions support this notion.

References:

Research supported by Swiss National Science Foundation, grant 3100-053005.97, the Human Frontiers Science Program grants RG-81/96 and RG-0131/2000, Swiscom (experiment 1), the Swiss Federal Office of Public Health (experiment 2)
Results: Parasympathetic activity, as indexed by high frequency spectral power, was significantly higher in the control group throughout NREM (p < .05) and REM sleep (p < .01). Mixed effects analyses revealed a significant group and group by time interaction for autonomic tone profiles across NREM sleep cycles (Figure 1). In the control group, parasympathetic activity significantly increased across each subsequent NREM period (p < .01). A more gentle, but significant, decrease across subsequent NREM periods was seen in the stress group (p < .01). Parasympathetic tone remained constant across REM periods; levels were higher in the control group during each REM period (p < .01). Finally, logistic regression revealed that reactivity to the experimental manipulation was a significant predictor of parasympathetic tone during NREM sleep (Figure 2). Regardless of group, greater cardiovascular reactivity during task notification was associated with lower parasympathetic tone during NREM sleep (p’s < .05).

Conclusions: Stress had a significant impact on autonomic tone during both NREM and REM sleep. Greater levels of stress, defined by experimental group or cardiovascular reactivity to the experimental manipulation, were associated with lower levels of parasympathetic activity during NREM and REM sleep. In contrast, the greatest increase in parasympathetic activity across the night was seen in control group subjects who showed the least amount of cardiovascular reactivity during the experimental manipulation. Results suggest that stressful life events can significantly affect parasympathetic predominance during sleep, which may then impact sleep depth and continuity. The relationship between psychological stress, autonomic tone, and sleep may be especially important in sleep disorders associated with psychiatric illness or insomnia, where stressors may both precipitate and perpetuate clinically-significant sleep disruptions.

References:

Research supported by MH01554, MH24652, MH30915, MH52247, RR00056

183.B

Sleep Onset has a Major Effect on Autonomic Control of Cardiac Activity

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Introduction: A number of papers have demonstrated a 24-hour rhythm in the autonomic control of cardiac activity, showing that the sleep-wake cycle is a major determinant of the rhythm. One remaining consideration is the role of the circadian system. In a previous study (1), using a constant routine procedure, a circadian influence over vagal tone was observed, as indicated by the High Frequency (HF) component of Heart Rate Variability (HRV). In contrast, there was a sleep influence over Sympathetic Nervous System (SNS) activity, as indicated by Pre-ejection Period (PEP). However, a subsequent study (2), using a delayed sleep onset procedure, failed to replicate the circadian influence over vagal tone, instead showing a strong sleep influence. The current study was designed to reconcile these differences.

Methods: Seven subjects were run in each of 3 conditions in an independent group design. In conditions 1 and 2, subjects were administered a modified constant routine. They slept in the laboratory on night 1, remained in the laboratory during the following day, being in a recumbent position from 9 hours before their Normal Sleep Onset (NSO), and then went to sleep on night 2, 3 hours after their NSO. The two groups differed in their expectations as to when they would go to sleep. Subjects in group three were permitted to go about their normal activities during the intervening day and were put to bed 2 hours before their NSO on night 2. As with the other groups, lights were turned out 3 hours after subjects’ NSO. It was hypothesised that, consistent with the original study (1), subjects exposed to the modified constant routine procedure would show a circadian influence over vagal tone. This would be identified by an increase in the HF component of HRV during the period immediately before and after subjects’ NSO time. In contrast, and consistent with our more recent study (2), subjects in the delayed sleep onset condition would not show an increase in HF activity at this time, but rather, would show an increase at sleep onset. It was hypothesised that the fall in SNS activity (PEP and the LF component of HRV) would be related to sleep onset in all conditions. Sleep-wake state was recorded during all periods that subjects were recumbent. Autonomic activity was measured by the HF (vagal tone) and LF (SNS) components of HRV, and by PEP (SNS). In addition, HR and BP were recorded.

Results: In all 3 conditions the HF component of HRV increased and the LF component decreased abruptly at sleep onset, while PEP increased (decreased SNS) progressively over the recording period.

Conclusions: The results were consistent with the data of Trinder et al., (2) indicating a critical role for sleep onset, but not the circadian system, in determining autonomic control of cardiac activity during the time of the normal sleep period.

References:
(2) Trinder, J., Carrington, M., Breen, S., Kleiman, J., Kim, Y., & Tan, N. (2000). Sleep and circadian control of sleep period cardiac activity. Sleep, 23(suppl.2), A147.

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184.B

Reflex Activation On Arousal From Sleep: An Investigation Of Factors That May Modulate Its Intensity

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Introduction: An arousal from sleep is associated with significant cardio-respiratory activation. The cardiac component is at least in part due to a reflex response elicited by the act of awakening (waking reflex). It is thought to have an energy mobilisation protective function. A question of considerable interest is whether the intensity of the waking reflex can be modified. In this paper we report two experiments that attempted to modulate the magnitude of the cardiovascular response at arousal from sleep. The first varied the properties of arousing stimuli, while the second assessed the influence of individual differences in fearfulness.

Methods: In the first experiment the intensity of the arousal response was assessed during arousals elicited by threatening (eg enactments of rape, murder) or pleasant (eg music, seashore sounds) auditory stimuli. Eight subjects were run on one night in each stimulus condition (threatening versus pleasant sounds), with 10 variations of each stimulus type being presented in random order in each condition. On average 49 (range 36 to 60) stimuli were presented during stage 2 sleep on each night. Stimulus intensity was varied using a staircase procedure designed to maintain stimulus intensity near to threshold and produce an arousal on approximately 67% of trials. In the second experiment the response to a spontaneous arousal was assessed in two groups consisting of high (N=8) and low (N=10) fearful individuals. Fearfulness was assessed by the Fear Survey Schedule, with average item ratings of 3.26 and 1.56 (N=8) and low (N=10) fearful individuals. Fearfulness was assessed by the Fear Survey Schedule, with average item ratings of 3.26 and 1.56 respectively. An average of 36 spontaneous arousals were identified for each subject during sleep stages 1 and 2. Sleep was assessed according to standard procedures and an arousal was defined according to ASDA criteria in both studies. Cardiovascular activation was measured by Heart Rate, Blood Pressure, Pre-ejection Period, and Peripheral Resistance. Responses to both stimulus evoked (experiment 1) and spontaneous (experiment 2) arousals were analysed for each dependent variable by comparing the 10 pre-arousal heart beats with both the average of the first 10 post arousal responses and the peak response.

Results: No cardiac variable differed as a function of stimulus valance (experiment 1) or subject’s level of fearfulness (experiment 2). A serendipitous finding of the first experiment was a bradycardia response to both stimulus types. This response occurred on the first one or two post-stimulus-onset beats, while the tachycardia response of the waking reflex peaked on the 5th beat.

Conclusions: We conclude that the reflex activation response at an arousal from sleep is not modulated by cognitive meanings associated with the arousing stimulus or by psychological traits of the individual sleeper. With respect to the bradycardia, this response has not been observed following spontaneous arousal, or arousal elicited by neutral stimuli, such as tones. Its presence at an arousal to meaningful stimuli suggests it reflects an orienting reflex, confirming earlier studies which had indicated that the cardio-respiratory activation response at arousal from sleep was not the orienting reflex.

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185.B

Objective and Subjective Sleep Disruption Following Dietary Salt Restriction in Normal Subjects

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Introduction: Patients with primary insomnia (PI) exhibit multiple signs of autonomic arousal including increased urinary catecholamines(1). Daytime alertness is increased in PI, despite nocturnal sleep disruption, suggesting physiologic hyperarousal (2). While it remains unclear whether sympathetic nervous system (SNS) activation is a cause or consequence of the insomnia, previous work has demonstrated that induction of SNS activity in normal subjects (through dietary salt restriction) can produce significant nocturnal sleep fragmentation (3). The purpose of this study is determine whether induced SNS activity can reproduce other aspects of PI.

Methods: Eleven healthy, young subjects (18-34y, 5f:6m) were studied in the laboratory for six consecutive days and nights, receiving a normal hospital diet (>100 mEq Na/day) on the first day (Day 0), and a low-salt diet (<17mEq Na/day) thereafter (Days 1-5). Dependent measures included urinary catecholamines collected in 8-hour aliquots beginning at lights-out, polygraphic and subjective sleep measures, MSLT; mood scales, and daytime performance measures. Efficacy and safety of the dietary manipulation were monitored using urine sodium measurements and orthostatic vital signs. Ratings of thirst and salt-craving were obtained with each MSLT. Statistical comparisons were made between baseline values (Day 1) and the day on which urine sodium was minimal (Day 3, 4 or 5) using paired t-tests (Systat, SPSS, Inc.).

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Low-salt</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine catecholamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE (ug/g Cr)</td>
<td>18.6</td>
<td>21.7</td>
<td>.052</td>
</tr>
<tr>
<td>Objective sleep measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>91.4</td>
<td>81.5</td>
<td>.024</td>
</tr>
<tr>
<td>Stage 1 (min.)</td>
<td>38.2</td>
<td>50.7</td>
<td>.009</td>
</tr>
<tr>
<td>Sleep latency (min.)</td>
<td>15.3</td>
<td>25.8</td>
<td>.004</td>
</tr>
<tr>
<td>Subjective sleep measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep quality (1-4)</td>
<td>5.0</td>
<td>3.7</td>
<td>.008</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>1.7</td>
<td>3.7</td>
<td>.002</td>
</tr>
<tr>
<td>Subj. sleep lat. (min.)</td>
<td>18.2</td>
<td>100.0</td>
<td>.066</td>
</tr>
<tr>
<td>MSLT (min.)</td>
<td>10.2</td>
<td>11.9</td>
<td>.050</td>
</tr>
</tbody>
</table>

*Paired T-test, df=10 except MSLT, df=9

Results: One subject developed symptomatic orthostatic hypotension on Day 3 and was discontinued. No other subject experienced significant changes in vital signs, or daytime symptoms. The range of minimal urine sodium values was 2.6 to 42.5 mEq/24h. Results for the dependent measures are summarized in the Table. Urine NE increased with salt-restriction, and nocturnal sleep showed disruption on multiple measures including increased sleep fragmentation, increased NREM Stage 1 sleep, and prolonged sleep latency. Multiple subjective sleep measures also showed consistent and robust effects. Despite nocturnal sleep disruption, MSLT determinations showed a trend to longer latencies.

Conclusions: Dietary sodium restriction resulted in SNS activation as
evidenced by increased urinary norepinephrine. The levels of NE produced were comparable to those reported in patients with PI (1). SNS activation was associated with significant objective sleep disruption without evidence of consequent daytime sleepiness. In addition, subjective assessments of sleep quality showed effects as large or larger than objective measures. This pattern of sleep disruption and daytime arousal is suggestive of that seen in primary insomnia, and provides support for an etiologic role of SNS activation in that disorder.

References:
(2) Stepanski E, Zorick F, Roehrs T, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. Sleep, 1988;11(1):54-60.

186.B
Effect of the GABA₅ Agonist Gaboxadol on Nocturnal Sleep and Endocrine Activity in Elderly Subjects
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Introduction: Aging is associated with distinct alterations in sleep and hormone secretion. The most prominent sleep changes are a decrease in sleep efficiency, due to an increased number and duration of arousals, and a decline in sleep intensity, as reflected by reductions in slow wave sleep efficiency, due to an increased number and duration of arousals, hormone secretion. The most prominent sleep changes are a decrease in slow wave sleep (SWS) and low-frequency activity in the EEG. These age-related alterations predispose older people to insomnia. Previous studies have demonstrated that the selective GABA₅ agonist 4,5,6,7-tetrahydroisoxazo- zolo(5,4-c)pyridin-3-ol (gaboxadol) increases non-REM sleep, the duration of non-REM episodes and slow wave activity in the EEG within non-REM sleep in rats, while it increases both sleep efficiency, SWS and low-frequency activity in the sleep-EEG in young subjects(1). The objective of the present double-blind, placebo-controlled study was to investigate the effect of gaboxadol on nocturnal sleep and on sleep-related hormone secretion in healthy, aged subjects.

Methods: Ten subjects (age range 61-78 years, 4 males), without sleep complaints, slept in the sleep laboratory during two randomized conditions. Each condition consisted of 3 consecutive nights. On night II and III, shortly before bedtime, the subjects ingested placebo during one and 15 mg gaboxadol during the other condition. Throughout night II polysomnographic recordings were made and questionnaires assessing subjective sleep quality were completed shortly after rising. During night III blood samples were taken at 30-min intervals to measure the circulating levels of ACTH, cortisol, growth hormone and prolactin. Differences between the conditions were analyzed with non-parametric Wilcoxon matched pairs signed rank tests (subjective and objective sleep variables and hormone levels) or repeated measures ANOVAs (EEG power densities).

Results: Sleep quality during the placebo night was rather poor. In agreement with the literature on sleep the elderly, our subjects displayed a low sleep efficiency (81.5%), caused by a high amount of intermittent wakefulness, and little SWS. Compared with placebo, gaboxadol significantly (p < 0.05) shortened self-rated sleep latency, from 23.5 ± 13.1 to 15.5 ± 11.2 min and increased perceived total sleep time, on average by 42 min. Furthermore, gaboxadol significantly increased sleep efficiency, approximately by 4.5%, which was mainly related to a significant reduction in the number of awakenings and decrease in intermittent wakeful-ness. While it did not significantly affect total time in any of the sleep stages, gaboxadol powerfully augmented EEG activity in the delta and theta frequencies within non-REM sleep. The elevations were most pronounced during the first half of the night and gradually diminished thereafter. The hormonal profiles did not differ between the placebo and gaboxadol condition

Conclusions: The present study shows that gaboxadol increases sleep consolidation and sleep intensity, without suppressing REM sleep, in elderly subjects. These effects are not mediated by or associated with alterations in endocrine activity. These findings suggest that this compound is able to reverse the most robust age-related sleep changes and may therefore have beneficial effects in the treatment of sleep disturbances that typically occur in the aged.

References:
(1) Lancel M: Role of GABAsAs receptors in the regulation of sleep: initial sleep responses to peripherally administered modulators and agonists. Sleep 1999;1:33-42.

Research supported by Lundbeck

187.B
Cerebral Oxygenation Response to Arousal During Sleep in Old & Young Adults
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Introduction: Sleep provides an ideal opportunity to monitor basic regulatory processes that influence cerebral oxygenation. Older adults with low cerebral oxidative reserves are more likely to have impaired oxidative responses to cerebral challenge during sleep and are at greater risk for hypoxic injury to the brain. The specific aims of this study are to determine if noninvasive cerebral oximetry can detect changes in regional cerebral hemoglobin oxygen saturation (rcSO2) induced by arousal challenge and to compare differences in rcSO2 and oxygen utilization in a sample of young and old adults.

Methods: We monitored 10 older (65-84, 5M, 8 rt-handed) and 10 younger adults (21-39, 4M, 10 rt-handed) at a General Clinical Research Center. We used a standard protocol with a 6-hour period of sedentary activity followed by a 2-hour sleep-nap (10pm-12am). Right- and left-sided rcSO2 and blood volume indices (BVI) were measured with the INVOS 4100 (Somanetics Inc, Akron OH). Standard methods were used to record sleep and arousals (central and posterior EEG, 2-channel EOG, submental EMG), respiratory movements (Respirtrace, AMI, Ardelsey NY), and arterial oxygen saturation (Nellcor, San Diego, CA). Signals were stored to computer using Windaq Waveform Acquisition Software at 250/s and divided into 5-minute segments for analysis. Oxygen utilization was examined by changes of rcSO2 and BVI from baseline.

Results: Older adults took longer to go to sleep, but once asleep, spent more time in SWS and had fewer arousals than younger adults. All subjects had normal SaO2 values (95-97%). Regional cerebral hemoglobin saturation ranged from 56-77% in older and 72-97% in younger adults. Older adults had greater differences in rt- and lt-sided rcSO2 (3-5%) than younger adults (1-2%). The older adults had lower rcSO2 values than the younger adults at the start (rt: xold=60.4%, xyoung=72.7%; lt: xold =64.7%, xyoung=71.4%). Once asleep, older adults rcSO2 values decreased (xrt= -6.8%, xlt= -1.5%) while rcSO2 values in the younger adults tended to increase (xrt= 2.3%, xlt= -1.%). Arousal in older adults were associated with a decrease in both rcSO2 (xrt= -
Conclusions: Older adults have lower rcSO2 values at sleep onset and show significant decreases in rcSO2 during sleep as compared to younger subjects. Older adults showed a significant decrease in rcSO2 and BVI in response to arousal. These results suggest that older adults may have lower oxygen reserves and be at greater risk for hypoxic injury during sleep. Finally, cerebral oximetry is a potentially useful method for monitoring regional cerebral oxygen changes during sleep. Future studies will examine how patterns of rcSO2 and BVI responses during arousal vary across the night in older adults.

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188.B

The MSLT Across the Menstrual Cycle in Young Healthy Females

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Introduction: Neurohormonal changes characterize the menstrual cycle of normal, ovulatory women. It would be expected that these physiological variations have repercussions on the systems that regulate sleep mechanisms. However, research in this area has failed to demonstrate systematic changes across the menstrual cycle. Some studies have suggested that stage 3 NREM sleep and nocturnal awakenings fluctuate across the menstrual cycle. Interestingly, fluctuations in subjective sleepiness levels have been documented, but no systematic MSLT data are available. The purpose of this study was to characterize the patterns of nocturnal sleep and investigate the hypothesized differential effects of phase on the MSLT across the menstrual cycle.

Methods: Twelve female subjects (age=25.6 Begin + End 5.2) were screened to assure they maintained regular sleep schedules, experienced no acute life stresses, had regular menstrual cycles, and displayed no evidence of premenstrual syndrome. Those using hormonal contraceptives were excluded. All subjects underwent medical/toxicology screens to assure they maintained regular sleep schedules, experienced no acute life stresses, had regular menstrual cycles, and displayed no evidence of any sleep disorder. Subjects were required to possess no evidence of any sleep disorder. All subjects underwent medical/toxicology screens to assure they maintained regular sleep schedules, experienced no acute life stresses, had regular menstrual cycles, and displayed no evidence of any sleep disorder. Subjects were required to possess no evidence of any sleep disorder. Those using hormonal contraceptives were excluded. All subjects underwent medical/toxicology screens to assure they maintained regular sleep schedules, experienced no acute life stresses, had regular menstrual cycles, and displayed no evidence of any sleep disorder. Subjects were required to possess no evidence of any sleep disorder.

Results: The mean progesterone level during the follicular phase was 9 ± 3 ng/mL (range: 5-14 ng/mL) and 7.7 ± 4.4 ng/mL during the luteal phase (range: 2.5-15.5 ng/mL). The percentage of stage 1 sleep on the nocturnal PSG was significantly less (p<.02) during the luteal phase (3.6 ± 1.1%) when compared to the follicular phase (5.1 ± 2.4%). All other nocturnal parameters including sleep architecture and sleep continuity were not significantly different across the menstrual cycle. Sleep propensity on the MSLT exhibited shorter latencies to sleep during the luteal phase (mean=9.0 ± 4.3 min) when compared to the follicular phase(mean=11.6 ± 4.9 min; p<.09). Sleep efficiencies on the MSLT displayed a significant effect of phase (p<.05). An overall higher sleep efficiency was documented during the luteal phase of the menstrual cycle (see Table). There was also a main effect of nap (p<.03). A phase by nap interaction was absent. There were no significant effects of phase on the POMS or the positive affect scale of the PANAS. However, higher ratings of negative affect were documented on the PANAS during the luteal phase (11.2 ± .8) when compared to the follicular phase ratings (10.5 ± ; p<.01).

Table 1

<table>
<thead>
<tr>
<th>Nap (hrs)</th>
<th>Follicular</th>
<th>Luteal</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30</td>
<td>66 (23)</td>
<td>42 (30)</td>
<td>44 (25)</td>
</tr>
<tr>
<td>11:30</td>
<td>58 (25)</td>
<td>42 (23)</td>
<td>42 (27)</td>
</tr>
<tr>
<td>13:30</td>
<td>45 (35)</td>
<td>34 (30)</td>
<td>41 (29)</td>
</tr>
<tr>
<td>15:30</td>
<td>42 (24)</td>
<td>60 (24)</td>
<td>53 (19)*</td>
</tr>
</tbody>
</table>

*p <.05

Conclusions: The results of this study, consistent with previous reports, found minimal effects of menstrual cycle phase on nocturnal sleep variables. However, a differential propensity to fall asleep was documented on the MSLT. Importantly, five of the twelve subjects (42%) experienced a decrease of more than 2 minutes on the MSLT during the luteal phase, while one subject experienced an increase of greater than 2 minutes during this phase. A differential ability to stay asleep, reflected in MSLT sleep efficiencies, corroborate luteal phase effects on sleep regulatory mechanisms. Further research is required to determine what specific neurohormonal changes are responsible for these effects.

189.B

Pineal Calcification is Related to Seasonality in Humans

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Introduction: The pineal hormone melatonin is the natural transducer of the environmental light-dark signal to the body. In animals, changes in the duration of melatonin secretion, which are induced by the seasonal changes in night length, trigger seasonal phenomena such as breeding, migration and hibernation. The responsiveness of physiology to photoperiodic changes is well preserved in humans (1). As a consequence, seasonal affective disorder (SAD), as the extreme end of the spectrum of seasonality in humans that affects a large percentage of the general population, has been suggested to be the remainder of hibernation. But, since not all humans experience seasonal changes such as in mood and behavior, humans at least partly seem to have adapted to the seasonal changes in daylength. The aim of the study was to obtain first evidence for the hypothesis that the degree of pineal calcification (DOC), an intraindividual marker for a melatonin deficit (2), is related to seasonal phenomena in humans.

Methods: DOC was determined in 352 patients in which a cranial computed tomography was performed for diagnostic reasons. After evaluation of final files, 44 patients were excluded, because they revealed signs for organic psychiatric disorder (ICD 10: F00–F09 e.g. dementia). From the 308 patients included 155 were female (mean-age: 57.6±16.5years;range 20–90) and 153 males (mean-age: 54.1±16.7years;range 17–85). Patients were asked for seasonal occurrence of increased need for, but
still unrestorative sleep. Answer categories were “no”, “yes – intense” and “do not know or maybe like anybody”.

Results: From the 308 patients 189 (61.4%) reported “no”, 68 (22.1%) “do not know” and 51 (16.6%) “yes – intense” experience of an increased, still unrestorative sleep need during fall and/or winter. Two patients reported increased sleep need during spring, none during summer. Further evaluation included only extreme groups “no” (n=189) and “yes – intense” (n=51). Females (39vs.82) experienced significantly more often seasonal phenomena than males (12vs.107) (chi-square=17.586;p<0.001), and had a significantly lower DOC than males (Mann-Whitney-U: p<0.001). Subjects experiencing seasonality were significantly younger (t=2.83,df=81.69,p=0.01), whereas DOC increased with age (Spearman`s rho=0.23,p<0.01). Patients with no seasonal changes in sleep need had significantly higher DOC values as those with seasonal changes (Mann-Whitney-U: p<0.05).

Figure 1

Conclusions: Because the distribution of seasonal phenomena with respect to incidence, sex and age confirms results of earlier studies, our study population can be considered to be representative for the general population. The presented data show that a high DOC as a marker for low intraindividual melatonin secretion is positively associated with non-seasonality in humans. This result is not in contradiction to earlier studies, in which low melatonin was not related to seasonal phenomena in humans. The high inter-individual variation in the amount of melatonin secretion is due to the high variation in the size and weight of the pineal gland (2). Thus, the result furtherly emphasizes the need for an intraindividual deficit marker such as DOC. We suggest that the calculation process represents a human adaptation process to modern life.

References:

190.Q

CSF Hypocretin-1 Levels in Schizophrenics and Controls: Relationship to Sleep Architecture

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Introduction: Sleep disturbances are commonly observed in most patients with schizophrenia [1]. Prolonged sleep onset latency, decreased total sleep time, decreased total slow wave sleep time (SWS), and poor sleep efficiency have been reported in both acute and chronic schizophrenic patients. Hypocretins (orexins) are newly discovered peptides of hypothalamic origin. Deficiency in hypocretin neurotransmission (i.e., low CSF hypocretin levels) is specifically involved in narcolepsy (see Nishino et al in this issue), but, to a lesser extent, may also be involved in some other neurological diseases (see Ripley et al and Kanbayashi et al in this issue). Hypocretin excites the midbrain dopaminergic (DA) neurons and central administration of hypocretins also induces an increase in stereotypic and locomotor activity. The effects on stereotypic and locomotor activity are blocked by dopaminergic D2 antagonists [2], the class of compounds used for the treatment of schizophrenia. In the current study, we therefore investigated whether CSF hypocretin levels are altered in patients with schizophrenia accompanied by sleep disturbance.

Methods: Twenty-five male veterans were included in the study. Thirteen were psychiatric inpatients (chronic) hospitalized at the Veteran Affairs Health Care System, Palo Alto, California. The other 12 were paid volunteers (33.3±6.6 yrs [ SD ] ) (NCs). The 13 psychiatric patients (33.2±5.4 yrs) met Research Diagnostic Criteria (RDC) for schizophrenia (n=11) or schizoaffective disorder (n=2). Aside from the use of chloral hydrate for agitation, all psychiatric patients were free of psychotropic medications for a minimum of 2 weeks before the sleep recordings and the lumbar puncture. All NCs were in good health and had no sleep abnormalities. LPs were performed between 7 and 8 AM after a night of fasting and bed rest. Hypocretin 1 was measured in crude CSF using a commercially available RIA (Phoenix pharmaceutical company) (see Ripley et al in this issue). Polysomnograms began at approximately 22:00 hours and were terminated 8 hours later. The first polysomnogram was used to adapt subjects to the sleep laboratory and to our procedures; the adaptation recording was also used to screen out subjects with sleep apnea and/or sleep-related periodic leg movements. Two data collection nights followed the adaptation night. All measures of sleep architecture were averaged over the two data collection nights.

Results: There was no difference in CSF hypocretin levels between schizophrenic (272.2±38.9 pg/ml, range 167-312 pg/ml) and control (270.2± 34.8 pg/ml, range 224-318 pg/ml) subjects. As previously reported, these schizophrenic patients had a longer sleep onset latency (t = 2.90, p<.008), slept fewer minutes (t = 2.86, p<.009), showed less sleep efficiency (t = 2.92, p<.007), and had fewer minutes of stage 2 sleep (t = 2.59, p<.017) relative to the NCs [3]. We, however, observed no correlation between CSF hypocretin levels and any measure of sleep architecture in either the patients or NCs.

Conclusions: We conclude that CSF hypocretin levels are not altered in patients with chronic schizophrenia, and a change in hypocretin levels cannot explain their sleep abnormalities. It is, however, interesting to study whether hypocretin levels are altered in acute schizophrenia, especially since central administration of hypocretin induces stereotypy and enhances locomotor activity acutely by stimulation of the DA system.

References:

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191.Q

REM Activity Increase in PTSD Does Not Depend on a Depressive Diathesis and Alcoholism

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Introduction: Repetitive, stereotypical anxiety dreams characterize posttraumatic stress disorder (PTSD) and frequently prove intractable to pharmacological and psychotherapeutic treatments. Therefore, identifying the pathophysiology of this sleep disturbance assumes considerable clinical importance. Evidence of an increase in rapid eye movement activity during REM sleep (REM activity) in PTSD previously has been reported.1,2 However, such a change in REM sleep phasic activity has also been described in major depression and alcoholism, disorders commonly associated with PTSD and thereby potential confounders in polysomnographic studies. As a step in assessing whether elevated REM activity can be observed in the absence of these frequently co-occurring conditions, we compared non-depressed PTSD subjects who had no history of major depression prior to developing PTSD, and no familial depressive diathesis, with controls matched on alcoholism.

Methods: Ten male combat veterans (mean age 48.4 ± 3.4 (SD)) with chronic PTSD, without current major depression, without depression preceding the onset of PTSD, and with no family history of a mood disorder, were compared with 10 male control subjects (48.1 ± 6.2) without a history of primary depression, without a family history of a mood disorder, and with alcohol dependence recently (N = 3) or stably (N = 2) in remission. The remaining controls (N = 5) had never been alcoholic. The PTSD group had an equivalent distribution of alcohol dependence diagnoses. Polysomnography was carried out over 3 nights. Average REM activity (REM activity/ total sleep time) and average REM density (REM activity/ total REM sleep time) were analyzed using 2 (subject groups) x 3 (nights) ANCOVAs with repeated measures on night; age and alcohol dependence diagnosis were covariates.

Results: The PTSD group showed increases in average REM activity, F(1,16) = 6.23, p = .024, and average REM density, F(1,16) = 4.85, p = .043 (Table 1). Alcohol dependence diagnosis had no effect on either measure. There were no significant main effects for group in any tonic REM sleep measure, nor in any sleep continuity or non-REM sleep architectural measure.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Night</th>
<th>Average REM Activity</th>
<th>Average REM Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>1</td>
<td>.90 (.13)</td>
<td>5.86 (.63)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.06 (.11)</td>
<td>5.50 (.45)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.23 (.13)</td>
<td>5.77 (.49)</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>.69 (.13)</td>
<td>4.24 (.63)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>.81 (.11)</td>
<td>4.24 (.45)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>.81 (.13)</td>
<td>4.51 (.49)</td>
</tr>
</tbody>
</table>

Conclusions: Even when depression and alcoholism are minimized as possible confounders, subjects with PTSD show increased REM activity, which may be a sensitive polysomnographic marker of the disorder. REM activity putatively reflects central arousal level,3 and elevated REM activity in PTSD may indicate the hyperarousal that is a cardinal symptom of this disorder. Basic and clinical investigations of the physiological significance and pharmacological mechanisms of REM sleep phasic activity may have important implications for the development of more effective treatments for the sleep disturbance in PTSD.

References:

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192.R

Do Arousals Prolong Sleep Onset on the MSLT?

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Introduction: Several factors other than sleepiness affect an individual MSLT score (Bonnet & Arand, 2000). The present study addresses whether arousals during naps could be one of these factors. Arousals due to repetitive disturbances (apneas, hypopneas, or PLMS) which occur during the transition to sleep and prior to meeting the MSLT 16s sleep criterion, may result in longer sleep latencies thus underestimating the sleepiness of patients. The more frequent these disturbances (<16s), the longer the delay in meeting the sleep criterion. Because a respiratory montage is not used for recording the MSLT, the impact of these disturbances on sleep latency is unnoted. One could quantify the degree to which sleep transitions are interrupted by recording the amount of sleep of less than 16 s that accumulates prior to finally meeting the sleep onset criterion. Given the above statements it would be expected that a) sleep latency and the amount of accumulated sleep of less than 16s would be positively related; b) sleep latencies of patients with high levels of accumulated sleep (>16s) would be longer than patients with lower levels; c) respiratory related arousals and sleep latency would be positively correlated.

Methods: Nineteen patients (7 males) ranging in age from 31 to 75 years participated. Sixteen were diagnosed with obstructive sleep apnea and three with inadequate sleep hygiene. The MSLT was conducted according to the standard protocol however respiratory recordings were also included.

Results: To test the first hypothesis (a) a Pearson Product correlation was computed between sleep latency and sleep accumulated across all patients. The correlation was r = .52 which was significant at p<.05 level. For the second hypothesis (b), data were ordered according to the amount of sleep accumulated and then sleep latencies between the top vs the bottom half were analyzed. The mean latency of the group with high sleep accumulation was12.5 Min; for the low accumulation group it was 7.9 Min. These differences were significant. (t (17) = 2.2, p = .04). For the third hypothesis (c) the correlation between respiratory related arousals and sleep latencies was positive but not significantly so.

Conclusions: The argument that arousals occurring during the sleep transition period may impact on sleep latency is supported by the positive relationship found between sleep latency and accumulated sleep. Presumably this relationship is due to arousals interfering with meeting the sleep onset criterion of 16s. Although not independent, the MSLT
scores for the group with high levels of accumulated sleep were significantly longer than those with lower levels. The differences in mean sleep latency between those in the high accumulated sleep group (12.5 Min) and those in the low sleep group (7.9 Min) were substantial. This suggests that the MSLT, for some patients, may underestimate daytime sleepiness. It may also be one reason why some patients with a high RDI score fall within the normal alertness range on the MSLT. Perhaps the use of a shorter sleep latency criterion (e.g., 5s) would resolve this paradox.

References:

193.Q

Oral Contraceptives and Sleep in Depressed and Healthy Women

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Introduction: It is assumed that women who participate in sleep studies should currently be taking oral contraceptives (OCs) in order to minimize the effects of hormonal variation. While there has been some recent work on the effect of the menstrual cycle on sleep EEG, the effect of OCs on sleep has not been studied, and the assumption that OCs minimize group differences has yet to be proven. The present archival study evaluated the effects of OCs on sleep architecture in healthy women and in women with major depressive disorder (MDD).

Methods: Sixty-eight women with MDD and 37 healthy control women who had participated in a prior sleep study and who had indicated whether or not they were currently taking OCs were included in the sample. Data were collected over an eight-year period, but under identical conditions. The women with MDD were symptomatic but unmedicated, and were free from other Axis I disorders. The healthy control women had no personal or family history of psychopathy. Sleep EEG data were collected over two consecutive nights in the lab, and the data analyses were based on the second night only. The following sleep variables were derived from the sleep-stage score data: sleep latency, total sleep period (TSP), REM latency, sleep efficiency, and percentage of each sleep stage derived from the sleep-stage score data: sleep latency, total sleep period (TSP), REM latency, sleep efficiency, and percentage of each sleep stage in relation to TSP (1). A between-groups multivariate analysis of variance (MANOVA) tested for group and OC main effects and interactions.

Results: Effects of OCs were generally larger in healthy women than in those with MDD. Women on OCs had significantly less slow-wave sleep than women not on OCs (6.24 vs. 10.23 minutes, p < 0.04). REM latency was also significantly shorter in the group of women on OCs (62.45 vs. 77.38 minutes, p < 0.02). In addition, a significant OC x Group interaction was found for two variables: sleep latency (p < 0.04) and %REM (p < 0.03). Least squares multiple comparisons indicated that OC use significantly decreased sleep latency in the healthy controls but had no effect in those with MDD. Among those not on OCs, sleep latency was longest in the MDD group. Healthy women also showed larger OC effects on %REM than were evident in those with MDD.

Conclusions: Healthy women showed larger effects of OCs on sleep than women with MDD, contrary to the suggestion that women with MDD may be more sensitive to exogenous hormones (2). Moreover, the shorter REM latency and the smaller amount of slow-wave sleep in women on OCs suggests that OCs may minimize differences between patients and controls. Thus, OC use may represent a confound in previous sleep studies which compare healthy and depressed men and women.

References:

194.Q

Alteration in Central Control of Spontaneous Nocturnal Erections in Psychogenic Erectile Dysfunction

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Introduction: The registration of nocturnal erections is an important tool in the diagnosis of erectile dysfunction. Up to now, only peak tumescence and peak rigidity as well as duration of erectile events are assessed in order to detect an organic component in the etiology of impotence. However, nocturnal erections are a phenomenon controlled by the central nervous system with a close temporal association with REM sleep. Previous investigations in healthy men (Mann et al 2000) indicated different mechanisms underlying the control of REM sleep and nocturnal erections, respectively. On the assumption that psychogenic erectile dysfunction is based on distinct disturbances of the central nervous system, the present study was performed in order to find out if the relationship between REM sleep and nocturnal erections is altered in patients with psychogenic erectile dysfunction.

Methods: 24 male patients, 25-57 years old, suffering from psychogenic erectile dysfunction according to the criteria of DSM-IV were investigated. The patients had no lifetime diagnosis of any other psychiatric disorder. Based on detailed case history, comprehensive clinical examination and routine laboratory parameters including hormones, there was no evidence of organic factors relevant for sexual function. In addition, an age-matched control group consisting of 24 healthy male volunteers, 26-56 years old, without sexual dysfunctions was also studied. None of the subjects had sleep disturbances. Each subject spent 3 successive nights in the sleep laboratory. After an adaptation night 2 polysomnographies (EEG, EOG, submental EMG) were carried out over 8 hours for each subject. In addition, nocturnal penile tumescence and rigidity were measured applying the Rigiscan device (Dacomed Corp., USA). Due to technical manipulation, the data digitally stored in the Rigiscan were converted on-line to analog signals; thus, exact synchronization with the sleep EEG was guaranteed. As an inclusion criterion, all subjects revealed normal nocturnal erections regarding peak tumescence and peak rigidity. Sleep EEG were scored visually according to the criteria of Rechtschaffen and Kales.

Results: Regarding number and mean duration of nocturnal erections, no difference between patients and controls became obvious. Also, the mean latency between REM episodes and erections was not different, although the temporal overlap was less in the patient group. A regression analysis based on all erectile events and REM episodes registered in the study groups revealed a significant decrease of the latency in the course of the night in the control group; in contrast, this was not the case for the patients.

Conclusions: The decrease of the latency between REM episodes and erections reported for healthy men was not found in the patient group. This might indicate possible alterations of the central control of nocturnal erections in psychogenic erectile dysfunction. This supports the opinion that psychogenic erectile dysfunction has a biological basis.
A Prospective Study on the Treatment of “Complex Insomnia”—Insomnia plus Sleep Disordered Breathing—in a Small Series of Crime Victims with PTSD

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Introduction: Sleep complaints are common in crime victims with post-traumatic stress disorder (PTSD), but are usually explained as a consequence of psychiatric processes. A recent study of crime victims with PTSD, however, observed an increased prevalence of “complex insomnia” in which both psychophysiological insomnia and sleep disordered breathing appeared as co-morbid conditions in the same patients (1). These patients were initially treated for nightmares and insomnia with standard sleep and dream behavioral therapies, including sleep hygiene, stimulus control, sleep restriction and cognitive-imagery. After a three-month follow-up, treatment outcomes were assessed and then patients were treated for SDB with continuous positive airway pressure (CPAP) to determine what impact this might have on patients’ persistent sleep complaints. We hypothesized that treatment of SDB would provide further treatment gains for insomnia and sleep quality beyond that achieved in the behavioral program.

Methods: Seven female crime victims who enrolled in a nightmare and insomnia treatment program were diagnosed with complex insomnia. Mean (SD) age was 42.6 (13.8) and BMI was 28.5 (5.6). The participants underwent objective sleep testing and their mean apnea/hypopnea plus RERA index (AHIR) was 39 (AHI = 10; RERA index = 29). Participants were treated with CPAP and were given three months to adapt to it. At follow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3). A repeat-folllow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3). A repeat-follow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3). A repeat-follow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3). A repeat-follow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3). A repeat-follow-up, they completed two validated sleep instruments: Sleep Quality Index (PSQI) measured global sleep quality (3).

Results: Marked improvement was noted for insomnia in six patients and for sleep quality in five patients (Table 1). An overall analysis of variance showed improvement for SII (Wilks’ Lambda = 0.15, F (2,5) = 14.31, p < .01, eta2 = 0.85). In a simple effects analysis of SII, behavioral treatment (Cohen’s d = 1.1, p > .10) and CPAP therapy (Cohen’s d = 1.6, p < .01) had large effect sizes for insomnia severity. For PSQI, an overall analysis of variance showed improvement (Wilks’ Lambda = 0.40, F (2,5) = 14.31, p< .01, eta2 = 0.85). In a simple effects analysis of PSQI showed that behavioral treatment had a large effect size (Cohen’s d = 1.0, p > .10) and CPAP therapy had a medium effect size (Cohen’s d = .5, p > .20) for sleep quality. Given these substantial effect sizes, we believe that larger samples, which will be presented at APSS, will manifest statistical significance.

Table 1: Mean (SD) for baseline, CBT, and CPAP

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>post-CBT</th>
<th>post-CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SII</td>
<td>26.00 (4.0)</td>
<td>20.86 (5.6)</td>
<td>13.71 (4.0)</td>
</tr>
<tr>
<td>PSQI</td>
<td>13.86 (2.9)</td>
<td>10.14 (4.2)</td>
<td>8.29 (4.6)</td>
</tr>
</tbody>
</table>

Conclusions: Treatment with sleep and dream behavioral therapies produced clinically meaningful improvements in insomnia severity and sleep quality in crime victims with PTSD. With the addition of CPAP therapy, large and medium treatment effects were noted for both insomnia severity and sleep quality respectively. These treatment effect sizes, albeit in a small sample, suggest that CPAP had an impact on insomnia and sleep quality beyond that of behavioral treatment in these patients. Furthermore, it suggests that SDB plays a crucial role in the disruption of sleep in certain PTSD patients. Future prospective treatment trials will assess the impact of CPAP on PTSD and related psychiatric distress.

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196.Q

Rating Scales for Inattention and Sleepiness are Correlated in Sleep Disordered Patients, but not in Patients with Attention Deficit-Hyperactivity Disorder

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Introduction: Questions have been raised whether patients with attention deficit really have a primary disorder of sleep or of daytime sleepiness. Conversely, do patients with excessive daytime sleepiness have problems with attention?

Methods: Fifty-one consecutive patients presenting with sleep disorders were administered the Epworth Sleepiness Scale (ESS) and the ADHD Rating Scale (created by rating each of the 18 DSM-IV Attention Deficit-Hyperactivity Disorder (ADHD) symptoms on a scale of 0 to 3, for a maximum possible score of 54). The maximum possible score was 27 each for the Inattention sub-group (A Score) and the Hyperactivity-Impulsivity sub-group (H Score). Forty-five consecutive patients presenting with attention deficit symptoms were also administered the ESS and the ADHD Rating Scale. The sleep disorder patients were 35 males and 16 females ranging in age from 19 to 84 (mean 48.6±14.8). The attention deficit patients included 27 children (21 males, 6 females) ranging in age from 5 to 17 (mean 10.7±3.7) and 18 adults (18 males, 3 females) ranging in age from 18 to 56 (mean 31.9±12.2). All 51 sleep disordered patients underwent polysomnography, and 38 of them were administered the Multiple Sleep Latency Test (MSLT). Data were analyzed separately for sleep disorder and attention deficit patients.

Results: For the sleep disordered patients, mean ESS was 12.1±5.9, a score 9.3±6.2, H score 5.4±5.1, REI 26.3±25.0/h sleep, lowest saturation 83.1±12.1%, MSLT 5.9 ±3.9 min. For the entire group of 51 patients, a score was significantly correlated with ESS (r=0.44, p=0.001). H score and A score were significantly correlated and REI and lowest saturation were significantly correlated. The significant correlation between ESS and A score was still obtained with the 38 patients who were administered an MSLT (r=0.49, p=0.002). Lowest oxygen saturation was correlated with REI (r=.59, p=.001), MSLT (r=.353, p=.029), and H score (r=-.36, p=.025). For the attention deficit patients, data were
analyzed separately for children and adults. Children had a mean ESS of 2.5±2.8 (range 0 to 8), mean A score of 20.1±5.5, and mean H score of 14.0±8.8. For children, age was correlated with A score (r=0.42, p=0.028). There were no other significant correlations, including between ESS and either A score or H score. Adults had a mean ESS of 8.3±5.6 (range 1 to 20). Mean A score was 19.1±3.5, and mean H score was 10.3±6.4. There were no significant correlations, including between ESS and either A score or H score.

Conclusions: Scores on rating scales for sleepiness (ESS) and inattention (A score on the ADHD Rating Scale) are significantly correlated in patients with sleep disorders, but not in patients with ADHD. This suggests that increasing sleepiness (in sleep disordered patients) may impair attention. On the other hand, in patients with ADHD, sleepiness does not correlate with, much less explain, the inattention.

References:

197.Q

Spectral analysis of REM sleep EEG in Asperger’s Syndrome

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Introduction: Asperger’s Syndrome (AS) is a Pervasive Developmental Disorder related to autism. Neuropsychological and brain imagery observations suggest that frontal functions and visuo-perceptual processes may be impaired in AS. Low visual counts of EEG spindle activity during stage 2 non-Rapid Eye Movement (REM) sleep have also been reported in patients with AS. The present research sought to determine whether abnormal EEG is also present during REM sleep in AS using quantified EEG analysis.

Methods: Six adult patients with AS (5M, 1F, 26.0 ± 5.6 years) were compared to six age- and gender-matched participants (5M, 1F, 26.8 ± 5.9 years) screened for psychiatric, neurologic and clinical sleep disorders. All participants were recorded for two consecutive nights in the sleep laboratory, using a 12-electrode montage. Sleep stages were determined for night 2 according to Rechtschaffen and Kales (1968) using 20 sec. epochs. Power amplitude values (V) of the night 2 Beta frequency band (13.75 - 20.0 Hz) from both groups of participants were compared using the Mann-Whitney U-test for independent samples.

Results: AS patients showed a significantly lower absolute Beta over the primary (O1, O2) and associative (T5, T6) cortical visual areas.

Conclusions: These results support the hypothesis of an abnormal visuo-perceptual functioning in the autistic spectrum. Using brain imagery techniques, recent studies have shown decreased blood flow in the temporo-occipital region of high-functioning (i.e., normal IQ) patients with autism during face recognition tasks. The present results extend these observations to REM sleep and may provide neurophysiological support for the poor quality of dream reports in autistic disorders (see Daoust et al., this meeting).

References:

Supported by “Fonds de la recherche en santé du Québec” and “Fondation de l'Hôpital L-H. Lafontaine”.

Figure 1

EEG montage with significantly different derivations between AS patients and control participants.

Figure 2

Bilateral absolute power amplitude for bilateral homologous electrode derivation, for significant placements.
Sleep Debt in Healthy Young Individuals is Inversely Related to Habitual Sleep Duration and Associated with Excessive Daytime Sleepiness

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Introduction: A survey by the National Sleep Foundation found that ~67% of adults sleep less than the recommended 8 hours per night (1). Since inter-individual variation in sleep need may exist, it remains unclear whether habitual sleep duration (HSD) of less than 8 hours leads to a sleep debt. We quantified the relationship between HSD and sleep debt in healthy young individuals in a protocol in which the ratio of scheduled sleep to scheduled wakefulness was 2:1 for at least three 24-h days. Hereby we could assess whether an individual’s choice of HSD reflects sleep need and whether a sleep debt exists.

Methods: 13 young healthy subjects (6 male, 7 female) ages 22±4 years were studied. For three weeks prior to admission they were instructed to abstain from the use of all medication, health food supplements, caffeine, tobacco and alcohol, and to record their sleep-wake times. For 3 weeks prior to admission, the subjects were enrolled in a protocol in which the ratio of scheduled sleep to scheduled wakefulness was 2:1 for at least three 24-h days. Hereby we could assess whether an individual’s choice of HSD reflects sleep need and whether a sleep debt exists.

Results: Reported HSDs ranged from 6.1 to 10.3 hours. Sleep latencies on the MSLTs during the first wake episode were correlated with HSD: all individuals with HSDs of <=9.1 hours fell asleep on all 5 MSLTs, all these individuals had at least one sleep latency less than 5 minutes, and 66% of the MSLTs had latencies less than 5 minutes. For individuals with HSD > 9.3 hours, 60% of MSLTs included sleep and 7% of these (1/15) were within 5 minutes. The average TSTs during the first, second and third days of the protocol were 12.5 ± 0.4 (s.e.m.), 11.0 ± 0.5 and 10.3 ± 0.6 hours, respectively; the decline in TST from day 1 to day 3 was significant (p = 0.008). On day 1, TST was greater than HSD for all individuals. On days 2 and 3, the only individuals with TST <=HSD were those with HSD >= 9.1 hours. On the first two days, there was no correlation between TST and HSD, indicating that those with the shortest HSD had the greatest increase in TST. On the third day, there was a significant negative correlation (r = -0.83, p=0.003) between TST and HSD (Figure 1), indicating that the individuals with the shortest HSD had the greatest TST.

Figure 1

Conclusions: These results demonstrate that many young adults carry a sleep debt that dissipates over days of increased sleep opportunity. This sleep debt appears greatest in those reporting the shortest HSD. The levels of sleepiness seen during the MSLTs in some of these healthy young individuals are comparable to those with narcolepsy and untreated obstructive sleep apnea.

References:

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Association Between Daily Energy Expenditure and Sleep in Physically Active Adults

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Introduction: Although random surveys have suggested that people perceive that exercise may be the most important behavior for promoting sleep (1), laboratory experimental studies have failed to support this perception (2). The purpose of this experiment was to examine the association between daily variation in energy expenditure and sleep in active adults.

Methods: We examined 71 physically active, normal sleepers (n= 38 ages 18-30; n=33 ages 60-75). During seven consecutive days of home recording, participants wore a wrist-mounted Actillume that recorded activity. Daily total energy expenditure (TEE) was estimated from diary-assessed physical activity ratios (PAR) and estimated basal metabolic rate (BMR) (TEE=PARxBMR)(3). Sleep-wake was estimated from wrist movement with a validated algorithm. The sleep variables assessed were sleep onset latency (SOL), total sleep time (TST), and wake after sleep onset (WASO). Volunteers recorded subjective estimates of SOL, TST, WASO, and insomnia with a daily sleep diary. Between-subjects associations between average TEE and average Actillume and subjectively assessed sleep were examined by Spearman rank-order correlations. To normalize the data, z-transformations were performed on all sleep variables. To examine whether within-subject daily variations in TEE moderated variations in the sleep variables, repeated measures ANCOVAs were conducted, with TEE as the covariate.

Results: A significant between-subjects correlation between TEE and SOL was found (rs=-0.26, p=0.04). A significant, but modest, within-subjects moderating effect of TEE was found for subjective WASO (p=0.01, beta=-0.40).

Conclusions: The results suggest little association between TEE and sleep in physically active good sleepers. The association found might be influenced by confounding factors we have not yet assessed (e.g., light exposure). Limitations of our analysis include a low daily variability in TEE, a restricted assessment of physical activity, a reliance on self-reported activity, and a sample of normal sleepers (ceiling effect).

References:
Results: The main predictors of fatal accidents became: male gender (Odds Ratio=2.29; 95% Confidence interval = 1.56-3.56), sleep problems (1.82; 1.18-2.87) and shift work (1.68; 1.12-2.52). Age, SES, "hctic work", >50h overtime/week, physically strenuous work, and fatigue showed to fail any significant relation to fatal accidents. Since gender was a major factor a second analysis was carried out separately for men and women. This yielded the following predictors for men: sleep problems (OR=2.10;1.20-3.55) and shift work (1.75; 1.08-2.85). For females the predictors became: fatigue (2.14; 1.11-4.13) only.

Conclusions: The results clearly indicate that, apart from gender, the main prospective predictors of having a fatal accident was perceived sleep disturbance, fatigue, and shift work. Fatigue was more important for women, whereas disturbed sleep was more important for men.

201.U

Fatigue, Alcohol and Serious Road Crashes in France


Introduction: Whilst only limited data worldwide (1) are available on fatigue and/or sleep related road crashes, fatigue may be a major causal factor for crashes on French roads (2). However, there has been no systematic analysis of the French national database on road crashes (3), or any comparisons made with alcohol, which is a well known risk factor.

Methods: We obtained from the French Ministry of Transport, data on all road crashes for the period 1994 to 1998 inclusive (n= 640670), involving at least one person injured (confirmed by attending paramedics) or dead. Road crashes are frequently multi-causal, and as fatigue related road crashes can be difficult to identify (compared with the breathalyser for alcohol related road crashes), we applied criteria previously used by Horne and Reyner (2) to identify these particular crashes. The technique eliminates many of the confounding factors. We identified four categories of road crashes: 1) ALCOHOL RELATED – blood alcohol levels over 10mg ethanol/100ml blood, estimated by breathalyser or blood analysis; 2) FATIGUE RELATED – driver could have avoided crash but no avoidance manoeuvres were taken (i.e. nil braking or swerving), with blood alcohol levels less than 10mg/100ml (as above); 3) ALCOHOL AND FATIGUE RELATED – fatigue related crash with blood alcohol levels over 10mg ethanol/100ml blood (as above); 4) NO ALCOHOL OR FATIGUE – not a fatigue related crash, and with blood alcohol levels less than 10mg/100ml (as above); This left 67671 crashes, from which death and severe injury rates were calculated. The crashes were sub-divided into three periods: day (07:00-19:59h), evening (20:30-23:59h), and early morning (00:00-06:59h).

Results: Fatigue related road crashes comprised about 10% of the 67671 crashes, whereas for alcohol (blood alcohol levels over 10mg ethanol/100ml blood) this was larger, at 23%. Alcohol related road crashes had a higher fatality risk during the evening and early morning period Vs the day period, (Wald X2 = 4.88, p = 0.02, Wald X2 = 18.04, p < 0.01). In contrast, fatigue related crashes had a higher fatality risk during the day Vs early morning period (Wald X2 = 5.37, p = 0.02).

Conclusions: Our results show a very strong relationship between time of the day and causes of road crashes. As many alcohol related crashes occur during the evening and the night, the further contribution of fatigue to these may not always be clearly evident. Undoubtedly, for many drivers nocturnal driving is done under the influence of fatigue, and worsened by extensive periods of wakefulness and/or sleep restriction (4). The taking into account of all possible confounding factors for fatigue related crashes, with the adoption of clear criteria (2), would further facilitate the detection of these often very severe road crashes.

References:

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202.U

Factors Associated With Behavioral Alertness in Pilots Flying Simulated Night Flights

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Introduction: Annually there are hundreds of thousands of night flights in commercial aviation worldwide. Like other groups of individuals exposed to night work, long-haul airline pilots characteristically display
large inter-individual differences in behavioral alertness and sleepiness when operating aircraft through the circadian nadir. Factors associated with these differential responses to night schedules were systematically investigated using data from NASA studies of long-haul commercial airline pilots.

Methods: Using a B747-400 flight simulator, n = 44 male experienced long-haul pilots flew an uneventful 6-hr night flight (0200 – 0800 hr) from Seattle to Honolulu. Behavioral alertness during the night flight was operationalized by the increase from 0000 hr to 0600 hr in performance lapses on a 10-minute psychomotor vigilance task (PVT) administered hourly prior to, during, and after the flight. Three levels of response were identified: category 1 increase in lapses ≤ 1 (n = 14, mean lapse increase = 0.57); category 2 increase in lapses ≥ 3 but ≤ 8 (n = 16, mean lapse increase = 5.38); category 3 increase in lapses ≥ 11 (n = 14, mean lapse increase = 22.64). Five types of outcome were tested for discriminating the three lapse categories: (1) pilot ratings of sleepiness throughout the flight using the Karolinska Sleepiness Scale (KSS); (2) continuous EEG and EOG recordings throughout the flight, scored for theta activity and REMs, as well as stages 2 and 3 NREM sleep; (3) background questionnaires containing information on demographics, sleep history, flying experience, etc.; (4) actigraphy recordings of rest-activity cycles 3 days prior to the night flight; and (5) flight crew performance operating the aircraft during the simulated night flight.

Results: Differences among the three categories of behavioral alertness were mirrored in KSS scores (p = 0.008), with category 3 (largest increase in PVT lapses) associated with significantly higher KSS scores than category 1 (lowest increase in PVT lapses)—KSS ratings from category 2 respondents were in between. Pilot age, BMI, EDS, the likelihood of apnea as assessed by the multivariate apnea index (MAP), and habitual sleep duration were not related to category of behavioral alertness. However, self-reported global morningness-eveningness discriminated category 1 from category 2 pilots (but not category 3 pilots), with category 2 pilots being more “morning” people than category 1 pilots (p = 0.05). Questions concerning difficulty sleeping, especially legs feeling jumpy or jerking at bedtime, discriminated category 3 pilots from both categories 1 and 2 (p = 0.009 and p = 0.002, respectively). Category 3 pilots also reported more frequent use of alcohol to help them sleep (p = 0.004), but not more frequent use of alcohol overall.

Conclusions: Results to date suggest that differential vulnerability to loss of behavioral alertness during night flights is associated with two factors. Habitual circadian phase preference contributes to relatively modest differences in behavioral alertness during night flights, while sleep disturbances from as yet unidentified causes—that do not appear to be associated with symptoms of sleep apnea—may underlie a more severe impairment of behavioral alertness at night in a subset of pilots. With completion of data reduction for EEG and EOG, actigraphy, and operational performance measures, hierarchical regression analyses will be performed to identify the combination of factors that optimally predict the level of behavioral alertness experienced by pilots during night flights.

References:

Research supported by NASA NCC 2-1077 and NCC 9-58 through the NSBRI

Evening Naps Reduce Daytime Sleep Time During a Week of Simulated Night Shifts

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Introduction: Napping is nearly universally recommended for night shift workers, with the rationale that additional sleep will reduce the associated sleepiness and performance deficits and improve safety. Indeed, night workers take naps before approximately 40% of their 8-hour night shifts. The present study systematically examines the effects of napping before five consecutive simulated night shifts (5NAP), or before the first two of five consecutive simulated night shifts (2NAP), as compared to a no-nap group (0NAP). The impact of these conditions upon the main daytime sleep period is the focus of this report; the effects on alertness and various performance measures during night shift hours are presented in a companion abstract. These reports are preliminary as additional subjects are being run and not all variables have been analyzed to date.

Methods: Subjects were screened clinically and by PSG for sleep disorders and were required to have a mean sleep latency > 5 minutes on a screening MSLT. All were free of medical and psychiatric illness, and psychotropic medications. Shift workers or individuals with usual rise times after 0800 were excluded. Thirty-three subjects (14 m, 19 f; mean age 47 ± 12.3) randomly assigned to one of the three nap conditions (N=11 for each) are included in this report. Sex representation was similar and mean age did not differ among groups. Each subject participated during five consecutive nights and the intervening four days. Evenings were taken from 1930 to 2200. The simulated night shift, during which sleep was prohibited, began at 2300 and ended at 0735. All subjects left the laboratory from 0800 to 0830 during which time they were exposed to indoor sunlight. Daytime PSGs began at 0830 and ended with the subject’s time-naïve request after 1430, or at 1630.

Results: Mean minutes of sleep during each of the nap opportunities did not differ within or between the nap groups: 92 and 103 minutes for the 2NAP group and 84, 79, 77, 67, and 63 minutes for the 5NAP group. Daytime sleep data are presented in the table. ANOVA indicated that daytime total sleep time (TST) differed significantly among groups (mean TST across 4 days was 374.5 min for 0NAP, 336.8 min for 2NAP, 292.8 min for 5NAP; p<.01). Post-hoc analyses showed that TST was significantly greater for 0NAP than for 5NAP for all sleep periods (p<.05); there was a trend for a difference in the same direction between 0NAP and 2NAP on day sleep periods 1 and 2 (p=.06). When 24-hour TST was calculated by adding minutes of sleep during the evening nap to TST for the subsequent daytime sleep period, no differences were found among groups; however, there was a linear decrease in TST across days (p<.01). Sleep efficiency (SE) was lower for 5NAP (73.0%) as compared to 0NAP (85.8%; p<.01). SE for 2NAP was lower than that for 0NAP for day sleep period 1 (p<.05) and there was a trend for SE to be lower on days 2 and 4. The longer TST for 0NAP, compared to 5NAP, was the result of significantly more stage 2 and REM.
Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Daytime Sleep Period</th>
<th>TST (min.)</th>
<th>SE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0NAP</td>
<td>1</td>
<td>385</td>
<td>86.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>382</td>
<td>85.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>369</td>
<td>85.9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>362</td>
<td>85.4</td>
</tr>
<tr>
<td>2NAP</td>
<td>1</td>
<td>324</td>
<td>73.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>316</td>
<td>74.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>368</td>
<td>84.7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>339</td>
<td>76.2</td>
</tr>
<tr>
<td>5NAP</td>
<td>1</td>
<td>312</td>
<td>73.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>296</td>
<td>71.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>283</td>
<td>72.7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>280</td>
<td>73.9</td>
</tr>
</tbody>
</table>

Conclusions: Evening naps of approximately 60-90 minutes duration appear to significantly interfere with sleep on the subsequent day. Uncontrolled studies have suggested that shift workers who nap have reduced daytime sleep quality, as compared to non-nappers. This may reflect a lower homeostatic drive, or may be related to social/behavioral influences. The significantly lower SE for daytime sleep following nights with naps, combined with the equivalent 24-hour TST for the three groups, suggest that there is a reduced homeostatic drive for sleep during the day following evening naps.

References:
(2) Schweitzer PK, Randazzo AC, Stone KL, Walsh JK: Alertness and neurobehavioral performance on simulated night shifts following evening naps. Sleep, this volume.

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204.U

Effects of Call and Gender on Medical Resident Driving Simulator Performance

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Introduction: Sleep deprivation among residents often receives too little attention from the medical community. Typically, the risks associated with resident sleep deprivation are expressed as a greater safety concern for the patient rather than the resident. Samkoff, et al., (1991) performed a literature review of studies that examined the effects of sleep deprivation on resident performance. Most studies were only concerned with performance outcomes that would affect patient safety rather than resident safety. In addition, there were few that looked at gender differences as a potential contribution to this problem. This study used a driving simulator to measure the effects of being on-call.

Methods: 23 medical residents signed the IRB approved consent form agreeing to complete a 60-minute trial in a PC-based driving simulator after a night on-call and after a night off-call. They wore actigraphs for at least 24 hours prior to both tests. The tests, completed between 12 and 3 p.m., were at least one week apart. The simulator consisted of a steering wheel, gas and brake pedals, 50 x 50 in. projection screen, and sound. Subjects completed a 10-minute practice drive through a city scenario followed by a 60-minute drive designed to replicate a highway driving scenario. Lane position variance (ft) was continuously sampled.

Results: The 19 residents who completed the task were counterbalanced to call condition (12 males and 7 females). Overall, for the on-call condition, subjects had more activity (p = .004), reported less sleep (p < .001), poorer quality sleep (p < .001), more sleepiness (p < .001), and more caffeine use (p = .027). The lane variability measure indicated that call impaired the driving of the males but not the females (p = .012, See Figure). The amount of caffeine used during the 24 hours prior to the post-call test correlated with post-call driving performance (r = .657, p = .003) i.e., the more caffeine used, the poorer the driving performance.

Figure 1

Conclusions: Call impairs next day performance for male residents. The absence of a performance effect for females post-call may be due to reduced sensitivity because of fewer female subjects. There may also be gender differences in maintaining alertness and driving ability. Previous studies have found differences in sleep deprived residents with simulated patient monitoring tasks that require a response to specific events (Denisco, et. al., 1987). This type of task design may more readily unmask the performance deficits associated with sleep deprivation. Therefore, future driving performance studies will include environmental variables that require driver response (e.g. brake reaction times) to assess situation awareness as a function of fatigue.

References:

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205.U

Sleep and Stress: The Mediating Role of Coping Style

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Introduction: Research on the relationships between stress and sleep have provided two seemingly contradictory patterns of findings (1). In many studies sleep is associated with sleep difficulties and fragmented sleep as intuitively expected but in many other studies stress is associated with deeper sleep or higher arousal threshold. We hypothesized that there are two factors explaining this incompatible findings: (a) the nature of the stress; and (b) the coping style of the individual. In the present study we assessed the mediating role of personal coping style.
Methods: Thirty-six graduating students in psychology (age range 22-32) participated in the study. All the students applied to the most demanded Clinical Psychology Graduate Programs. During a non-stressful baseline period their sleep was assessed by actigraphy and daily sleep logs. In addition their coping style was assessed by Carver’s “Ways of coping” questionnaire. The stressful period, approximately 2-3 months following the baseline period, was the specific week during which the students were interviewed and tested as candidates for the Graduate Programs. It has been demonstrated earlier that this is a highly stressful period for these students. Their sleep was reassessed during this period using actigraphy and daily sleep logs. On the basis of the coping questionnaire the students were divided into two groups: High and Low focus on emotions during coping with stress.

Results: Sleep was significantly altered during the stress period. As predicted, the coping style played a significant mediating role (see Fig. 1). Significant interaction was found between the period and the coping style (F=18.1; p<.001) for the actigraphic measures of true sleep time. Emotion-focused coping was significantly correlated with the reduction in sleep period (r=.46, p<.005). Sleep of those who tend to focus on emotions was shortened during the stress period and the opposite occurred to those who avoid emotions. Other interactions and correlations between the subjective and objective measures indicated that stress affects both sleep and daytime alertness.

Figure 1

Conclusions: The results indicate that people who tend to focus on their emotions while coping with stress are more likely to shorten their sleep time during stressful periods (“unsafe to sleep”), whereas individuals who tend to ignore emotions are more likely to extend their sleep (“escape into sleep”). The mediating role of coping style may explain some of the conflicting results reported in the literature on the relationships between sleep and stress.

References:

Research supported by National Institutes of Health HL-65270

207.G

The Pulse Transit Time as a Measure of Respiratory Arousal in Children with Sleep-Disordered Breathing

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Introduction: Brief arousals during sleep that result from obstructive events may lead to daytime neurocognitive deficits. In children however, obstructive apneas frequently occur without visible electrocortical (EEG) arousals. Thus, esophageal manometry (Pes) is regarded as the diagnostic gold standard for the diagnosis of non-apneic, non-hypopneic respiratory effort-related arousals (RERA’s). The pulse transit time (PTT) has been introduced as a noninvasive marker of blood pressure and therefore subcortical arousal. Blood pressure elevation associated with respiratory arousal from sleep, results in a marked drop in the PTT. The optimal threshold PTT decline for scoring subcortical arousals, and its utility in the diagnosis of the upper airway resistance syndrome (UARS), has yet to be established in children. We hypothesized that; 1) The PTT decline associated with pediatric respiratory arousal would be lower than the 15 msec proposed in adults; 2) PTT is a more sensitive measure of arousal than EEG; 3) The PTT arousal index can distinguish children with UARS from primary snorers.
Methods: Polysomnography with Pes was performed in 22 children with symptoms of sleep-disordered breathing and 7 normal controls. The PTT tracing was averaged over 4 seconds to remove respiratory variation. PTT declines ranging between 7 – 15 msec, of at least 5 seconds duration, were quantitated and validated with Pes scoring of RERA’s. Indices for RERA’s, PTT arousals and EEG arousals were obtained.

Results: OSA, UARS, and primary snoring were found in 10, 8 and 4 patients, respectively. A total of 412 respiratory effort-related arousals, 730 PTT arousals and 866 electrocortical arousals were analyzed. Compared to the Pes scoring of obstructive events, a subcortical arousal defined as a PTT decline of 12 msec resulted in a sensitivity of 85% and a false positive rate of 14%. RERA’s terminated in a PTT arousal 83% of the time and in an EEG arousal in 43%. The PTT arousal indices for patients with primary snoring, UARS and OSA, were significantly different at 1.9, 4.9, and 8.3, respectively (Figure).

Conclusions: The PTT subcortical arousal definition best suited to children is a decline of 12 msecs. Obstructive events in children are more likely to be associated with a subcortical PTT arousal than an EEG arousal. The PTT arousal index accurately reflects the RERA index and may replace Pes in the diagnosis of UARS in children.

Research supported by PCRU RR-00052, NHLBI #HL58585-01, ALA(MD)

208.G

Dynamic Pharyngeal Airway Responses In Children With The Obstructive Sleep Apnea Syndrome (OSAS)

Johns Hopkins University

Introduction: We have previously shown that normal children have a less collapsible upper airway in response to subatmospheric pressure (PNEG) administration than normal adults, and that the upper airway response appears to be modulated by the central ventilatory drive (1). Children have a greater ventilatory drive than adults (2). We therefore hypothesized that normal children have increased reflex activation of their pharyngeal airway compared to adults, and that this compensatory mechanism is deficient in children with OSAS.

Methods: We compared the upper airway pressure/flow relationships during sleep in 10 non-snoring, prepubertal children, 10 non-snoring adults and 8 children with OSAS. Measurements were made by correlating maximal inspiratory airflow with the level of nasal pressure applied via a mask during NREM sleep. The slope of the pressure/flow curve (SPF) was used to characterize upper airway function. Reflex activation was assessed in 2 ways: (i) Administering CO2 sufficient to raise transcutaneous PCO2 by 3 torr; (ii) Evaluating the response to pressure changes by either gradually increasing PNEG in a stepwise fashion so as to recruit upper airway reflexes (step method), or suddenly dropping nasal pressure from a positive level to PNEG for 3 breaths, so that the airway remained hypotonic (intermittent method).

Results: We found that (i) Hypercapnia resulted in increased flow for a given nasal pressure in the normal children, resulting in a steeper SPF (P < 0.05). Children with OSAS and adults had a variable response, with some individuals showing a steeper SPF, but no overall group changes. (ii) Normal children had a more collapsible airway with the intermittent vs the step method (P < 0.05), whereas children with OSAS and adults had a variable response with no significant group changes.

Conclusions: We conclude that normal children have vigorous upper airway reflexes in response to PNEG whereas children with OSAS and adults have a variable response. We speculate that the vigorous pharyngeal airway reflexes present in normal children are a compensatory response for a narrower upper airway. Further, we speculate that this compensatory mechanism is lacking in those children who develop OSAS.

References:

Research supported by NIH grants RR-00052 and HL58585-01

209.G

Enuresis in Children with Obstructive Sleep Apnea

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Introduction: Several anecdotal reports describe a relationship between nocturnal enuresis and obstructive sleep apnea (OSA) in children. To test the hypothesis that the presence of nocturnal enuresis is related to the severity of OSA, we examined the relationship between the Respiratory Disturbance Index (RDI, apneas plus hypopneas per hour of sleep) and the presence and severity of enuresis in 160 children age four years and older who were referred to our sleep medicine center for suspected sleep disordered breathing.

Methods: All children underwent a detailed history, including a standard questionnaire, and a full physical examination. Patients were asked whether or not they currently wet the bed and how frequently, and whether or not they had ever been dry for a six month period. The severity of current enuresis was defined by the following criteria: frequently (three times a week or more), sometimes (1-2 times per week), rarely (less than once a week). All patients underwent full overnight polysomnography (PSG). The type, number, and duration of respiratory events were noted, as well as the median and minimal oxyhemoglobin saturation. The RDI was calculated as the average number of respiratory events per hour of sleep. The relationship between RDI and enuresis was examined by linear regression and chi-square analysis. p<.05 was considered to be statistically significant.

Results: The mean age of the 160 children was 9.6±3.58 SD years, ranging from 4.2 to 17.9 years. There was no relationship between age and RDI (r=.02, p=.80). There were 90 boys and 70 girls. 49% of the boys were enuretic, compared with 31% of the girls (p<.05). There was no
difference between the RDI of the boys and the girls (p=.48). The mean body mass index (BMI, kg/m squared) was 22.6±8.7, ranging from 12.9 to 64.2. There was no relationship between BMI and the presence of enuresis (p=.55). At all ages, enuresis was more prevalent in our patients than literature controls. 64% of the children had primary enuresis while 36% had secondary enuresis. Children with an RDI of one or less had a significantly lower prevalence of enuresis (17%) than did children with an RDI>1 (47%) (chi square=4.13, p<.05). Fourteen percent of children with an RDI of one or less had frequent enuresis, compared to 32% of children with an RDI>1. (chi square =4.52, p<.05) There was no significant difference in the prevalence of enuresis in children with an RDI 1-5, 5-15, or >15 (chi square =.18, p=.92).

Conclusions: Nocturnal enuresis is more prevalent in children with an RDI greater than one. More severe OSAS does not further increase the risk of enuresis.
On the Role of Posterior Hypothalamus Neurons in the Control of Paradoxical Sleep

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Introduction: According to our previous studies posterior hypothalamus takes part in the inhibitory control of paradoxical sleep. In particular, it was shown that high-frequency electrical stimulation of the posterior hypothalamus caused a reduction of the REM sleep duration and phasic events (1). In order to further test this hypothesis the sleep-waking discharge patterns of neurons in the posterior hypothalamus have been studied.

Methods: Chronic experiments were conducted on 7 adult unanesthetized cats. Under nembutal anesthesia (40 mg/kg) electrodes for polygraphic sleep monitoring and special appliance for indolent head fixation were implanted. Single-unit neuronal activity was recorded in the posterior hypothalamus (F+=+10, ML=1.5-2, H=-4) with glass-insulated tungsten microwires. At the end of the recording sessions histological verification of electrodes localization was performed.

Results: Neurons recorded during each phase of sleep-waking cycle (n=72) were subdivided into three populations. The neurons of the first one (39%) discharged with the high frequencies both during waking and PS and decreased their discharge rates during slow-wave sleep. The firing frequencies of neurons belonging to the second population (47%) were at their maximum during waking, decreased in slow-wave sleep and reached their minimum during paradoxical sleep. The firing rates of these neurons were higher in tonic stage of paradoxical sleep than in phasic one. The neurons of the third population (14%) discharged tonically at a very low rates during waking, decreased their firing rates in slow wave sleep and nearly ceased discharging during PS. According to literature data (2), neurons with such firing properties are histaminergic.

Conclusions: Our results suggest that the neurons both of the second and the third populations are waking-related and their functional activity is at its minimum during paradoxical sleep. We suppose that these neuronal populations play an important role in waking maintenance and participate in the inhibitory control of brain stem paradoxical sleep centers.

References:

Opioid Regulation of the Sleep-active Cells in the Ventrolateral Preoptic Nucleus (VLPO)

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Introduction: Administration of the opioid peptide dynorphin increases sedation and sleep. The putative target cells and receptors involved in mediating dynorphin effects on sleep are unknown. We recently demonstrated that cells within the ventrolateral preoptic nucleus (VLPO) are active during sleep, show immunoreactivities with inhibitory substances like galanin and GABA and are connected to brain regions associated with arousal including the tuberomammillary nucleus, the dorsal raphe nucleus and the locus ceruleus. In this study, we examined the hypothesis that dynorphin may influence sleep by activation of kappa opioid receptors on VLPO neurons.

Methods: 1. To examine whether sleep-active cells in the VLPO contain the kappa opioid receptor, we examined c-Fos by immunohistochemistry and kappa receptor mRNA (in situ hybridization) in rats (n = 5) that were aslepp 1.5-2.5 hours prior to perfusion. 2. To examine the effect of the kappa receptor agonist dynorphin on sleep, we scored EEG/EMG recordings following microinjection of dynorphin (4.0 nmoles) into the VLPO region (n=10). 3. To examine whether VLPO cells could mediate the behavioral effects of dynorphin via the kappa receptor, we examined sleep in animals with unilateral VLPO lesion (n = 6) either after dynorphin injection ipsilaterally or with prior injection of a kappa receptor antagonist Nor-BI (10 nmoles, n = 6) into the VLPO region. 4. To identify a putative source of dynorphin-containing cells in the CNS that innervate the VLPO, we injected the retrograde tracer Cholera toxin subunit B (CTB) into the VLPO region (n = 3) and looked for cells double-labeled with CTB (CY3) and dynorphin (fluorescence FTIC).

Results: 1. Greater than 90% of the c-Fos positive cells in the VLPO expressed kappa receptor mRNA. 2. Injection of the kappa receptor agonist dynorphin into the VLPO region increased NREM sleep by 51% (p<0.01), but had no significant effect on REM sleep. 3. Dynorphin had no significant effects on sleep when administered to VLPO-lesioned animals. The antagonist Nor-BI blocked the effects of dynorphin on sleep. Injection of Nor-BI followed by dynorphin had no effect on sleep. 4. Dynorphin containing cells in the dorsolateral and central lateral subnuclei in the parabrachial nucleus (PB) were labeled following CTB injection into the VLPO, indicating that dynorphin-containing cells in this region may be involved in the regulation of sleep-active VLPO cells.

Conclusions: The data show that kappa receptors are expressed in sleep-active VLPO cells. The behavioral response following injection of receptor antagonist into the VLPO is consistent with the proposed role of the VLPO in mediating NREM sleep. Results with the retrograde tracer CTB suggest a pathway by which dynorphin-containing cells in the dorsolateral and central lateral subnuclei in the PB could influence the activity of VLPO cells to promote NREM sleep.

Immunohistochemical Study Of Serotonergic Neurons In Rats Neonatally Treated With Clomipramine

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Introduction: It has been demonstrated that neonatal treatment with clomipramine (CLI), an anti depressant and REM sleep inhibitor that produces adult depressive behavior including diminished sexual activity, decreased aggressive behavior, reduced pleasure seeking, increased locomotion and increased REM sleep in rats (1,2). We found that the firing rate of 5-HT neurons in dorsal raphé nuclear (DRN) was decreased in rats neonatally treated with CLI (CLI rats) (3). In order to further study the pathological changes in CLI rats, the following experiment was performed by methods of immunohistochemistry.

Methods: Ten neonatal Long Evan rats, born in our lab, were divided as two groups. Five were treated with CLI (20mg/kg, twice daily) and five were treated with equivolume saline (SAL). The treatment window was from postnatal day 8 through 21. At the age of 4 months old, rats were transcardially perfused with fixative solution (250ml/rat) under Nem-
butal deep anesthesia. Then the brains were removed and immersed in 30% sucrose overnight. Coronal sections were cut at 30µm thickness on a freezing microtome. Six series of adjacent sections were collected for immunohistochemical processing using the peroxidase-antiperoxidase technique. Mouse anti 5-HT transporter antiserum (1:4000; Chemicon International, Temecula, CA), was used as primary anti body and horse anti mouse IgG was used as secondary anti body. 5-HT transporter stain was emphasized with standard ABC kit and cells were revealed with DAB kits from Vector lab (Vector Laboratories, Burlingame, CA). One series control in the absence of primary antibodies and in the presence of normal sera was run in both CLI and SAL groups to ensure the absence of nonspecific single immunostaining in the material. Sufficient rinses were performed with phosphate buffer solution between the major steps. Cells were counted under light microscope and averaged from three adjacent sections.

Results: Results showed that immunostaining by anti-5-HT transporter was specific since no immunostaining was observed with sections incubated in the absence of the antibodies (not shown in graphs). A dense immunolabeling was found in DRN, median raphé and ventral pontine reticular nuclei in both groups (Fig. 1). 5-HT transporter immunostained cells in the entire DRN including dorsal part, ventral part and lateral part were counted in both CLI and SAL groups. Cells of CLI rats was 203 ± 25.8 and of SAL were 188.8 ± 12.7 (Fig. 2). t-Test showed that there was no significant difference between treatments (p=0.34).

Figure 1

Figure 2

Conclusions: In conclusion, there is no difference in 5-HT cells immunostained with 5-HT transporter between SAL and CLI rats. However, we speculate that even though CLI and SAL rats have similar numbers of 5HT cells, differences in cells function may still exist that account for differences in behavior.

References:

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213.A

DBH-Saporin Lesions the Locus Coeruleus, but does not Produce Cataplexy or Abnormal REM Sleep Triggering

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Introduction: Recently, canine narcolepsy was associated with a mutation in the hypocretin-2 receptor , which binds the neuropeptide hypocretin, also known as orexin. The locus coeruleus receives a very heavy projection of HCRT/OX fibers, and the LC also contains HCRT receptor-1 mRNA and protein. HCRT-1 administered to the LC excites LC neurons, increases wakefulness and decreases REM sleep. HCRT-2 microinjections have no effect on sleep indicating that the effect of HCRT on LC neurons is via the HCRT-1 receptor. It has been hypothesized that the HCRT innervation of the LC is responsible for inducing wakefulness and inhibiting REM sleep. Silence of LC neurons is hypothesized to be key in triggering cataplexy and REM sleep. To test this hypothesis, anti-DBH-saporin was used to selectively lesion the LC in rats. Use of DBH-saporin provides a more specific lesion restricted to the LC neurons where the HCRT-1 receptors are localized.

Methods: Male Sprague-Dawley rats (400-620 g) instrumented for recording sleep were given a single bilateral microinjection of anti-DBH-saporin (100 ng/100ul) or pyrogen-free saline. Then continuous 24h sleep recordings were made for 18 days. Recordings made on the 3rd, 6th, 12th and 18th days post injection were analyzed. On the 19th day in order to identify whether cataplexy was induced, the alfa-1 antagonist, Prazosin was administered (1500h, 500mg/kg, IP) and then sleep and behavior recordings were made for the next three hours. In all cases brains were removed for histological assessment.

Results: Anti-DBH-saporin completely lesioned the LC neurons but did not affect the adjacent cholinergic neurons. There were no significant changes in wakefulness, nonREM or REM sleep time after anti-DBH-saporin lesions. Video recordings also did not reveal any cataplexy episodes. The application of Prazosin did not induce cataplexy or diminish muscle tone in DBH-saporin LC treated rats.

Conclusions: Previously, a number of studies have shown that lesions of the LC (electrolytic, excitotoxic, or pharmacological) do not increase
NREM or REM sleep, and our findings are consistent with established results. Moreover, the LC contains the HCRT-1 receptor, but in the narcoleptic dog, it is the HCRT-2 receptor that is mutated. Mice lacking the HCRT-2 receptor gene display narcoleptic sleep behavior but HCRT-1 receptor knockouts do not. These findings do not support the hypothesis that LC neurons are key for maintaining wakefulness, muscle tone or inhibiting REM sleep.

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214.A

Gene Expression In The Cerebral Cortex Of Djungarian Hamsters During Sleep And Wakefulness

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Introduction: Recent work using mRNA differential display and cDNA microarrays has systematically examined changes in gene expression in the rat brain after short periods (3-8 h) of spontaneous sleep, spontaneous wakefulness and sleep deprivation (Mol Brain Res 56:293, 1998; Brain Res, 885:303,2000). The majority of the 10,000 genes screened were not differentially expressed. However, several genes were upregulated after wakefulness and/or sleep deprivation relative to sleep, including immediate early genes/transcription factors (e.g. Fos, NGFI-A, Arc), genes related to energy metabolism (e.g. cytochrome oxidase subunit I), growth factors/adhesion molecules, chaperones/heat shock proteins (e.g. BiP), synaptic-related genes, neurotransmitter receptors and transporters and enzymes (e.g. aryl sulfotransferase). In addition, a few unknown genes were upregulated after sleep relative to wakefulness and sleep deprivation. At least two of the genes upregulated during wakefulness in the rat (BiP and cytochrome oxidase c subunit I) were also upregulated during wakefulness in Drosophila melanogaster (Science 287:1834, 2000). Thus, changes in gene expression across behavioral states may affect basic cellular functions and may be a conserved phenomenon across species. To further test this hypothesis, we performed a systematic screening of gene expression in the cerebral cortex of Djungarian hamsters after 4 h of sleep and sleep deprivation.

Methods: Male Djungarian hamsters (Phodopus sungorus, weight approximately 35 g, LD 8:16, L: 9-17 h or LD 16:8, L: 7-23 h) were sacrificed between 11.10 - 15.07 h after being mostly asleep (n=3+5) or totally sleep deprived by gentle handling (n=3+5) for 4 hours. A systematic screening of gene expression in the cerebral cortex was performed using the rat Atlas cDNA arrays 1.0 and 1.2 (Clontech). All differentially expressed transcripts were cloned and sequenced and the results were confirmed using ribonuclease protection assay and/or real time quantitative PCR.

Results: In agreement with previous results in rats and flies, most transcripts were expressed at the same level after sleep and sleep deprivation. However, several transcripts were expressed at higher levels after sleep deprivation than after sleep. The majority of these transcripts (e.g. Arc, VGF, TrkB, BiP, aryl sulfotransferase) corresponded to those previously identified in the rat. In addition, the transcript corresponding to an unknown gene that is expressed at higher levels in the cortex of sleeping mice related to energy metabolism, growth factors/adhesion molecules, chaperones/heat shock proteins, synaptic-related genes, neurotransmitter receptors and transporters and enzymes was also identified.

Conclusions: Several transcripts are differentially expressed in the hamster cerebral cortex after sleep deprivation relative to sleep, many of which had been shown to undergo similar changes in rat and Drosophila. The consistency of results across different species strengthens the conclusions that 1) significant changes in gene expression occur in the brain across behavioral states, and 2) basic cellular functions such as RNA and protein synthesis, neural plasticity, neurotransmission and energy production may be affected at the molecular level by the transition from sleep to wakefulness.

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215.A

Effects of Melatonin Microinjections Into the Medial Preoptic Area

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Introduction: Previous studies have indicated that sedative/hypnotic compounds from diverse pharmacologic classes induce sleep in the rat when microinjected into the medial preoptic area of the anterior hypothalamus. In the current study we have administered two doses of melatonin to determine whether any possible effects it might have on sleep and waking might be mediated by an action at the MPA.

Methods: Nine male Sprague Dawley rats were anesthetized and implanted with cortical EEG screw electrodes and nuchal EMG wire electrodes according to standard techniques. After a one week recovery period, each animal underwent three experimental recordings, separated by at least 3 days each. Two hour sleep recordings were done after injection at 10:00 AM of melatonin 1 and 50 ug, and vehicle. Each animal received all 3 treatments, in random sequence. All records were interpreted in 30 second epochs by one investigator who was blind to the experimental conditions. Throughout the study, all animals were housed in cages with a 12:12 L:D cycle, such that lights came on at 8:00 AM.

Results: As can be seen in the Table, melatonin significantly increased total sleep time and reduced intermittent waking time (wake time after initial sleep onset). Sleep latency tended to be reduced, but did not reach statistical significance.

Table 1

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Melatonin 1ug</th>
<th>Melatonin 50ug</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency</td>
<td>17.3±2.2</td>
<td>15.7±3.6</td>
<td>9.5±1.7</td>
</tr>
<tr>
<td>Total Sleep</td>
<td>58.3±6.3</td>
<td>67.8±6.0</td>
<td>74.7±6.8*</td>
</tr>
<tr>
<td>REM Sleep</td>
<td>3.3±0.2</td>
<td>5.6±0.3</td>
<td>6.0±0.5</td>
</tr>
<tr>
<td>REM Latency</td>
<td>56.8±10.2</td>
<td>76.7±8.4</td>
<td>40.0±8.0</td>
</tr>
<tr>
<td>NREM Sleep</td>
<td>58.0±6.3</td>
<td>67.3±5.9</td>
<td>74.0±4.5*</td>
</tr>
<tr>
<td>IWT</td>
<td>47.8±6.1</td>
<td>35.9±2.3*</td>
<td>34.6±5.0*</td>
</tr>
</tbody>
</table>

All values represent mean ± SEM minutes. Abbreviations: IWT = intermittent waking time, *= differs by at least p<0.05 from the Vehicle condition, by use of the Least Significant Difference post-hoc test.

Conclusions: These data indicate a weak hypnotic effect of melatonin when microinjected into the MPA, and are in accord with a study of cats indicating that similar doses (15-30 ug) injected into the hypothalamus increase sleep for two hours (1). The mechanism by which it induces this effect is not certain, but may be related to the GABAergic system, insofar as it has been reported to increase GABA concentrations in the rat hypothalamus (2). It is presumably because of dose and the nature of administration in this study (microinjection into a specific nucleus in the CNS) that these results differ from reports that large peripheral doses of melatonin given in the daytime enhance wakefulness in rats (3).

References:
The recent studies which suggest that hypocretin 1 may be involved in the sleep disorder narcolepsy and possibly in the normal regulation of sleep and wake functions. These two peptides are derived from a single precursor molecule called prepro-hypocretin. We have cloned a 450 bp fragment from the 5′-flanking region of the human prepro-hypocretin gene and have demonstrated that this fragment has promoter activity in vitro. The 450 bp fragment contains a number of potential transcription factor binding sites including an interferon response element. Our studies demonstrate that alpha-interferon (alpha-IFN) strongly inhibits the promoter activity in a dose-dependent manner. The inhibitory effect of alpha-interferon is consistent with the recent studies which suggest that hypocretin 1 may be involved in modulating arousal states and with the literature indicating involvement of immune-related molecules in sleep regulation.

Methods: The 450 bp 5′-flanking region of the human hypocretin gene (hcrt) with a mutant IFN-stimulated response element (ISRE) was generated by PCR. The PCR product was first cloned into pPCR-ScriptTM Amp SK(+) plasmid (Stratagene, La Jolla, CA) for sequencing before it was subcloned into pGL3-Basic for the expression studies. The cells were transfected with the expression plasmid and after recovery in growth medium for 24 h, they were treated with different concentrations of alpha-IFN (Biosource International, Camarillo, CA) in 1 ml of growth medium. Following overnight incubation, cells were lysed and the lysates were assayed for luciferase activity.

Results: The 450 bp fragment had the ability to promote luciferase expression in SY5Y, COS-7, NS20Y, and CHO cells. The expression levels varied in different cell lines and ranged between 2- and 20-fold over the background of pGL3-Basic. Since the best expression was obtained with SY5Y cells, this cell line was selected for further studies. The 450 bp upstream of human hcrt contained two AP4, two Sp1, two E4TF1, one AP3, and one AP5 site; an ISRE; and a CAAT box. When the two Sp1 sites, one of the two AP4 sites, and the only AP5 site were deleted the activity of the pGL3(450) was reduced by ~50%. When the second AP4 site was additionally deleted the promoter showed almost no activity. Treatment with alpha-IFN (500 U/ml) for 24 h, resulted in a significant (50-70%) reduction in luciferase activity with both plasmids. The cytokine response in the cells transfected with pGL3(450) plasmid was dose-dependent. When the ISRE sequence was mutated, the promoter activity was not inhibited by treatment with alpha-IFN.

Conclusions: Our studies demonstrate that 450 bp from the 5′-flanking region of the hcrt gene is sufficient to promote gene expression in vitro. We have identified a number of transcription factor binding sites in this region including an ISRE. Furthermore, we have shown that the ISRE is active and down-regulates the expression of hcrt gene upon treatment with alpha-IFN. Future efforts will determine whether alpha-IFN has similar effects on the native gene.

Orexin Promotes Wakefulness in the Freely Behaving Rats

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Introduction: Orexins A and B are novel neuropeptides which are known to regulate the appetite system. Recent studies showed that canine narcolepsy is caused by deficit in the orexin-2 receptor gene (Lin et al., 1999), and that prepro-orexin knockout mice exhibited similar behavior to human and canine narcoleptics (Chemelli et al., 1999). Orexin-containing neurons are localized in the lateral hypothalamic area and densely project to the monoaminergic locus coeruleus, dopaminergic ventral tegmental area, serotonergic dorsal raphe nuclei and histaminergic tuberomammillary nucleus. Hence, brain vigilance state seems to be regulated by the orexin network systems. In this study, we investigate the effects of intracerebroventricular (icv) infusion into the third cerebral ventricle of orexins A and B on the sleep-waking cycle in the freely behaving male Sprague-Dawley rats.

Methods: Cortical EEG and neck EMG were monitored for three consecutive days during continuous icv saline infusion at a rate of 10 ul/h. For 5-h diurnal period, either orexin A (0.1-10 nmol/50 ul saline) or B (1-40 nmol/50 ul saline) replaced the icv infusion of saline.

Results: Orexin A at the dose of 10 nmol markedly increased the amount of wakefulness by 228.6 % (p<0.01) whereas orexin B at the same dose caused an increase of 99.8% (p<0.01) over the baseline value. Both orexins caused dose-dependent increase in wakefulness. The enhancement of arousal was due to a marked reduction in both non-REM sleep and REM sleep.

Conclusions: Icv infusion into the third ventricle of both orexins A and B induced significant arousal effect in the freely behaving rats. The data indicate that orexin A is more effective in causing a state of arousal than orexin B at the same dose. It has recently been reported that administration of orexin A into the lateral ventricle of rats increased wakefulness, whereas the same dose of orexin B into the same site does not change the sleep-waking cycle (Smith et al., 1999). Since orexin A has equal affinity for both the orexin-1 and orexin-2 receptors but orexin B only shows affinity for the orexin-2 receptor, thus exogenous administration of orexin A might be more effective in enhancing a state of arousal than orexin B. Consequently, orexins A and B may play important physiological roles in the regulation of sleep-waking cycle through both the orexin-1 and orexin-2 receptor sites.

References:
Orexin-A/Hypocretin-1 Microinjections into the Ventromedial Medulla Facilitate Muscle Tone in Decerebrate Rats

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Introduction: Narcolepsy, whose major motor symptom is a loss of muscle tone called cataplexy, is caused by the loss of orexin/hypocretin cells.1 The mediodorsal medulla receives moderate projections from orexergic hypothalamic cells,2 and participates in muscle tone facilitation and locomotion.3 In the current study we examined the role of orexin-A (OX-A) in muscle tone regulation using microinjections into the mediodorsal medulla.

Methods: OX-A (Peptide Institute, Osaka, Japan, 50 µM, 0.2 ml, 2 and 10 nl/s) was injected into 28 sites located in the alpha part (GiA) and 20 sites located in the ventral part (GiV) of the gigantocellular reticular nucleus in precollicular-postmammillary decerebrate rats (Wistar, 250-300g, n=12). GiA and GiV sites producing muscle tone facilitation were previously identified by electrical stimulation (40 Hz, 30-120 µA, 0.2 ms) via tungsten microelectrodes. Muscle tone was recorded bilaterally in two hindlimb muscles (gastrocnemius and tibialis anterior). Bipolar stimulation electrodes (stainless steel, 100 µm) for antidromic neuron excitation (3 pulses, 500 Hz, 100-300 µA, 0.2 ms) were implanted at the L1 level of the spinal cord. Unit activity was recorded within 0.2-0.3 mm of the cannula tip. All values are means ± SEM.

Results: OX-A microinjections into previously selected GiA sites evoked muscle tone facilitation in the same muscles where electrical stimulation produced muscle tone increase. The latency and duration of muscle tone facilitation were 143±12 s and 668±70 s (n=17), respectively. OX-A microinjections into the GiV did not produce hindlimb muscle tone facilitation. Activity of 14 reticulospinal neurons (RSN) was analyzed during 11 microinjections into the GiA producing muscle tone facilitation. The firing rate of 8 RSN increased by an average of 186±25% (n=8) after OX-A microinjections and correlated with ipsi- or contralateral hindlimb muscle tone facilitation. These RSN were excited antidromically with latency 2.0±0.05 ms (n=8) during stimulation of the spinal cord. The discharge rate of 2 RSN was decreased by 50-80% compared with baseline and 2 RSN were completely inhibited by OX-A microinjections. The latency of antidromic spikes in these RSN was 2.18±0.07 ms (n=4). Two RSN did not respond to OX-A microinjections.

Conclusions: OX-A microinjections into the GiA produce hindlimb muscle tone facilitation in decerebrate rats. Muscle tone facilitation after OX-A microinjections may be related to excitation of RSN, exciting spinal motoneurons and inhibition of RSN, inducing spinal motoneuron suppression. Orexin induced facilitation via activation of the GiA and locus coeruleus, as we reported at the 14th APSS Meeting, may contribute to the maintenance of muscle tone, thereby preventing the loss of muscle tone in cataplexy.

References:

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219.A

Nitric Oxide Level in the Feline Pontine Reticular Formation is Similar during Waking and NREM Sleep and is Decreased by Morphine

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Introduction: Cholinergic neurotransmission in the feline medial pontine reticular formation (mPRF) plays a key role in sleep cycle control1. REM sleep and mPRF acetylcholine (ACh) release also are significantly decreased by morphine sulfate2. Previous studies using microdialysis delivery of nitric oxide synthase (NOS) inhibitors demonstrated stereospecific inhibition of REM sleep and mPRF ACh3. Such data are consistent with the hypothesis that mPRF nitric oxide (NO) modulates mPRF ACh release and sleep. An acknowledged problem of all research using NOS inhibitors is that such experiments are limited to indirect inferences regarding NO. The present experiments are obtaining direct measures of NO in an effort to test the hypothesis that mPRF NO will vary across the sleep cycle and that opioids will decrease mPRF levels of NO.

Methods: Adult male cats are implanted with electrodes for recording sleep and waking and are trained to sleep in the laboratory. During polygraphically defined quiet waking, a microdialysis probe is positioned for mPRF dialysis. The mPRF is perfused at a flow rate of 3 µl/minute and 20 µl dialysis samples are collected during waking and NREM sleep. In separate experiments data are obtained under halothane anesthesia where the samples are collected before and after intravenous (iv) morphine administration. Data are analyzed using analysis of variance (ANOVA), Tukey-Kramer post-hoc comparison, and t-test.

Results: Figure 1 shows quantification of mPRF NO levels (mean ± sem. pmol) during waking (29.22 ± 13.73) and NREM sleep (24.6 ± 11.67). There was no significant difference between NO levels in waking (n=31 samples) and NREM sleep (n=38 samples). Figure 2 shows that administration of morphine (300 µg/kg, iv) significantly decreased (−37%) mPRF NO levels (*, p<0.01).

Figure 1
Conclusion: This study provides the first direct measures of mPRF NO during waking, NREM sleep, and after systemic morphine administration. As with mPRF ACh release, mPRF NO levels during waking and NREM sleep were not significantly different. Ongoing studies aim to quantify mPRF NO levels during REM sleep, when mPRF ACh release is increased. The previous findings that NOS inhibitors and morphine decrease mPRF ACh release, and the Fig. 2 data, are consistent with the possibility that opioid inhibition of mPRF ACh release is modulated by mPRF NO. This speculation is open to future investigation.

References:

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220.A

Effects Of Early Intervention With Antidepressant, Imipramine On Sexual Behavior In Rat Model Of Human Endogenous Depression

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Introduction: Our lab has established a rat model of human endogenous depression (ED), which is produced by neonatal treatment with clomipramine (CLI). Rats neonatally treated with either pharmacological REM sleep suppressants such as CLI or instrumental REM sleep deprivation exhibit diminished sexual activity, decreased aggressive behavior, reduced pleasure seeking, increased locomotion and increased REM sleep in rats which resemble symptoms of human ED (1,2). These results suggested the hypothesis that neonatal REM sleep deprivation is a mediator of depression and that the rats neonatal treated with CLI are a valid rat model of human ED. These results imply that the pathology of ED is developed during the early life and might be prevented by the early intervention. Present experiments test whether early intervention alleviates the depressive symptoms in rat model of human ED.

Methods: Thirty seven neonatal Long Even male rats, born in our lab, were cross fostered next day after birth. Neonates were divided as CLI (n=32) and SAL (n=8) groups. Rats of CLI group were treated with 20 mg/kg, sc twice daily and rats of SAL group were treated with equimolar SAL. Rats were weaned at 4 weeks old and then group (2-4/cage) hosted in standard conditions. Anti depressive treatments (of CLI rats) were performed during postnatal 6th week (P36-42) in two groups and during postnatal 9th week (P57-63) in another two groups (8/group). Each two groups include one group of imipramine treatment (10 mg/kg, oral twice daily), called as CLI-IMP group, and one group of control (equimolar water, oral), called as CLI-Water group. SAL group had no anti depressive treatment, and served as a normal control. Sexual behavior tests were conducted 3 times starting at 4 months of age. Six variables including mount, intromission, ejaculation, mount latency, ejaculation latency and post ejaculation interval were measured visually. Mean sexual index (MSI) was calculated according to the formulas developed previously (3). Ranks Sum and t-test were used to evaluate the significance.

Results: According to the treatment age (postnatal day), four sub-groups of CLI rats named as CLI-IMP36, CLI-Water36, CLI-IMP57 and CLI-Water57. As shown in figure 1, three of four groups of CLI rats, except CLI-IMP36, had significant lower sexual activities than SAL rats. The p value was 0.088 in t-Test between CLI-IMP36 and SAL rats. Mean of MSI was reduced to 37.7% in CLI-IMP36, 15.1% in CLI-Water36, 23% in CLI-IMP57 and 36.7% in CLI-Water57 respectively. There was no statistically significant difference between CLI-IMP36 and SAL rats. However, the low MSI of CLI-IMP36 group (37.7% at a p value of 0.088) suggests that rats of CLI-IMP36 were depressed. Neither comparison between CLI-IMP36 and CLI-Water36 nor comparison between CLI-IMP57 and CLI-Water57 was statistically significant.

Conclusions: Early anti depressive treatment with imipramine does not prevent the continuation of the depressive behavior produced by CLI neonatal treatment. This suggests that (1) The depressive pathology developed prior to the intervention; (2) Imipramine may alleviate depressive symptoms temporally while it present but not affect the depressive behavior generating processors fundamentally.

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CPPene, a Competitive NMDA Antagonist, Increases NREM Sleep and Eating Time

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Introduction: The uncompetitive NMDA receptor antagonist MK-801 induces a 3 h period of intoxication that is followed by increased NREM duration and elevated NREM delta power. The EEG spectral changes in NREM and REM sleep resemble those produced by 12 h sleep deprivation, suggesting that MK-801 has increased the need for NREM homeostatic recovery(1). We hypothesized that MK-801’s stimulation of metabolic rate in plastic (limbic) structures caused the increased homeostatic need. Here we test whether CPPene, a competitive NMDA antagonist that does not elevate brain metabolism when injected systemically, would produce changes in sleep and EEG similar to those produced by MK-801.

Methods: EEG was recorded continuously for 24 h on saline and drug days in 7 rats implanted with EEG and EMG electrodes. In a random order, all rats received 0.625, 1.25 and 2.5 mg/Kg CPPene injected midway through the dark period. Drug injections were separated by at least one week. EEG was digitized and analyzed with the FFT and period amplitude routines of PASS PLUS (Delta Software, St.Louis). Using a computer display, each 10 sec epoch was scored as NREM, REM or wake. Eating time was approximated by the number of epochs with eating-associated high frequency EEG artifacts.

Results: In the 6 hours of the dark period post drug, NREM min was elevated above saline levels in a dose dependent manner. The majority of this elevation came in hour 2 and 3 post drug. Eating was elevated in the first hour post drug and was depressed in hours 2 and 3 when sleep increased. Behaviorally, a striking response to the drug was an apparent competition between eating and sleep drives so that the animals would often fall asleep at the food bin. The NREM increase was accompanied by a decrease in waking time; REM time was not significantly changed. The 2.5 mg/Kg dose significantly decreased NREM EEG 4-20 Hz power. All doses significantly elevated REM EEG above 20 Hz with the greatest increase in the 25-30 Hz “rho” band, a frequency whose amplitude is specifically elevated in REM(2).

Conclusions: The sleep and EEG effects of the competitive NMDA antagonist CPPene are quite different than those of the uncompetitive antagonist MK-801. These differences could result from different sites of action and/or separate neuronal modes of action. The combination of sleep and eating effects suggests a hypothalamic site of action for CPPene. An attractive possibility is that CPPene affects the hypocretin/orixin systems. However, elevated sleep with elevated eating is difficult to reconcile with the combined alerting and food intake roles currently attributed to hypocretin. Independently, CPPene’s enhancement of NREM sleep raises the possibility that decreasing excitatory rather than increasing inhibitory neurotransmission could lead to a new class of hypnotics.

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We thank Novartis Pharm. for the generous gift of CPPene.

Effects of Propofol on the Sleep State-Dependent Midlatency Auditory Evoked P13 Potential in the Rat

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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 mesopontine neurons may help generate the P50 and P13 potentials). The amplitude of the P50 potential may be decreased in narcolepsy, autism and Alzheimer’s disease. Using a paired stimulus paradigm, sensory gating deficits of the P50 potential have been identified in such psychiatric disorders as schizophrenia, depression and posttraumatic stress disorder. The P13 potential also undergoes decreased amplitude and/or sensory gating after interventions which modulate arousal, such as following ethanol, halothane or barbiturate administration. This study determined the effects of propofol (PRO), a rapidly-acting, sedative-hypnotic on the manifestation of the P13 potential.

Methods: Adult male rats (n=6) were implanted with transcranal 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 trains of stimuli (5 clicks, 0.1 msec duration each at 1kHz, 103 dB, 500 msec inter-train interval) presented 5 sec apart in a sound-attenuating chamber. Evoked potentials were digitized and averaged (32 trials) every 2-10 min up to 1 hr after an injection via indwelling jugular vein catheter of PRO (5, 7.5 or 10 mg/kg) compared to saline injection.

Results: The amplitude of the P13 potential induced by the first stimulus of a pair (initial responsiveness) was significantly decreased by 60% only during the first 2 min after PRO 5 mg/kg, while it was reduced by over 90% by PRO 7.5 and PRO 10 mg/kg (p<0.01). Amplitude recovered to saline control levels by 15 min after PRO 7.5 mg/kg (p<0.01), but not until 30 min after PRO 10 mg/kg (p<0.05). Sensory gating was not affected after PRO 5 or PRO 7.5 mg/kg, but was decreased from 25% after saline to 60% 20-30 min after PRO 10 mg/kg (p<0.01).

Conclusions: These results show a dose-dependent reduction in P13 potential amplitude after sub- and anaesthetic doses of PRO, and transient effects on sensory gating of the P13 potential after the highest (anaesthetic) dose. PRO may have a selective effect on elements of the RAS and only transiently affect higher systems known to modulate input to the RAS (sensory gating).

Effects of Rotation on the Sleep State-Dependent Midlatency Auditory Evoked P13 Potential in the Rat

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Introduction: The vertex-recorded midlatency auditory evoked 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 mesopontine neurons may help generate the P50 and P13 potentials). Using a paired stimulus paradigm, sensory gating deficits of the P50 potential have been identified in such psychiatric disorders as schizophrenia, depression and posttraumatic stress disorder. Sensory gating is a critical function to filter out extraneous information and to focus attention on newer, more salient stimuli. By monitoring sensory gating capability, the ability to appraise and filter out unwanted stimuli can be assessed, and the chances of successful subsequent task performance determined after exposure to a stressor.

Methods: Adult male rats (n=6) 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 trains of stimuli (5 clicks, 0.1 msec duration each at 1kHz, 103 dB, 500 msec inter-train interval) presented 5 sec apart in a sound-attenuating chamber. Evoked potentials were digitized and averaged. First train of stimuli was used for analysis and averaged over 30 min. Decreases in sensory gating were rotation duration-dependent, but in general peaked after decreases in amplitude.

Results: The amplitude of the P13 potential induced by the first train of a pair (initial responsiveness) was significantly decreased by 50% during the first 10 min post-rotation, regardless of rotation duration (p<0.01). The 7.5 min duration led to amplitude recovery within 20-30 min, whereas recovery after 15 min rotation was evident by 50-60 min, but after 30 min rotation recovery was not evident until 90-100 min. Sensory gating, the ratio of the response to the second train of a pair to the first train, was statistically decreased from the normal 25-30% in sham rotated animals, to 50-60% after 7.5 min rotation; to 60-70% after 15 min; and to 80-90% after 30 min rotation (p<0.01).

Conclusions: These results show a rotation-duration dependent effect such that longer duration of rotation induced greater and longer-lasting decreases in amplitude of the P13 potential. Decreases in sensory gating were also rotation-duration-dependent, but in general peaked after decreases in amplitude.

Hypocretin-1/Orexin-A (hcrt-1/OX-A)-Induced G Protein Activation in Rat Locus Coeruleus (LC) Varies as a Function of the 24 hr Light-Dark Cycle

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Introduction: Hypocretin/orxin (hcrt/OX) neuropeptides contribute to the regulation of arousal states. LC, receives dense projections from hcrt/OX containing neurons in the lateral hypothalamus. Administration of hcrt-1/OX-A into LC decreases REM sleep dose-dependently1. In ratpons there is diurnal variation in hcrt-1/OX-A immunoreactivity with high levels during the dark phase and low levels during the light phase2. We recently showed that hcrt-1/OX-A causes concentration-dependent activation of G proteins in LC3. This ongoing study is testing the hypothesis that hcrt-1/OX-A-induced G protein activation in LC varies with the light-dark cycle.

Methods: Two groups of male Sprague-Dawley rats housed in an environmental light:dark (LD) 12:12 cycle were decapitated 3-4 hrs into either the dark phase or the light phase. Brains were removed and coronal brainstem sections (20 μm) were incubated in 2, 20, or 200 nM hcrt-1/OX-A and [35S]GTPγS. In vitro [35S]GTPγS autoradiography is the only method currently available to visualize agonist-induced activation of inhibitory G proteins while preserving brain anatomy. G protein activation was quantified in nCi/g and data were analyzed using one-way analysis of variance (ANOVA) and t-test comparison tests are used to identify the minimum releasing concentration. Analysis of variance (ANOVA) and Tukey-Kramer post-hoc comparison tests are used to identify the minim-

References:

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Muscarinic Autoreceptors of the M2 Subtype Modulate Release of Acetylcholine in Mouse Frontal Cortex

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Introduction: Functional studies of human brain during sleep document inactivation of prefrontal cortex during the REM phase1. Acetylcholine (ACh) is essential for the cortical activation that occurs during waking and REM sleep. We recently presented data consistent with the hypothesis that levels of ACh in mouse frontal association cortex (FrA) are modulated by muscarinic autoreceptors2. The present study extends these findings by testing the hypothesis that FrA ACh is modulated by muscarinic autoreceptors of the M2 subtype, and that measured ACh represents synaptic release.

Methods: C57BL/6J mice are anesthetized with isoflurane to hold arousal state constant. Mice are placed in a stereotoxic frame and CMA/11 microdialysis probes (1 mm X 0.24 mm membrane) are aimed for FrA. Probes are dialyzed with Ringers solution at a rate of 2.0 μl/min. Reverse dialysis delivers to FrA the muscarinic cholinergic receptor (mACHR) antagonists scopolamine, AF-DX116 (gift from Boehringer-Ingelheim), pirenzepine and, in separate experiments, tetrodotoxin. ACh levels in FrA are determined by HPLC/EC. Each antagonist is tested at a range of concentrations, and the lowest concentration to cause a significant increase in ACh release is defined as the minimum releasing concentration. Analysis of variance (ANOVA) and Tukey-Kramer post-hoc comparison tests are used to identify the mini-

SLEEP, Vol. 24, Abstract Supplement 2001
Results: Concentration-dependent increases in FrA ACh release were induced by scopolamine (p<0.0001), AF-DX116 (p<0.0001), and pirenzepine (p<0.01). Table 1 reports the minimum releasing concentration for each antagonist. Tetrodotoxin (1 µM) significantly reduced ACh release (p<0.001).

Table 1

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Maximum Non-Releasing Concentration (nM)</th>
<th>Minimum Releasing Concentration (nM)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine</td>
<td>1</td>
<td>3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AF-DX116</td>
<td>0.3</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pirenzepine</td>
<td>100</td>
<td>300</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: The tetrodotoxin data confirm synaptic release of ACh. There currently are no subtype selective mAChR antagonists. Scopolamine has an equal and high affinity for all mAChR subtypes. AF-DX116 has its highest affinity for M2 and M4 subtypes, whereas pirenzepine has its highest affinity for M1 and M4 subtypes. The finding that AF-DX116 was more potent than pirenzepine in evoking ACh release indicates that in the C57BL/6J mouse FrA ACh release is modulated by the M2 subtype. These functional data extend anatomical evidence for cortical M2 autoreceptors.

References:

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226.A

Nitric Oxide-Sensitive Soluble Guanylate Cyclase Modulates Acetylcholine Release in the Medial Pontine Reticular Formation

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Introduction: Acetylcholine (ACh) release in the feline medial pontine reticular formation (mPRF) is greatest during rapid eye movement (REM) sleep. Inhibition of nitric oxide synthase (NOS) decreases mPRF release of ACh suggesting ACh modulation by nitric oxide (NO). The foregoing data have led us to test the hypothesis that administration of 1H-[1,2,4]oxadiazolo-[4,3-a]quinoxalin-1-one (ODQ), a selective inhibitor of soluble guanylate cyclase (sGC), would reduce release of ACh during waking, non-REM sleep, and REM sleep. There are no specific antagonists for the NO-sensitive sGC inhibitor ODQ. Potent volatile agents, however, have been shown to inhibit the nitric oxide-guanylate cyclase signalling pathway. As a further test of the hypothesis, we have used halothane anaesthesia to block the ability of ODQ to significantly decrease ACh release.

Methods: Under general anaesthesia adult male cats were implanted stereotaxically with standard electrodes for recording sleep. Cats were allowed to recover for at least four weeks before experiments were begun. Microdialysis probes were positioned stereotaxically in the mPRF and dialysed at 3 µl/min first with Ringers (control), then with 10 µM ODQ in Ringers. Sleep/wake states were determined polygraphically. ACh release was quantified by HPLC/EC. In separate experiments animals were anesthetized with 1.4% halothane and the mPRF was dialysed with Ringers, then with 10 µM ODQ. Results were analysed by descriptive statistics, ANOVA, and t-test (single-tailed for state data and two-tailed for halothane data).

Results: Two way ANOVA showed that mPRF ACh release varied significantly as a function of state (F=4.5; d.f.=2,100; p<0.05) and drug (F=9.75; d.f.=1,100; p<0.01). ODQ significantly (p<0.05) decreased ACh release during wakefulness (-28%), non-REM sleep (-33%) and REM sleep (-37%). Halothane anaesthesia eliminated the ODQ-induced decrease in mPRF levels of ACh (Figure 1).

Figure 1

Conclusions: In many brain regions a transmembrane signal transduction cascade involving NO-sensitive sGC and cyclic GMP powerfully modulates neurotransmitter release. The finding that selective blockade of sGC decreased mPRF ACh release supports the hypothesis that NO-sensitive sGC and cyclic GMP modulate mPRF ACh release. The ability of halothane anaesthesia to block the ODQ-induced decrease in ACh release is consistent with in vitro data and with the fact that halothane decreases mPRF ACh release. We conclude that in the mPRF, NO-sensitive sGC is an enzymatic modulator of ACh release.

References:

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Active Sleep In Infant Rats

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Introduction: Myoclonic twitching is a ubiquitous feature of infant behavior that is used as a metric of active sleep. Myoclonic twitching is also a component of REM sleep in adults. This behavioral similarity has led some to suggest that active sleep and REM sleep are homologous states, whereas others have suggested that active sleep is a behavioral state unique to infants that is unrelated to REM sleep in adults. The hypothesis of homology, however, has not yet been tested. In order to test this hypothesis, the neural substrates of active sleep in infants must be identified and then compared with the neural circuitry known to contribute to the expression of REM sleep in adults. In adults, the mesopontine region has been shown to contribute to the expression of REM sleep, but little is known about the neural source of active sleep in infants. Recently, the neural source of active sleep in infant rats was investigated (Kreider & Blumberg, 2000). In this experiment, caudal pontine, mid-pontine and caudal midbrain decerebrations were performed in week-old rats. It was found that caudal pontine and mid-pontine decerebrations disrupted the normal expression of active sleep in week-old rats, whereas caudal midbrain decerebrations did not. These data indicate that the mesopontine region contributes to the expression of active sleep in infant rats. The present study seeks to selectively identify mesopontine nuclei that may contribute to the expression of active sleep in infant rats. To do this, the distribution of mesopontine c-Fos immunoreactivity is investigated during active sleep and wakefulness.

Methods: Previous results indicate that ambient temperature reliably modulates the expression of active sleep and wakefulness in infant rats (Blumberg & Stolba, 1996; Sokoloff & Blumberg, 1998). Thus, in this experiment, 7-day-old rats are acclimated for two hours to one of three test temperatures: 36°C (thermoneutral), 30°C (moderate cold challenge), or 18°C (extreme cold challenge). During the test, behavioral data are recorded to videotape. After the test, immunohistochemical data are collected.

Results: Preliminary results indicate that pups tested at 36°C and 30°C exhibit normal rates of twitching, and low rates of awake behavior, whereas pups tested at 18°C exhibit low rates of twitching, and high rates of awake behavior. Moreover, the highest counts of fos- cells are found in the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus in the 36°C condition but not in the 18°C condition.

Conclusions: These data suggest that the mesopontine nuclei known to contribute to the expression of REM sleep in adults also contribute to the expression of active sleep in infants. Additional data are currently being collected to confirm these results.

References:

This work was supported by NIMH grant MH50701 and NICHD grant HD38708.

Gene Expression Profiling of the Response to Sleep Deprivation in Mouse and Rat Cortex Using Affymetrix DNA Chips

Introduction: The function of sleep and the biochemical nature of the restorative process which occurs during sleep are among the great mysteries of neuroscience. We have previously reported (Terao et al., 2000) changes in gene expression in mouse cortex during sleep deprivation (SD) and during recovery sleep using the Atlas Mouse 1.2 array (CLONTECH). In those studies, only a small subset of genes were affected by SD that fell into two categories: immediate early genes (c-fos, fosB, junB, egr1, nur77, and Arc) and heat shock proteins (ERp72, GRp78). In the present study, we have used Affymetrix GeneChips, which enabled screening of several thousand genes simultaneously, and have used this technology to survey gene expression in both mouse and rat cortex during SD.

Methods: After 6h of sleep deprivation (SD) in baseline studies conducted in both mouse and rat, significant increases in sleep bout length and EEG delta power were observed during the subsequent recovery sleep, indicating that a sleep debt had been achieved. SD and control animals were sacrificed at ZT6, just after a 6h SD period and brains were dissected into multiple regions. For mouse studies, biotinylated and fragmented cRNAs were made from cortex poly A+ RNA pooled from 10 individuals and hybridized to Mul11k suba array (Affymetrix). For rat studies, RNAs were pooled from 6 individuals and hybridized to rat U34A and Neurobiology arrays (Affymetrix). Candidate genes from the arrays were further verified by RT-PCR and/or Northern hybridization and only those genes that were confirmed by these methods were subsequently assayed by real-time PCR (TaqMan).

Results: Relatively few genes and ESTs were affected by SD in mouse cortex, since 6337/6584 (96.2%) from the Mul11ksuba array were categorized as “no change”. However, 212 (3.2%) genes were categorized as up-regulated and 35 (0.5%) genes were categorized as down-regulated during SD. Relatively few genes and ESTs were affected by SD in the rat cortex as well, since 8257/8799 (93.8 %) from the U34A array and 1301/1321 (98.5 %) from the Neurobiology array were categorized as “no change”. In rat cortex, 272 (3.1%) genes were categorized as up-regulated and 270 (3.1%) genes were categorized as down-regulated during SD from the U34A array. Most of the genes previously reported to be affected by SD in the Atlas Mouse 1.2 array (CLONTECH) were also confirmed by Affymetrix GeneChip studies. Candidate gene confirmation is ongoing.

Conclusions: These results indicate that the expression of only a subset of genes in the cerebral cortex change in response to SD in both mouse and rat. Convergence of information obtained in two species should help identify those genes that are truly responsive to sleep deprivation and recovery sleep.

References:

Research supported by RO1 HL/MH59658
Restraint Stress Induces a Pronounced Increase in Prolactin and a Specific Increase in Rapid Eye Movement (REM) Sleep in C57BL/6 Mice but not in BALB/c Mice

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Introduction: Sleep is generally considered to be a recovery from prior wakefulness. The architecture of sleep not only depends on the duration of wakefulness but also on its quality in terms of specific experiences. We studied the effects of restraint stress on sleep in C57BL/6J and BALB/cJ mice. The aim of this experiment was to determine if the REM sleep promoting effect of restraint stress previously reported for rats (1) also occurs in different strains of mice. In addition, we examined whether the effects of restraint stress on sleep are different from the effects of social defeat stress, which has NREM sleep promoting effects (2). We further measured corticosterone and prolactin levels as possible mediators of restraint stress-induced changes in sleep.

Methods: The study was performed with adult male C57BL/6J mice and BALB/cJ mice maintained in a 12h:12h LD cycle. In a first group of animals (n=8 for each strain), EEG and EMG electrodes were implanted to examine the effects of 1h restraint stress on sleep. To control for possible effects of sleep loss per se, the animals were also kept awake for 1h by gentle handling. The mice were subjected to restraint stress or gentle handling during the sixth hour of the light phase. Recovery sleep was measured for 18h after the manipulation. A second group of mice was used to collect blood after 1h restraint or gentle handling for analysis of prolactin and corticosterone levels (n=10 for restraint and handling, each strain).

Results: In both strains, restraint stress resulted in a mild but significant increase in NREM sleep compared to baseline but, overall, this effect was not different from sleep deprivation by gentle handling. In C57BL/6J mice, there was a significant increase in REM sleep during the dark phase after restraint stress compared to handling. This increase in REM sleep could not be attributed to a rebound from sleep loss and it was disproportionally larger than the increase in NREM sleep. In the BALB/cJ mice, the total amounts of REM sleep after restraint stress and gentle handling were not significantly different. Compared to gentle handling, corticosterone levels after restraint were significantly and similarly elevated in both strains. In C57BL/6J mice, restraint stress induced a very pronounced and significant increase in prolactin that was 10-fold higher than the response to gentle handling. In the BALB/cJ mice prolactin levels after restraint stress were low and not different from levels after handling.

Conclusions: This study shows that in mice the increase in REM sleep after restraint stress is strain-dependent. The concomitant increases in prolactin and REM sleep in the C57BL/6J mice, but not in BALB/cJ mice, suggests that prolactin may be involved in the mechanism underlying restraint stress-induced REM sleep. Furthermore, this study confirms that different stressors differentially affect NREM and REM sleep. Whereas in C57BL/6J mice restraint stress promotes REM sleep, we previously found that social defeat stress in the same strain promotes NREM sleep (unpublished results). As such, studying the consequences of specific stressful stimuli may be an important tool to unravel both the underlying mechanisms and functions of different sleep stages.

References:


Research supported by NIH grants AG-11412, AG-18200, and HL-59598

Effects of Gamma-hydroxybutyrate on Sleep States and EEG Power Spectra in Rats and Mice

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Introduction: Gamma-hydroxybutyrate (GHB) is a naturally occurring short chain metabolite of gamma-amino butyric acid (GABA) which has been reported to consistently stimulate slow wave sleep in humans. In animals, administration of GHB has been found to induce a sleep-like state associated with highly variable effects on specific sleep stages depending on the dose and the species (1). In the present study, the dose-response effects of GHB on sleep-wake patterns and EEG power spectra were characterized further in rats, and examined for the first time in mice. Additionally, the question was raised whether GHB would produce differential effects on sleep in the rat during the light and dark phases.

Methods: Pharmacological treatments were performed in adult male Wistar rats and BALB/cJ mice which were chronically implanted with EEG and EMG electrodes for standard polygraphic sleep monitoring. The rats received different doses of GHB (25, 50, 100, 200 or 300 mg/kg i.p., n=4 animals per dose) administered either 2 h after the onset of the light phase or at the onset of the dark phase. The mice were injected with 50, 150 or 250 mg/kg i.p. of GHB (n=8 mice per dose) at the beginning of the light phase. Sleep-wake patterns and EEG power spectra (Fast Fourier Transform) were compared to those of animals receiving saline injection under the same conditions.

Results: In rats: When GHB (25-200 mg/kg) was administered during the light phase, no effect was observed on the amount of sleep or EEG activity, except a slight increase in NREM sleep delta power during the first 2h after the dose of 200 mg/kg. In contrast, the same dose of GHB injected at dark onset produced a 27% increase in NREM sleep for 4h associated with a pronounced enhancement of delta power (+37%) in the first 2h following treatment. REM sleep amounts were not affected. Animals treated with 300 mg/kg GHB in the light phase showed a continuous hypersynchrony of the EEG for 2h while exhibiting a behavioral waking state. In mice: Administration of GHB (150 and 250 mg/kg) during the light phase induced an elevation of the EEG delta power in NREM sleep-like state during the first 30 to 60 min after the injection. However, behavioral observation revealed that the animals showed a flat body posture that might not reflect physiological sleep.

Conclusions: The results indicate that GHB has differential effects on EEG sleep in rodents depending on the time of administration. At doses that do not produce abnormal behavioral effects, GHB can induce a pronounced increase in both the time spent in NREM sleep and in EEG delta activity which was evident only during the physiological active period of the rat.

References:

Research supported by NIH grant AG-11412
Carbachol Activates G Proteins in Pontine Reticular Formation of C57BL/6J Mouse

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Introduction: Rapid eye movement (REM) sleep is modulated by cholinergic mechanisms in the pontine reticular formation¹. In cat, a pertussis toxin-sensitive G protein modulates cholinergic REM sleep enhancement². In rat, carbachol binding to muscarinic cholinergic receptors (mAChRs) activates G proteins in REM sleep-related brainstem nuclei². Despite recent enthusiasm for mouse as a model system for sleep research, no previous studies have characterized G protein coupled receptor systems in mouse pontine reticular formation. This ongoing study is using in vitro autoradiography of cholinomimetic-stimulated [³⁵S]guanylyl-5'-[γ-thio]-triphosphate ([³⁵S]GTPγS) binding to test the hypothesis that carbachol activates mAChR coupled G proteins in pontine reticular formation of mouse.

Methods: Brains from adult male C57BL/6J mice are rapidly removed, frozen, and serially sectioned at 20 micron thickness. Coronal sections are thaw mounted onto gelatin coated slides, dried in a vacuum dessicator on ice for 2 hours and stored at -80°C until assayed. For the [³⁵S]GTPγS assay, single concentrations of carbachol (1.0 mM) and atropine (0.1 mM) are used to activate G proteins and assess mAChR mediation of G protein activation in the pontine reticular nucleus, caudal part (PnC) and pontine reticular nucleus, oral part (PnO). Autoradiograms are analyzed using the Scion Image® program (version 1.62C). Brain regions examined are localized using the atlas of Franklin and Paxinos. The data are analyzed using one-way ANOVA for repeated measures and post hoc Tukey-Kramer multiple comparison tests.

Results: Binding of [³⁵S]GTPγS in the presence of carbachol was significantly increased (* p<0.01) in PnC and PnO when compared with basal (control) binding (Figure 1). G protein activation was significantly greater in PnO († p<0.01) than in PnC (Figure 2). In the presence of atropine, the activation of G proteins by carbachol was antagonized to the level of activity quantified for the basal binding condition.

Figure 2

Conclusions: Carbachol activates G proteins in PnC and PnO of the C57BL/6J mouse. Activation of G proteins by carbachol was antagonized by atropine, demonstrating mediation by mAChRs. These data provide the first direct measures of mAChR activated G proteins in brainstem nuclei of the mouse, and support the use of murine models for neurobiological studies of sleep.

References:

Research supported by NIH grants HL65272, HL40881, HL57120, MH45361, NCCR T32 RR07008, and Department of Anesthesiology and Unit for Laboratory Animal Medicine

232.A

Suppression of Rapid Eye-Movement Sleep in Older Rats does not “Rescue” the Age-related Loss of a Developmentally Regulated form of Synaptic Plasticity.

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Introduction: Rapid eye-movement (REM) sleep may contribute to brain maturation. Both younger and older rats exhibit a form of long-term potentiation (LTP) recorded in layer 2/3 after stimulating layer 4 of visual cortex. However, only in the younger rats, still in a maturational phase of visual brain plasticity (the “critical period”), is it possible to produce LTP by stimulating the underlying white-matter and recording in layer 2/3. It was recently shown that REM sleep-deprivation maintains cortical plasticity for up to ten days beyond the usual end of the critical period, as indicated by the persistence of white matter-stimulated LTP (1). Age-matched controls, housed on larger pedestals, observe the usual developmental pattern, i.e., white matter-stimulated LTP is not observed after the critical period. Is this a developmental effect? Or can REM sleep-deprivation cause similar effects in older, post-critical-period animals?

Methods: Eight pigmented rats were obtained at P21 and housed in communal cages until P40. Four were then moved to individual aquaria containing only three small platforms sitting just above a water level, a classical environment for REM sleep-deprivation. Similar aquaria with three larger platforms over water housed three age-matched rats to con-
trol for the REM sleep-deprivation setting and isolation. After at least 7 days, one animal from either condition was removed each day from its aquarium and decapitated. The brain was rapidly removed to ice-cold artificial cerebral-spinal fluid, and 400 micron-thick coronal slices of visual cortex were prepared for LTP studies (1). One rat remained in its home cage until P58.

Results: The large-platform animals were observed to sleep without falling off their platforms and contacting the water. On the other hand, small-platform rats either woke abruptly or fell into the water at variable times after assuming a sleep posture. At P58, the cage-control animal was the oldest rat tested. In tissue from this animal, layer 4-stimulated LTP was only partially produced (~110% of baseline values) and white matter-simulated LTP was not observed. One of the three large-platform controls did not exhibit LTP at either stimulation site. In the other two, after layer 4 stimulation LTP was observed, but not after the white matter was stimulated. Likewise, in three small platform rats, white matter stimulation failed to produce LTP, though it was observed after layer 4 stimulation. LTP was not observed after stimulation at either site in brain slices from one small platform rat.

Conclusions: REM sleep-deprivation in older rats failed to “rescue” the developmentally regulated form of LTP, which had been observed in cortical slices taken from REM sleep-deprived, critical-period rats (1). These preliminary results indicate that REM sleep-deprivation in young animals slows the developmental processes that would otherwise end the critical period of brain plasticity. Accordingly, this effect appears to be limited to the critical period of visual brain maturation.

References:

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233.A
Orexin-A Containing Lateral Hypothalamic Neurons Project both to the Cholinergic Basal Forebrain and Subcoeruleus Pontine Reticular Formation: A Retrograde Tracing Study
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Introduction: Recent work indicates that the orexin/hypocretin neurons of the lateral hypothalamus (LH) are involved in behavioral state regulation such that an absence, or reduction, of orexin peptide or orexin receptors decreases wakefulness (W) and enhances REM sleep, whereas increases in endogenous orexin are thought to promote W and suppress the appearance of REM sleep. Recently, we have shown that microdialysis perfusion of antisense oligonucleotides against orexin type II receptor mRNA into the subcoeruleus (SubC) reticular region of the brainstem increased REM sleep and induced cataplexy-like episodes in freely behaving rats. In contrast, microdialysis perfusion of orexin-A peptide in the basal forebrain (BF) induced wakefulness. To examine the projections of orexin-A containing neurons of the LH to the BF and SubC region, we used the combination of retrograde tracer cholera toxin subunit B (CTB) and orexin-A double-labeling immunohistochemistry.

Methods: Male Sprague Dawley rats were anaesthetized for microinjection of the retrograde tracer CTB(1% CTB, 3 ul). After seven days, the animals were sacrificed and perfused (4% paraformaldehyde). The areas of interest, the injection site (either BF or SubC) and the LH were blocked and 40 um coronal sections were made. The injection sites were identified by CTB immunohistochemistry. Further, we performed ChAT immunohistochemistry to confirm the location of the injection site in the cholinergic BF. The LH was processed for orexin-A and CTB double-labeling immunohistochemistry. The CTB immunohistochemistry was performed by using the standard peroxidase-diaminobenzidine protocol whereas FITC-conjugated secondary antibody (fluorescence) was used to identify orexin-A containing neurons of the LH. The LH double-labeled sections were mounted and cover-slipped using Prolong Antifade Kit (Molecular Probes) and examined using an Axiosplan 2 microscope (Zeiss) with a Sensicom digital camera.

Results: Preliminary results of our study indicate that: 1) CTB microinjected in the cholinergic BF retrogradely labeled a moderately large subpopulation of the orexin-A containing neurons in the LH. Out of a total of 202 orexin-A containing neurons counted, 60 (~ 29%) were double-labeled with the retrograde tracer CTB. 2) Similarly, CTB microinjected in the SubC retrogradely labeled a fairly large subpopulation of the orexin-A containing neurons the LH. Out of a total of 186 orexin-A containing neurons counted, 62 (~ 34%) were double-labeled with the retrograde tracer CTB. Work is in progress to identify whether the BF and the SubC region receive orexin projections from the same subpopulation of orexin-A containing neurons or whether there are two distinct subpopulations of orexin-A containing neurons that project to BF and SubC regions.

Conclusions: In summary, our preliminary data suggest that a substantial subpopulation of orexin-A containing neurons of the LH send projections to either BF or SubC region.

This work was supported by the Department of Veterans Affairs (RWM) and by the National Institutes of Health Grant R37MH39683 (RWM) and KO1MH01798 (MMT).

234.A
Increased Non-Rapid Eye Movement (NREM) Sleep Duration and EEG Slow Wave Activity (SWA) in Mice after an Aggressive Social Interaction but not after a Sexual Interaction
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Introduction: Sleep architecture and sleep EEG not only depend on the duration of prior wakefulness but also on its quality. A recent study showed an increase in NREM sleep SWA in male rats after a confrontation with an aggressive conspecific (1). Since SWA is generally considered as an indicator of sleep intensity this finding suggested that sleep is intensified by social conflict. In the present experiment we extended this finding to mice and investigated whether the increase in SWA is a specific response to a social conflict or whether it generalizes to other arousing social stimuli, in this case, sexual interaction.

Methods: Male mice (C57BL/6J, n=8) were implanted with permanent electrodes for recording EEG and EMG to examine the effects of social conflict and sexual interaction on sleep. After recovery from surgery, the mice were placed in the cage of either an aggressive dominant male or an estrous female for 1h in the middle of the light phase. On another occasion, the animals were kept awake for 1h by means of gentle handling to control for the possible effects of sleep deprivation per se. Recovery sleep was recorded for 18h after the three experimental manipulations (the remainder of the light phase and the subsequent dark phase).

Results: After a conflict with an aggressive conspecific there was a pronounced increase in NREM sleep time compared to the levels under
baseline conditions, after gentle handling, or after sexual interaction. NREM sleep SWA following the conflict was increased and in the course of the recovery period the animals accumulated significantly more slow-wave energy (SWE) than in the other conditions. REM sleep was significantly suppressed for 5-6h after the conflict, which led to a rebound increase later during the recovery phase. The sexual interaction, in contrast, had only mild effects. Both NREM sleep and REM sleep were slightly suppressed for 1-2h after the interaction but the total amounts of NREM and REM sleep during the whole recovery period were not significantly affected. NREM sleep SWA after the sexual interaction was increased compared to SWA after gentle handling. However, this was probably due to the fact that the animals were not only awake during the sexual interaction but also had more wakefulness afterwards. The total accumulated SWE during the recovery period after sexual interaction was the same as after sleep deprivation by handling and under baseline conditions.

Conclusions: The results demonstrate that a social conflict has a strong stimulatory effect on NREM sleep mechanisms but at least one social interaction, mating, does not, even though the latter induces a strong physiological activation and arousal as well.

References:

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235.A

Indirect Projections from the Suprachiasmatic Nucleus to Wake-related Neuronal Groups in the Forebrain and Brainstem in rat.

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Introduction: The suprachiasmatic nucleus (SCN) houses the principal clock for many circadian rhythms in mammals, including the daily sleep/wake cycle. The understanding of the neuronal mechanism by which the circadian clock imposes its temporal control over sleep/wake state is yet rudimentary. In a previous study [1], we identified several hypothalamic nuclei as potential intermediary nuclei to relay SCN output to the ventrolateral preoptic area, a site of sleep-active neurons. These included the medial preoptic area, subparaventricular zone and paraventricular hypothalamic nucleus, and dorsomedial hypothalamic nucleus. The present study examined whether these or other hypothalamic nuclei convey SCN output to wake-related neurons in forebrain and brainstem, specifically, the basal forebrain, hypocretin/orexin-containing and histaminergic neurons. The data suggest that these hypothalamic nuclei may mediate SCN circadian signals not only to sleep-related neurons in the ventrolateral preoptic area as previously reported [1], but also to wake-related neurons in both forebrain and brainstem.

Conclusions: We identified several possible relay nuclei for the indirect SCN projections to wake-related neuronal groups in the forebrain and brainstem. These include the medial preoptic area, dorsal hypothalamic area, and dorso- and ventromedial hypothalamic nucleus. These results suggest that these hypothalamic nuclei may mediate SCN circadian signals not only to sleep-related neurons in the ventrolateral preoptic area as previously reported [1], but also to wake-related neurons in both forebrain and brainstem.

References:

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236.A

Peripheral Administration of Interleukin-1b Increases Nuclear Factor Kappa B Activation in Visceral Nucleus Tractus Solitarius

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Introduction: An intraperitoneal injection of the cytokine, interleukin 1b (0.5 m g/kg) at dark onset increases non-rapid eye movement sleep (NREMS) and brain expression of IL1b mRNA. Subdiaphragmatic vagotomy blocks this increase, suggesting that vagal afferents are used to signal systemic cytokine levels to the central nervous system (Hansen et al., 1997; 1998). The transcriptional factor, nuclear factor kappa B (NFkB), is used by the brain in the biochemical cascade between the cytokine receptor and regulation of gene expression, e.g. IL1b mRNA production is enhanced by NFkB activation. When cytokine signals activate the cascade, the inhibitory subunit Ik B is phosphorylated, which releases the heterodimer of p50 and p65 subunits of NFkB allowing for their translocation into the nucleus to regulate gene expression [Baeuerle and Baltimore, 1988].

Methods: To evaluate whether NFkB is involved in the induction of NREMS, we used antibodies to the phosphorylated Ik B subunit (Santa Cruz; 1:1000) and an activated subunit of NFkB (Chemicon, 1:1000), the nuclear-translocated NF-p65 subunit to determine whether peripheral IL1b injection at dark onset stimulates NFkB activation within the nucleus tractus solitarius (NTS), the brain region where the primary afferents from the viscera synapse. Utilizing the NIH image density pro-
Conclusions: These data indicate that systemic IL1b rapidly induces the transcription factor, NFκB, within specific regions of the visceral NTS, supporting the hypothesis that peripheral cytokine signaling of the brain via vagal afferents involves NFκB activation.

References:

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237.A

Orexin Neurons Contain Dynorphin

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Introduction: Orexin is a peptide neurotransmitter found in neurons of the perifornical region and lateral hypothalamic area. Defects in orexin transmission have been associated with narcoleptic symptoms in mice, rats, dogs, and humans. While mice that genetically lack the orexin ligand display narcolepsy-like symptoms, mice with genetic ablation of the orexin neurons also eat less and become obese (1). Because mice lacking orexin neurons have a different phenotype than mice lacking only orexin, we hypothesized that orexin neurons contain other functionally important neurotransmitters. In particular, we studied whether orexin neurons contain dynorphin, because dynorphin neurons are also found in the perifornical region and lateral hypothalamic area.

Methods: Double-label in situ hybridization was performed as previously described (2) using orexin and dynorphin riboprobes labeled with 35S or digoxigenin. We also performed double-label immunohistochemistry for orexin and dynorphin using fluorescently labeled secondary antibodies.

Results: Double-label in situ hybridization in rats and mice showed that virtually all neurons containing prepro-orexin mRNA also express preprodynorphin mRNA. In the perifornical region and lateral hypothalamic area, the converse was also true: nearly all preprodynorphin expressing neurons also expressed prepro-orexin mRNA. This high degree of colocalization of orexin and dynorphin was confirmed at the protein level using double-label immunohistochemistry.

Conclusions: Dynorphin may be a useful alternative marker for the orexin neurons when the orexin ligand is absent, as in most forms of human narcolepsy. Identification of dynorphin in the perifornical region and lateral hypothalamus of human narcoleptics may help identify whether the orexin neurons are absent, or simply failing to express orexin. Most importantly, dynorphin in the orexin neurons may play a crucial physiologic role, possibly contributing to the regulation of energy balance and metabolism.

References:
(1) Hara J, Sakurai T, Beuckmann CT, et al., “Genetic ablation of orexin neurons in mice causes a sleep disorder similar to human narcolepsy, hypophagia, and obesity.” Submitted to Neuron, 2001.

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REM Sleep and SWS Whisker EMG Activity in the Rat

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Introduction: In the adult mammal, non-pathological activation of the musculature within sleep is thought to occur exclusively during rapid-eye-movement (REM) sleep. However, the activity of rat whisker musculature has never been tested across all behavioral states.

Methods: We recorded neck and whisker EMG activity from 6 adult, male, Sprague-Dawley rats across multiple sleep/wake cycles. Cortical EEG was recorded between a screw electrode placed at the lateral margin of bregma and another above parietal cortex and underlying hippocampus. High levels of neck EMG and desynchronized or theta-rhythmic cortical EEG activity identified wakefulness. Reduced neck EMG tone and presence of delta activity in the cortical EEG identified slow-wave sleep (SWS). Tonically reduced neck EMG tone and the presence of theta-frequency EEG activity characterized REM sleep.

Results: Theta-rhythmic whisker EMG activity (whisking) was clearly present during waking periods; although, arrhythmic activity predominated. During deep SWS, 1-2 second bursts of rhythmic whisker twitches were observed with amplitudes often matching or exceeding those observed during REM sleep. Power spectral density (PSD) analysis of rectified whisker EMG revealed, in each animal, whisker twitches in SWS occurring with rhythmicity in the 9-11 Hz frequency range. Similar activity was also observed during transitional periods between quiet wake and light SWS. EEG activity was found to contain 9-11 Hz activity during 9-11 Hz whisker twitches during quiet waking, but not in SWS. In addition, whisker twitches in SWS were not temporally associated with cortical EEG sleep spindles. Within REM sleep, phasic bursts of whisker EMG activity occasionally interrupted longer periods of tonic REM sleep. PSD analyses of the cortical EEG in REM sleep revealed that: 1. tonic periods of REM sleep were associated with prominent peaks only in the theta-frequency range; 2. PSD analyses from periods of REM sleep associated with whisker EMG bursts (phasic REM) contained both prominent theta-frequency peaks and peaks in the delta-frequency range. In addition, the frequency of theta was found to increase during phasic REM. PSD analyses of whisker EMG activity revealed the virtual absence of rhythmic whisker movements (whisking) within REM sleep. Instead, bursts of arrhythmic activity, typically a few seconds in length, were observed similar to those observed in the awake rat.

Conclusions: The findings demonstrate that prominent bursts of EMG activity can occur during mammalian SWS. Such activity may or may not be limited to rhythmic whisker movement in rats. The dissociation of 9-11 Hz whisker twitching from cortical EEG activity during SWS, but not during waking, suggests that it may originate in subcortical structures. The lack of temporal relationship between EEG sleep spindles and rhythmic EMG whisker activity suggests the presence of 2 separate generators for spindle-frequency oscillations in SWS. Theta-rhythmic whisker EMG activity (whisking) normally associated with active tactile exploration is rare in REM sleep. Nevertheless, arrhythmic whisker EMG activity in REM sleep is correlated with changes in EEG power spectra.

Research supported by Neurosciences Research Foundation

Impairment of the Sleep Response to Influenza Infection in Mice with a Defective GHRH-receptor.

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Introduction: Sleepiness is a common experience during infectious diseases. Viral infections induce many cytokines, including interleukin-1β (IL-1β), which has somnogenic activity. Previous results suggest that IL-1β stimulates growth hormone-releasing hormone (GHRH), a peptide also implicated in promotion of non-rapid eye movement (NREMS). Recently via quantitative trait loci analysis, the GHRH-receptor (GHRH-R) was identified as a candidate gene responsible for NREMS responses of BALB/c and C57BL/6 mice to influenza challenge(1). To test the hypothesis that the GHRH-R is important for the excess NREMS induced by influenza we used the dwarf C57BL/6 (lit/lit) mouse which has a point mutation in the GHRH-R gene resulting in the loss of receptor function (2).

Methods: Mice (control C57BL/6, n=11: dwarf lit/lit, n=10) were implanted with electrodes over the frontal and parietal cortices for EEG recordings and with EMG electrodes in the dorsal neck muscles. Animals were individually housed in Plexiglas cages on a 12:12-h light-dark cycle at an ambient temperature of 30 degrees in sound-attenuated chambers. After 4-5 days of habituation, spontaneous sleep-wake activity was recorded for 48 h. Data from these two days were averaged and used as baseline values. Mice were then intranasally infected with A/PR/8/34 (H1N1) influenza virus (2.5 x 10⁶ TCID₅₀ in 50ml) at light onset. The EEG and EMG signals were collected by computers and states of vigilance were visually determined in consecutive 10-s intervals. The percent time spent in wakefulness, NREMS and REMS were calculated for each recording hour. Changes in NREMS and REMS were compared by means of two-way ANOVA for each day between groups.

Results: Lit/lit mice had significantly less NREMS and REMS than controls on the baseline day. In control mice influenza virus induced a long-lasting increase in NREMS and suppression of REMS, while lit/lit mice showed a progressive decrease in NREMS without a suppression in REMS. The sleep responses were statistically different. The lit/lit mice exhibited pathological EEG slow wave and spike activity after infection, an abnormality, that occurred only prior to death in normal mice. By day 4, 7 of 10 lit/lit mice died, whereas the mortality of the controls was 4/11.

Figure 1

After PR8 challenge (arrow), NREMS in lit/lit mice decreases. Each data point represents percentage of NREM sleep, ± SEM.
Conclusions: Results suggest that the GHRH-R is important for influenza-induced sleep responses and, perhaps, for survival.

References:

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Effects of IFN-gamma and TNF-alpha on Spontaneous Sleep in Mice

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Introduction: Cytokines play important roles in sleep regulation (1). It is hypothesized that sleep responses during infectious diseases are induced by cytokines. Furthermore, some cytokines, such as IL-1, TNF-alpha and IFN-gamma, induce nitric oxide, which is also involved in sleep regulation. TNF-alpha and IFN-gamma potentiate each other’s actions in terms of nitric oxide production (2) and in other systems. Thus we decided to determine the effects of TNF-alpha and IFN-gamma, plus the combination of both, on sleep.

Methods: Eight adult female mice were implanted with EMG and EEG electrodes. The mice were housed in individual cages placed in environmental chambers and kept on a 12:12 light-dark cycle with light onset at 08:00. Sleep recordings began a week after surgeries. Each mouse received 0.2 ml saline (i.p.) at dark onset on the first day as control and the following cytokines in the same volume; 10,000 units IFN-gamma on the second day and 1mg TNF-alpha on the third day. On the fifth day, the combination of 10,000 units IFN-gamma and 1mg TNF-alpha was given. The EEG data were processed by online Fast Fourier Transformation (FFT). Sleep-wakefulness status was scored visually offline using the EEG and EMG. Data were analyzed by two way repeated analysis of variance (ANOVA) followed by Student-Newman-Keuls (SNK) test.

Results: IFN-g or TNF-alpha increased non-rapid eye movement sleep (NREMS) during the first six hours after injection. The effects of IFN-gamma and TNF-alpha given together were additive, the time in NREMS was increased by over 55% (P<0.05) in the first 6 hours (Fig 1). TNF-alpha reduced low frequency EEG power but enhanced high frequency power. IFN-gamma itself had little effect on EEG power in contrast, the combination of the IFN-gamma and TNF-alpha significantly decreased the EEG power by 10-19% (P<0.01) (Fig 2). No significant effect was found on the rapid eye movement (REM) sleep.

Conclusions: Results suggest that the combination of IFN-gamma and TNF-alpha enhanced sleep in mice and changed the characteristics of the sleep EEG.

References:

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L-364,718, a CCK-A Receptor Antagonist does not Prevent the Somnogenic Effects of Interleukin in Rats

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Introduction: Several cytokines and cholecystokinin (CCK) have been shown to induce sleep. They have overlapping biological activities and have mutual stimulatory effects on each other’s secretion or function. For example, administration of interleukin-1 (IL-1) increases CCK plasma levels, IL-1 sensitizes peripheral vagus afferents to the effects of CCK. The effects of IL-1 on the vagus nerve and on food intake are suppressed by CCK-A receptor antagonists. CCK stimulate the production
of IL-1, tumor necrosis factor-a and granulocyte/monocyte colony-stimulating factor from monocytes. Increased feeding stimulates the secretion of CCK as well as the expression of IL-1b mRNA in the liver and the brain. The aim of the present experiments was to investigate the role of CCK in IL-1b-induced sleep by using L-364,718, a selective CCK-A receptor antagonist.

Methods: On the baseline day, rats received 0.5% methylcellulose (1 ml/kg, ip, solvent for L-364,718) followed by saline injection (1 ml/kg, ip). On the test day, one group of rats (n = 7) was treated with methylcellulose followed by rat recombinant IL-1 beta (1.0 mg/kg, ip). Another group (n = 7) was injected with the CCK-A receptor antagonist (L-364,718, 500 mg/kg, ip) followed by IL-1. Injections were made 10 min apart at dark onset. All recording sessions started at and lasted for 23 h. The amounts of NREMS, REMS, and the delta activity of EEG during NREMS (slow-wave activity, SWA) were measured.

Results: During the first four hours after injections, IL-1-treated rats showed a statistically significant increase in the amount of time spent in NREMS as compared to baseline (p < 0.05). REMS reached a significant increase in hours 5 - 6 after injections (p < 0.05). CCK-A receptor antagonist did not prevent the somnogenic effects of CCK. CCK-A receptor antagonist plus IL-1 treatment increased sleep for the first 6 hours after injections (p < 0.05). An increase in REMS was observed during hours 3 - 8 reaching significance (p < 0.05) in hours 3 - 4 and 7 - 8. SWA was not significantly affected by either IL-1 or IL-1 + CCK-A receptor antagonist treatments. Temperature was elevated in the first hour in both groups (p < 0.05).

Figure 1

Figure legend: The effect of IL-1 on the sleep of control and CCK antagonist-treated rats. Open symbols: Baseline day. Solid symbols: test days. Circles: NREMS. Triangles: REMS. Solid bars: Dark periods. Asterisks: p < 0.05. Time ‘0’: the time of injection.

Conclusions: Intraperitoneal injection of 500 m g/kg L-364,718 completely blocks the somnogenic action of exogenously administered CCK (1) and increased feeding (2). CCK-A receptor antagonist did not affect IL-1-induced sleep suggesting that the somnogenic effects of IL-1 are independent of CCK-A receptors.

References:

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242.A

Cortistatin is a Selective Regulator of Deep Slow-wave Sleep

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Introduction: A novel neuropeptide, cortistatin-14 (CST-14) shares 11 of 14 residues with somatostatin yet has distinct physiological activities.

Methods: Twelve rats were implanted with a classical set of electrodes for sleep monitoring and a guide tube for i.c.v. injection. Total sleep deprivation and REM sleep deprivation were performed by the gentle handling method (24 hours) and the platform method (8 hours), respectively. Preprocortistatin mRNA level was analysed by northern blot analysis (cortex) and in situ hybridization.

Results: Here we show that intracerebroventricular administration of CST-14 produced a dose-dependent two fold increase (100 ng and 1 mg; p<0.05) in the amounts of SWS2 (6 hours of recordings) during rest period (P<0.001) as well as in rats that have already achieved their physiological demand of sleep (reverse cycle, P<0.01 ) at the expense of W (reverse cycle; P<0.01). Decrease in wakefulness under normal cycle was not significant (p=0.07). CST14 acts as a sleep maintenance factor (increase in the duration of SWS 2 episodes (reverse cycle,P<0.01; normal; p<0.01; 0-6 h) but not in the number of SWS2 episodes. Steady-state levels of cortistatin mRNA are induced four-fold upon total 24 hour sleep deprivation (gentle handling method), return to normal levels after eight hours of rebound sleep and are not influenced by the circadian clock, neither specific REM sleep deprivation (as compared to controls). This CST mRNA induction is restricted to a particular subset of neurons since preprocortistatin mRNA positive cells increase in number in the visual cortex, where they partly co-localize with c-fos, a marker of neuronal activity.

Conclusions: Because wakefulness is characterized by alpha rhythms generated at the posterior cortical level under the control of the cholinergic system and since CST has been shown to antagonize the effects of acetylcholine, our data together suggest that CST14 accumulates during wakefulness and interacts with the cholinergic system at the posterior cortex to promote deep slow wave sleep and maintain cortical synchronization.

243.A

Role of 5-HT1A Receptors in the Regulation of Sleep and Wakefulness. Study in 5-HT1A Knock-out Mice

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Introduction: Numerous studies have investigated the role of serotonergic 5-HT1A receptors in sleep-wakefulness regulation by using various ligands of these receptors. In addition, it is not clear whether this serotonergic receptor subtype is involved in the well-known effect of selective serotonin reuptake inhibitors (SSRI) on sleep. To date, mutant

SLEEP, Vol. 24, Abstract Supplement 2001
mice which do not express 5-HT1A receptors (1) provide a good opportunity to further examine these questions. For this purpose, we analyzed sleep-wakefulness cycles in these mutant (5-HT1A-/-) compared with their wild-type controls of the 129Sv strain (5-HT1A+/-), under baseline conditions and after treatment with various doses of the SSRI citalopram.

Methods: Mice of both groups were implanted under sodium pentobarbital anaesthesia (70-75 mg/kg i.p.) with the classical set of electrodes for polygraphic sleep monitoring (2). After 10 days of recovery and habituation to the recording conditions (12 hours light-dark cycle, light on at 7:00), sleep-wakefulness cycles were recorded: firstly under spontaneous conditions during 48 hours, and secondly during 8 hours after injection (performed at 10:00) of various doses of the SSRI citalopram. In addition, sleep was examined in wild-type mice after a combined treatment of the 5-HT1A antagonist WAY 100635 followed by citalopram.

Results: 1- A clear-cut circadian rhythm of sleep and wakefulness, with more sleep during the light period than during the dark one, was observed in both groups of mice. As compared to their wild-type counterparts, 5-HT1A-/- mice exhibited significantly larger amounts of Paradoxical Sleep (PS) during both the light and the dark period (respectively 68.9±3.2 and 40.4±2.2 min as compared to 51.6±3.2 and 28.5±1.6 min). Amounts of the other states of vigilance were not significantly different between the two groups.2- In wild-type mice, the SSRI citalopram (1-5 mg/kg i.p.) induced a dose-dependent inhibition of PS during 3 hours post-injection (-90% for the dose of 5 mg/kg). This response was totally abolished in 5-HT1A-/- mutant mice, as well as in in wild-type mice pre-treated with the 5-HT1A antagonist WAY 100635 (0.5 mg/kg i.p.).

Conclusions: The excess of PS amounts in mutant mice which do not express 5-HT1A receptors suggests that the latter receptors have a tonic inhibitory influence on PS-inducing mechanisms. These data confirm those obtained in cats and rats, which indicate that such 5-HT1A regulation occurs at pontine “PS-on” executive cholinergic systems (3). In addition, the lack of effect of citalopram on sleep in mice when 5-HT1A receptors are either not expressed (in 5-HT1A-/- mutants) or inactivated (after 5-HT1A receptors blockade) suggests that the classical action of SSRIs on sleep-wakefulness cycles is accounted for by an action of serotonin at exclusively 5-HT1A receptors. The latter result is different from those obtained in rats with other 5-HT1A antagonists (4). Further investigations should allow to indicate whether such discrepancy is due to the different species and/or ligands used.

References:

244.A
Laser Capture Microdissection of Single Cells for Quantification of 5-HT Receptor Subtypes in XII Motoneurons.
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Introduction: We have hypothesized that sleep state-dependent withdrawal of serotonin at upper airway dilator (UAWD) motoneurons contributes significantly to suppression of UAWD muscle activity in sleep and obstructive sleep disordered breathing events. Broad spectrum serotoninergic drugs reduce obstructive sleep-disordered breathing in a natural animal model of the disease, the English bulldog. Determining which of the 14 receptor subtypes for 5-HT are present on upper airway dilator motoneurons may provide an important avenue for pharmacotherapeutics for this prevalent and morbid disease.

Methods: To determine the 5-HT receptor subtypes we have designed 3’ end primer pairs (100-150 bp) for all excitatory 5-HT receptor subtypes: 2A, 2C, 4, 5A, 5B, 6 and 7. To better assess quality of single cell samples, 3’ end primer pairs were also designed for choline acetyltransferase, a-tubulin, b-actin, neuron specific enolase and glial fibrillary protein. All primer sets were tested and were successful in detecting mRNA in 1mm3 samples of medulla or hippocampus. Rats (n=5) were anesthetized, perfused with saline, with brains immediately frozen and sectioned (10mm) onto sterile slides. Slides were processed also under sterile conditions using hemotoxolyn and eosin staining supplemented with RNase inhibitor. Laser capture was performed on single hypoglossal motoneuronal cell bodies within the rostral (0.8 AP CS) dorsolateral hypoglossal nucleus. For individual cells, RNA was purified, cDNA was made with selective 3’ primers for two of the mRNA’s and then run with standard PCR.

Results: On these single cell samples, PCR has shown the strongest signal for 5-HT2C, but also excellent signals for 5-HT2A,4, and 7 in samples with a strong signal for tubulin. In contrast, single cell samples have not detected 5-HT3A, 5B or 6 mRNA. The primers and molecular beacon probes have been designed for use with Taqman real time PCR to allow relative quantitation of receptor subtypes under resting conditions and conditions of respiratory challenges.

Conclusions: It is hoped that this work will reveal the intricacies of 5-HT receptor subtypes involved in post-synaptic excitation of UAWD motoneurons under normal conditions and in sleep apnea syndrome.

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245.A
Sex Differences in Adaptation to Environmental Change Indexed by EEG Coherence in the Rat
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Introduction: Recent studies have highlighted the importance of quantitative EEG analysis in identifying sleep abnormalities in patients presenting with major depressive disorder (MDD) 1. The principal measurement in these studies was EEG coherence, based on cross-spectral analysis of all-night EEG power within and between the two hemispheres. Patients with MDD were found to have substantially lower interhemispheric and intrahemispheric coherence in their sleep EEG than normal controls 1. This organizational dysregulation appeared as greater asymmetry between the two hemispheres and less coherence between beta and delta frequency bands in each hemisphere in the EEG of MDD patients. Importantly, sex differences were also noted: coherence measures were lowest in depressed women and highest in control men. Since MDD is marked by an abnormal stress response, we have hypothesized that EEG coherence may be correlated with stress adaptation. To test this hypothesis, EEG coherence was measured in their sleep EEG analysis of all-night EEG power within and between the two hemispheres.

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References:
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A147
ing, a second rat of the same strain, age and sex was introduced into the recording environment. EEG/EMG signals were then recorded for 5 weeks before the second animal was removed and recording continued for a further 5 weeks. EEG analysis, similar to that applied to signals recorded from human subjects in our laboratory (1), was used to derive interhemispheric and intrahemispheric coherence measures at all periodicities and frequencies.

Results: Significant variation was noted only at a periodicity of 13-15 min in the alpha (9 - 12 Hz) frequency band for mean interhemispheric coherence (alpha-left-right, ALR), and at the same periodicity between the sigma (12 - 16 Hz) and delta (1- 4 Hz) frequency bands for mean intrahemispheric coherence (sigma-delta left, SDL). In both males and females, ALR increased while rats were paired (0.80) and then decreased during re-isolation to levels recorded during the 3 week baseline period (0.65). In males, SDL decreased during group housing (0.45) and then returned to baseline levels (0.50) after re-isolation. In contrast, the change in SDL in females was significantly different: a slight increase was recorded during group housing (0.45), followed by a marked decline immediately on isolation (0.30) and then a gradual return to baseline levels (0.40) over the following 3-4 weeks.

Conclusions: 1. EEG coherence is a reproducible measure that can be recorded from rats; it may therefore provide an index for examining ultradian rhythm dysregulation in this species. 2. Chronic environmental change, in this study using group housing followed by re-isolation, is sufficient to affect coherence. 3. The reduction in SDL in female rats following re-isolation was the most significant effect noted in these experiments, suggesting that female rats may be particularly susceptible to isolation after group housing, and that SDL is a good indicator of the resulting effect of this stressor on EEG coherence.

References:

Research supported by an MSTP award to CMS.

246.A

Effects of Diazepam on Sleep in GABA_A Receptor Alpha-1 and Alpha-3 Mutated Mice

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Introduction: Benzodiazepines (BZ) are widely used as hypnotics and tranquilizers. They potentiate GABA neurotransmission, by binding to a modulatory site on the α1, α2, α3 and α5 (α=alpha) GABAA receptors. As these receptor subtypes are differentially distributed in the brain, distinct subtypes may mediate specific aspects of the wide pharmacological BZ profile. Recently, knock-in point-mutated mice have been developed, in which the α1 or α3 receptors are rendered diazepam-insensitive (1,2). In the α1-mutated mice, the sedative and amnestic properties of diazepam (DZ) could be attributed to the α1 GABAA receptor (1). We studied the effects of DZ on sleep and locomotion in α1 mutated mice and wild-type controls. Alpha3 GABAA receptors are expressed in the reticular thalamic nucleus, which is involved in the oscillatory processes related to the sleep EEG. We therefore investigated the role of α3 receptors in mediating the DZ effects on sleep.

Methods: Sleep was recorded for 12 h after DZ (3 mg/kg i.p.) or vehicle were administered (light onset) in male mice homozygous for a point mutation of the α1 subunit (α1MUT) or of the α3 subunit (α3MUT) and their respective homozygous wild-type controls (α1WT and α3WT; n=7-8 per genotype). Vigilance states and EEG spectra were analyzed as previously (3). Locomotion was recorded by infra-red sensors for 12 h after DZ (3 mg/kg i.p.) or vehicle administration (dark onset) in α1MUT and α1WT (n=11-12 per genotype).

Results: DZ decreased locomotion in α1WT (p<0.05), but not in α1MUT. Sleep latency and the amount of sleep were not affected but REMS was initially reduced in both genotypes (p<0.05). SWA (slow-wave activity in NREMS) was suppressed to a larger extent by DZ in α1MUT than in α1WT (Figure 1). The SWA suppression in α3MUT and α3WT showed regional differences. While the DZ-induced reduction of SWA in the occipital derivation was similar in both genotypes, in the frontal derivation it remained low over 12 h in α3WT (p<0.05), whereas the decrease lasted for only 6 h in the α3MUT (p<0.05).

Figure 1

Conclusions: We observed a dissociation between the DZ-induced sedation, which is mediated by the α1 GABAA receptor, and the effects on sleep which are partially mediated by the α3 receptor, demonstrating that these effects are differentially regulated. The data suggest a complex interaction between GABAA receptor subtypes in the modulation of sleep by DZ.

References:

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247.A

Effects Of Imipramine Treatment On Rat Model Of Human Endogenous Depression

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Introduction: Several findings suggest the hypothesis that REM sleep deprivation of neonatal rats produce depressive-like changes in behavior when the rats matured and that rats neonatally treated with clomipramine (CLI, CLI rat) are a valid model of human endogenous depression. As reviewed previously (1), compared with control rats treated neonatally with saline (SAL, SAL rat), CLI rats express several different behavioral, REM sleep, and physiological abnormalities found in human
endogenous depression (ED). Studies of neonates treated with other REM suppressant drugs such as desipramine, zimeldine, nomifensin, clonidine, and instrumental REM sleep deprivation demonstrate similar results (2).

Methods: Eighty neonatal Long Even hooded male rats, born in our lab, were cross fostered the day after birth. Neonates were divided as CLI (n=60) and SAL (n=20) treated groups. CLI rats received 20 mg/kg, sc twice daily and SAL received an equivalent volume SAL. Rats were returned to the mother and then weaned at 4 weeks of age and housed 2-4/cage under standard conditions. At 4 months of age baseline sexual behavioral testing was conducted twice. Thereafter rats received 2 weeks of daily oral anti depressive treatment consisting of either (1) CLI-IMP (CLI rats treated with imipramine, 15mg/kg, oral); (2) CLI-WAT (CLI treated with equi-volume water); (3) CLI-VAL (CLI rats treated with Valium) and (4) SAL-WAT (SAL rats treated with equi-volume water). Two postnatal sexual behavior tests were conducted at (1) first day post treatments and (2) one month post treatments. Mean sexual indices (MSIs) were calculated according to formulas developed previously (3).

Figure 1

Results: Sexual tests showed that (1) prior anti depressive treatment and sexual performance was significantly impaired in CLI rats. MSIs of three groups of CLI rats, assigned to IMP, water and VAL later treatments were reduced to 36.3%, 24.6% and 43.7% as compared to 100% of SAL rats (Fig.1, p values were not indicated in Fig 1); (2) After two weeks treatment, CLI-IMP group was the only outstanding group that showed a significant increase in sexual performance indicated by 147% increase of MSI (from 36.3% to 89.8%, p=0.041). One month later, sexual activities in all three CLI groups (including CLI-IMP, CLI-water and CLI VAL) of rats were reduced as compared to their prior test; except SAL rats which were higher. However, the MSI of CLI-IMP group was still higher than pretreatment level. (3) Valium, a non specific psychiatric drug did not affect sexual performance of CLI rats.

Conclusions: We conclude that imipramine treatment alleviates depressive symptoms in the rat model of human ED and that the treatment is a specific effect of anti depressive role. The results of imipramine treatment in depressed rats are consistent with results of human anti depressants treatment that shows fewer recurrences of depression with low dose maintenance with an anti depressant. This further supports the hypothesis that CLI rats are a valid model of human ED.

References:
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tal REM sleep deprivation on adult behavior: Depression and mania? See the same issue.
(3) Feng P, Ma Y and Vogel GW. The Critical window of brain development from susceptible to immune: Effects of clomipramine neonatal treatment on sexual behavior. Submitted to Brain Res.

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248.A

Protein Expression in the Rat Cerebral Cortex in Sleeping and Sleep Deprived Rats

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Introduction: A recent systematic screening of gene expression in the rat brain after 3-8 h of spontaneous sleep, wakefulness and sleep deprivation has identified several genes whose mRNA levels change as a function of behavioral state and whose differential expression may affect basic cellular functions (Mol Brain Res, 1998; 56: 293-305; Brain Res, in press). Changes in mRNA levels are usually, but not always, predictive of changes in protein levels. Moreover, protein expression can also be modulated through post-translational changes. Given the influence of all these factors, understanding the molecular changes occurring in the brain across behavioral states requires analysis of gene expression at transcriptional, translational, and post-translational levels. Protein expression has traditionally been analyzed with SDS-polyacrylamide gel electrophoresis using one dimension to separate proteins based on their molecular weight. However, the analysis of differential protein expression in brain tissue requires screening for hundreds or thousands of proteins, many of which have similar molecular weights. Recently, two-dimensional (2D) gel electrophoresis has made possible a more systematic analysis of differences in protein expression. This technique first separates proteins by isoelectric point and then by molecular weight. In this study, in order to identify changes in protein expression across behavioral states, 2D gel electrophoresis was performed on samples of cerebral cortex from sleeping and sleep-deprived rats.

Methods: Wistar WKY male adult rats (300-350 g) implanted for chronic EEG and EMG recording were sacrificed after 8 hours of either spontaneous sleep (n=4; total sleep >75% of total recording time) or total sleep deprivation by gentle handling and exposure to novel objects (n=4). For each rat, proteins were extracted from different cortical fractions including cytosolic, nuclear, microsomal, synaptosomal and mitochondrial fractions. Each fraction was quantitated for protein concentration, analyzed using 2D electrophoresis, and compared for differences in protein expression (i.e. changes in signal strength in a silver stained 2D gel) between each sleeping rat and its paired sleep-deprived rat. As a positive control, western blot analysis of specific proteins (e.g. Arc), which are already known to be upregulated during sleep deprivation relative to sleep, was performed.

Results: In agreement with previous results, Arc protein expression was found to be higher in the cerebral cortex of sleep deprived rats relative to sleeping rats. For each cortical fraction, 2D gel electrophoresis was able to resolve 100 to 200 different spots. The number and distribution of the spots for each fraction was consistent across different animals but varied from one fraction to another. For each fraction, several spots (10-20) were significantly different between the sleeping rat and its paired sleep-deprived rat. The isolation and protein sequence analysis of these spots is in progress.

Conclusions: A 2D gel electrophoresis protocol has been optimized to isolate hundreds of different proteins from cytosolic, nuclear, microsoma-
mal, synaptosomal, and mitochondrial fractions of the rat cerebral cortex. Several of these proteins appear to be differentially expressed between sleeping and sleep deprived rats.

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249.A
Effects of Glutamate on the Expression of Tumor Necrosis Factor a (TNF a) in Cultures of Hypothalamic Cells
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Introduction: TNF a has been shown to be an important physiological regulator of sleep. How the biosynthesis and release of TNF a is controlled to influence sleep under normal physiological circumstances are unknown. To begin to develop insights into this acute regulation of TNF a in the brain we have performed experiments on cultured cells from fetal rat hypothalamus. The use of cultured cells eliminates potential non-brain derived sources of TNF a. Because of the importance of the hypothalamus in the humoral regulation of sleep, we have performed these studies on cultures from hypothalamic tissue.

Methods: Hypothalamic cells were isolated from day-19 fetal rats according to previously published methods. Cells were cultured into 6-well poly-ic-fic-lysine-coated plastic culture dishes at an approximate density of one hypothalamic cell/well. Cells were grown in Dulbecco’s modified Eagle’s media (DMEM) supplemented with 5% fetal calf serum for 2 days and then in DMEM with serum replacement (insulin, transferrin, selenium). After 9 to 13 days in culture the cells were washed with DMEM and then challenged in DMEM with various conditions and lengths of time. Cell content of TNF a and the release of TNF a into the media were determined by a commercial ELISA kit.

Results: Both cell content and release of TNF a increased by at least 2-fold in 3 out of 3 separate isolations after exposure of cells to 1 mM glutamate for 2 hrs. The effect of glutamate was both time and dose dependent. At 2 hrs of treatment cell content was increased with 100 nM (14.5 pg TNF a/well) and 1 mM glutamate (49.8 pg/well) and media content was increased with 1 mM glutamate (9.5 pg/well). With 1 mM glutamate, cell content was initially suppressed at 30 min and then increased at 60, 120, and 240 min. Detectable levels of TNF a in the media were observed after 120 and 240 min.

Conclusions: These results support the hypothesis that TNF a biosynthesis and release is regulated in isolated brain cells in an acute manner by glutamate. Future work will focus on the role of other neurotransmitters and neuromodulators known to be important in sleep on the regulation of TNF a.

References:
(1) Takahashi S, Krueger JM. Inhibition of tumor necrosis factor prevents warming-induced sleep responses in rabbits. Am J Physiol 1997; 41;R1325-R1329.

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250.A
Preoptic Area Warming Suppresses The Discharge Of Neurons In The Perifornical/Lateral Hypothalamus.

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Introduction: Thermoregulatory neurons of the preoptic area (POA) are hypothesized to regulate sleep. Activation of the POA thermosensitive neurons is thought to induce sleep by the inhibition of various arousal regulating structures including the basal forebrain, posterior hypothalamus and dorsal raphe (1). Among the target sites, POA projections innervate the perifornical area of the lateral hypothalamus which is known to contain orexinergic neurons implicated in arousal (2). The perifornical area is reported to contain wake - related neurons (3). We hypothesized that POAH warming would inhibit the wake - related neurons of the perifornical lateral hypothalamus (PF/LH) including presumed orexin - containing neurons.

Methods: Two adult male Sprague- Dawley rats were chronically implanted with EEG and EMG electrodes, a mechanical microdrive with microwires aimed at the PF/LH. A water perfused thermode was placed into the medial POA. Seven days after surgery, extracellular activity of PF/LH was recorded across 2-3 spontaneous sleep-wake cycles. After the baseline recording, the POA was warmed to 1.72 ± 0.26 °C (0.97 - 2.7 °C) above baseline for two to three minutes while rats were kept awake. Recorded cells were classified, based on their REM/wake discharge ratio, into 2 types: wake-REM active (REM/wake ratio >0.2 - <0.5), and wake - related, REM - off (REM/wake ratio < 0.2).

Results: Of a total of 18 units, 9 were wake-REM active and 9 were wake - related, REM-off type. POA warming during waking suppressed the discharge rate of both types of neurons (mean decrease = -24.94 ± 8.19 % for 1 °C increase in temperature). The percentage decreases in discharge rate from baseline during POA warming were -14.39 ± 6.78 % for wake-REM type and -35.48 ± 13.29 % for REM-off type.

Conclusions: POA warming caused a reduction in the discharge rate of wake - active neurons of the perifornical area. This supports the hypothesis that POA activation by warming induces sleep by inhibiting arousal regulating regions including the perifornical area.

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(3) Alam MN, Xi X, McGinty D, Szymusiak R: Sleep-waking discharge patterns of neurons in the perifornical area of the rat lateral hypothalamus; Sleep 2000; 23, A10.

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SLEEP, Vol. 24, Abstract Supplement 2001
Changes in Gene Expression During the Sleep-wake Cycle after Lesions of the Serotonergic System.

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Introduction: Several genes, including immediate-early genes (IEGs) and genes associated with neural plasticity are expressed at higher levels during waking than during sleep. It has been hypothesized that systems with diffuse projections that fire at higher levels during waking than during sleep, such as the noradrenergic locus coeruleus (LC) and the serotonergic dorsal raphe (NDR) may coordinate such changes in gene expression. Recently it has been shown that the IEGs c-fos and NGFIA as well as molecular markers of neural plasticity such as P-CREB, BDNF, BiP and Arc are dramatically reduced after lesions of the LC. The present study was designed to evaluate whether the serotonergic system also modulates sleep-waking related changes in the gene expression.

Methods: Twelve male WKY rats, weighing 320g, were pre-treated with desipramine (25mg/kg), prior to unilateral injections of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into the right Medial Forebrain Bundle (MFB). Following surgery, rats were individually housed under a 12:12 light dark cycle with food and water available ad lib. On post-injection Day 14, rats were sleep deprived for 3 hours by gentle handling. The extent of the serotonergic lesion sections was evaluated using [3H]-citalopram, a selective inhibitor of the serotonin transporter. Fos (n=8), NGFIA (n=8), BDNF (n=8), Arc (n=8), Bip (n=6) and Nur77 (n=6) mRNA levels were evaluated using insitu hibridization.

Results: Rats recovered rapidly following injection of 5,7-DHT into the MFB. Sleep patterns were within the normal range of sleep values previously reported for rats within 3 days of the lesion and remained normal throughout the experiment. Mean [3H]citalopram binding expressed as percentage of the contralateral cerebral cortex ranged from -66% to -93% in animals judged to have had a successful lesion (n=8). Unilateral lesions of ascending serotonergic fibers did not alter the expression of either Fos or NGFIA mRNA in the ipsilateral cerebral cortex following three hours of TSD. Nor were we able to detect changes BDNF, Arc, Bip or Nur77 mRNA. In two animals which did not receive pre-treatment with desipramine, we were able to lesion both the 5-HT and NE fibers. In these animals, Fos and NGFIA were significantly reduced in the ipsilateral cortex.

Conclusions: It has been hypothesized that the ascending activating systems, including noradrenergic neurons in the LC, serotonergic neurons in the DR, dopaminergic neurons in the substantia nigra and histaminergic neurons in the tuberomamillary hypothalamus, mediate the diffuse tonic and phasic changes in both neuronal responses and of gene expression across the sleep-wake cycle. Support for this relationship has previously been obtained for the noradrenergic system. In contrast, depleting serotonin did not alter gene expression. Thus, the present data suggest that serotonergic innervation does not exert as strong an influence on gene expression in the cortex as does the noradrenergic system.

References:
(1) Tononi, Cirelli, Pompeiano, 1995, Arch. Italien. de Biologie., 134:21-37

Research supported by Neurosciences Research Foundation

Hypnotic Effects of Triazolam in the Medial Preoptic area are not Related to Changes in Brain Temperature.

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Introduction: Electrophysiological recordings have identified neurons in the preoptic area of the anterior hypothalamus (POAH) that are responsive to both sleep-wake and temperature changes (1). Experimental warming of the POAH enhances delta activity within NREM and microinjections of GABA-A-BZD agonists in this area have potent hypnotic properties (1,2). In this study, we investigated whether the hypnotic effects of triazolam (TR) in the mPOA were influenced by hypothalamic temperature (THy).

Methods: Seven male Sprague-Dawley rats (250-300 grams) were implanted with electrodes for electrocorticographic and electromyographic recordings. THy was measured using a midline recording thermistor (AP -.5, M-L ± 0.0, D-V -.7) and brain tissue was heated using bilateral (AP -.5, M-L ± 1.0, D-V -.7) thermodes. Each rat completed four experimental conditions (1)vehicle/baseline (2) vehicle/heat (3) triazolam/baseline (4) triazolam/heat, in random order. Microinjections of vehicle and TR (.5 ug) in a volume of .5 ul were given through the midline cannula before inserting the thermodes. During baseline trials, THy was passively recorded and during heating trials, the bilateral thermodes were heated, as needed, to hold THy constant at the initial temperature following injections. The thermodes were operated via feedback to a PC using a program developed by one of the investigators (BB). Sleep stages were visually scored in 30 second epochs.

Results: Analysis of variance (ANOVA) revealed that during TR/base-line and TR/heat trials, sleep onset latency, wake after sleep onset and wake time decreased, while NREM and total sleep times increased compared to vehicle/baseline and vehicle/heat (Table 1). There were no significant main effects or interactions between experimental conditions in mean temperature change from baseline, as measured in 15-minute epochs across the 2-hour recording period (Table 2). Similarly, a 3-way ANOVA showed no interactions between drug (triazolam, vehicle) x temperature treatment condition (baseline, heat) x time (15 minute epochs) for NREM sleep.

Table 1
Sleep/wake values (minutes) for 2- hour recordings.

<table>
<thead>
<tr>
<th></th>
<th>Wake</th>
<th>SOL</th>
<th>NREM</th>
<th>WASO</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
</tr>
<tr>
<td>Basal</td>
<td>47.00</td>
<td>19.78</td>
<td>72.5</td>
<td>29.57</td>
<td>73.00</td>
</tr>
<tr>
<td></td>
<td>(1.43)</td>
<td>(2.13)</td>
<td>(1.40)</td>
<td>(1.95)</td>
<td>(1.43)</td>
</tr>
<tr>
<td>TR(2)</td>
<td>2.76*</td>
<td>9.92*</td>
<td>40.57*</td>
<td>18.57</td>
<td>92.00</td>
</tr>
<tr>
<td></td>
<td>(3.29)</td>
<td>(1.55)</td>
<td>(4.25)</td>
<td>(3.08)</td>
<td>(4.04)</td>
</tr>
<tr>
<td>Heat</td>
<td>5(3)</td>
<td>47.50</td>
<td>7.17</td>
<td>71.5</td>
<td>31.50</td>
</tr>
<tr>
<td></td>
<td>(2.76)</td>
<td>(1.70)</td>
<td>(3.25)</td>
<td>(2.69)</td>
<td>(2.76)</td>
</tr>
<tr>
<td>TR(4)</td>
<td>29.42*</td>
<td>9.25*</td>
<td>89.42*</td>
<td>21.17</td>
<td>90.58*</td>
</tr>
<tr>
<td></td>
<td>(3.56)</td>
<td>(1.23)</td>
<td>(3.67)</td>
<td>(3.48)</td>
<td>(3.56)</td>
</tr>
</tbody>
</table>

Repeated-measures ANOVA for dependent variables with Scheffe post-hoc tests. p < .001; p <.01; p <.05. For example, 1.3 indicates that a cell is significantly different at p <.001 compared to vehicle (1) and vehicle (3) conditions. Means (S.E.).
Table 2

<table>
<thead>
<tr>
<th>Temperature (change from baseline) \times 15 minute epochs</th>
<th>16-30 min.</th>
<th>31-45</th>
<th>46-60</th>
<th>61-75</th>
<th>76-90</th>
<th>91-105</th>
<th>106-120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Btn</td>
<td>V</td>
<td>10.0 (0.6)</td>
<td>0.9 (0.9)</td>
<td>0.8 (1.1)</td>
<td>1.3 (1.2)</td>
<td>1.0 (1.3)</td>
<td>0.3 (1.6)</td>
</tr>
<tr>
<td>TR</td>
<td>19 (1.1)</td>
<td>38 (2.1)</td>
<td>37 (2.9)</td>
<td>36 (3.1)</td>
<td>32 (3.5)</td>
<td>35 (3.7)</td>
<td>28 (3.7)</td>
</tr>
<tr>
<td>Heat</td>
<td>V</td>
<td>15 (0.9)</td>
<td>12 (0.9)</td>
<td>13 (1.0)</td>
<td>13 (1.0)</td>
<td>15 (1.1)</td>
<td>20 (1.2)</td>
</tr>
<tr>
<td>TR</td>
<td>0.9 (0.9)</td>
<td>17 (0.9)</td>
<td>21 (1.1)</td>
<td>21 (1.1)</td>
<td>22 (1.2)</td>
<td>29 (1.6)</td>
<td>31 (1.9)</td>
</tr>
</tbody>
</table>

3-way ANOVA for repeated-measures. The three factors include (1) drug condition (vehicle, triazolam) (2) temperature condition (baseline, heat) (3) time (seven, 15 minute epochs). Temperature change from baseline was calculated as the difference between each epoch value and the first (1-15 minutes) epoch value. Group means (S.E.). There were no significant main effects or interactions.

Conclusions: These results indicate that microinjections of TR into the mPOA enhance sleep, but do not alter brain temperature compared to vehicle injections. Triazolam microinjections into the mPOA were previously shown to promote sleep with no effect on peripheral (2) or brain (3) temperature. A salient feature was that THy did not significantly change across 15 minute epochs of the 2-hour recordings following TR or vehicle injections (Table 2). Therefore, the hypnotic effects of TR were independent of changes in THy. In contrast to our original hypothesis, it was not necessary to activate the heating thermodes in the “heat” conditions, because endogenous THy remained at or above baseline throughout the recordings in all experimental conditions. In summary, these results indicate that the hypnotic effects of triazolam in the mPOA are independent of changes in THy.

References:

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254.A

Contributions of Neuronal and Glial PrP to the Sleep/Wake Cycle
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Introduction: Prion (PrP) diseases are neurodegenerative disorders of infectious, inherited, or sporadic origin in humans and animals. Fatal familial insomnia (FFI) is one of the genetic PrP diseases in humans. In FFI there is a significant reduction of sleep, loss of neurons and astrogliosis. It is still unclear whether these changes are consequence of loss of normal PrP protein function or the accumulation of abnormal prion protein. Because of the potential involvement of prion in sleep processes (1), we investigated the physiological role of glial (2) and neuronal (3) PrP gene in sleep/wake cycle.

Methods: We characterized the sleep patterns in GFAP-HPrPKO (expressing glial PrP) and NSE-HPrPKO (expressing neuronal PrP) transgenic mice whose PrP gene was knocked out (KO) and replaced with the hamster PrP gene by inoculation with a construct containing either, the glial fibrillary acidic protein (GFAP), or neuron-specific enolase (NSE) promoter. Also we studied PrPKO mice whose PrP gene had been KO and not replaced, and C57BL/10SnJ mice (wild type) as a control group. Animals were implanted with a set of electrodes for sleep recording. One week after surgery they were habituated to the recording conditions for 72h and recorded for 24h. The electroencephalogram was scored and wakefulness (W), slow-wave sleep (SWS) and rapid eye movement (REM) sleep were determined.

Results: PrPKO and C57BL/10SnJ control mice showed no significant differences in the frequency and total amount of W, SWS, or REM sleep. However, in contrast to C57BL/10SnJ, PrPKO mice showed a different REM sleep distribution and a significantly greater percentage of REM sleep during the second half of the dark period. The overexpression of PrP in neurons (NSE-HPrPKO) did not restore the changes observed in KO mice. Compared to C57BL/10SnJ mice, NSE-HPrPKO mice showed a significant decrease in the amount of W and a significant increase in SWS and REM sleep prior to the onset of the dark cycle followed by a significant increase in the number of and shifts between W and SWS events. On the other hand, GFAP-HPrPKO mice increased the amount of REM sleep only during the shift from the light to dark cycle, and also, a significant increase in the number of and shifts between SWS and REM sleep events during the light period.

Conclusions: These data suggest that the PrP expressed, in both glial and neuronal cells, may be involved in the modulation of the sleep/wake cycle.

References:

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254.A

Effects of a Non-selective Muscarinic Receptor Antagonist, Scopolamine, on REM Sleep Quantified EEG Activity in the Rat
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Introduction: Quantified EEG analysis during REM sleep in patients with Alzheimer’s Disease (AD) show a shift toward slow frequencies and this effect is particularly apparent for theta activity over the temporal cortex (1). Cholinergic deficits constitute prominent features of AD and this has led to animal models, including the acute effects of scopolamine, a non-selective muscarinic receptor antagonist, on cognitive performance in the rat. The aim of the present research was to evaluate the acute effects of scopolamine on REM sleep quantified EEG measures in the rat. Particular attention was paid to Rho activity (10-20 Hz), a cortical EEG-frequency thought to be selectively associated to REM sleep in the rat (2).

Methods: Twenty-three Long-Evans rats aged three to four months were implanted for sleep recording under pentobarbital anesthesia; EEG elec-
trodes were placed over frontal, centro-medial, and centro-lateral cortices; a reference electrode was placed over the cerebellum. After at least 7 days of recovery, rats were distributed in either one of two treatment groups: scopolamine (0.1 mg/kg s.c.; nine rats) or vehicle (0.5 c.c. NaCl 0.9%; 14 rats). Rats were injected at 06h00, i.e., two hours after the onset of the light period, and sleep recording was started immediately, for four hours. Sleep stages were determined visually in 10 sec epochs. Fifteen four-seCONDS epochs (60 sec) of artefact-free EEG were selected from epochs of REM sleep and submitted to Fast Fourier Transform with a cosine window smoothing and a resolution of 0.25 Hz. Power amplitude was calculated and six frequency bands were extracted: Delta (0.75-3.75), Theta-1 (4-6.75), Theta-2 (7-9.75), Sigma (10-13.75), Beta (14-19.75), and Rho (20-30). Relative activities were computed ([band power/total power] * 100) and results were compared using t-test for independent samples.

Results: Scopolamine generally increased EEG activity in all frequency bands at the three electrode sites with the exception of Rho activity which was decreased. The most salient results are presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Effect of scopolamine on quantified EEG (mean ± s.e.m.)</th>
<th>Saline</th>
<th>Scopolamine</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Delta</td>
<td>17.2 ± 0.3</td>
<td>18.7 ± 0.4</td>
<td>.01</td>
</tr>
<tr>
<td>Frontal Beta</td>
<td>14.9 ± 0.1</td>
<td>16.5 ± 0.7</td>
<td>.03</td>
</tr>
<tr>
<td>Frontal Rho</td>
<td>21.6 ± 0.7</td>
<td>17.1 ± 0.8</td>
<td>.0006</td>
</tr>
<tr>
<td>Centro-lateral Sigma</td>
<td>11.3 ± 0.4</td>
<td>13.0 ± 0.8</td>
<td>.06</td>
</tr>
<tr>
<td>Centro-lateral Rho</td>
<td>23.7 ± 1.0</td>
<td>19.5 ± 1.1</td>
<td>.02</td>
</tr>
<tr>
<td>Centro-medial Sigma</td>
<td>11.6 ± 0.1</td>
<td>12.9 ± 0.6</td>
<td>.03</td>
</tr>
<tr>
<td>Centro-medial Beta</td>
<td>12.9 ± 0.2</td>
<td>14.9 ± 0.4</td>
<td>.0005</td>
</tr>
</tbody>
</table>

*p t-test for independent samples

Conclusions: The present observation that scopolamine increases EEG activity replicates previous reports on conventional frequency bands. The fact that Rho activity was decreased may point to particular neuro-physiological networks involved in the rat model of AD.

References:


Supported by the “Fonds de la recherche en santé du Québec” and the Natural Sciences and Engineering Research Council of Canada.

255.A

Hypocretin (Orexin) Stimulates [35S] GTPγS Binding in Hcrtr 2 Transfected Cell Lines and Brain Homogenate

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Introduction: Although the genomic sequence of the two G-protein coupled hypocretin (orexin) receptors and the localization of mRNA are reported [1, 2], no functional data on binding sites using brain tissue is available. This is mainly due to the difficulties of conducting binding experiments using radiolabeled hypocretin ligands; hypocretins are relatively unstable in tissue homogenates, and hypocretins stick non-specifically to cell membranes, making it impossible to carry out binding studies on brain homogenates. Although receptor binding using a receptor-transfected cell line and iodinated hypocretins can be done, there are several limitations for these experiments; cell line binding is mainly used for screening of ligand affinity for transfected hypocretin receptors (either wild type or mutant) and cannot assess the binding affinity in selected brain areas to address functional and anatomical roles of the hypocretin system. In the current study, we therefore assessed whether hypocretin ligands stimulate the [35S] GTPγS binding site both in hypocretin receptor-transfected cells and in brain tissue homogenates in order to establish a functional binding assay for hypocretin receptors.

Methods: Control CHO cell lines and stably transfected CHO cell lines expressing human Hcrtr-2 and rat brain membranes were used for [35S] GTPγS binding assays. Cell pellets and dissected rat brain were suspended in cold homogenization buffer (20 mM of Heps/Na Heps, pH 7.4, 10 mM EDTA, protease inhibitor) and lysed using a Polytron P10 disrupter. The membranes were centrifuged at 40,000 g for 15 min at 4°C and the supernatant was removed. The wash procedure was repeated, and aliquots of membranes were resuspended in buffer (20 mM of Heps/Na Heps, pH 7.4, 0.1 mM EDTA) and frozen in aliquots at -70°C. Membranes were thawed and diluted with buffer (20 mM of Heps/Na Heps, pH 7.4, 100 mM NaCl, 10 mM MgCl2, 1mM of GDP). Membrane protein (4-20mg) was incubated with 0.1 nM [35S] GTPγS and (human or rat) hypocretin-1 (10-7-10-5 M) with or without selective hypocretin antagonists for 60 min at 25°C. Reactions were terminated by vacuum filtration over GF/B filters pretreated with 0.5 % BSA, and incorporated radioactivity was determined using liquid scintillation counting.

Results: We found that hypocretins dose-dependently stimulate [35S] GTPγS binding in human Hcrtr 2 transfected cell lines (230% at 10-5M of hypocretin 1 of the baseline without GTP). In the control CHO cell, hypocretin 2 has little effect, and [35S] GTPγS binding was increased to 120% only at 10-5M of hypocretin 1. The specific binding was dose-dependently blocked by a selective hypocretin antagonist (affinity: 1.2 nM for Hcrtr 2). In rat brain homogenate, we also obtained significant increased [35S] GTPγS binding by stimulation of hypocretin 1 (10-6 M) in the pons, midbrain and hypothalamus, but the increase was slight or little in the forebrain or cerebellum.

Conclusions: We have established a [35S] GTPγS binding assay for hypocretins in both cell lines and brain homogenate. The [35S] GTPγS binding method is a functional assay for the receptor/effector, and the binding is not influenced by high, non-specific binding of hypocretin ligands; the increase in the binding is proportional to the receptor stimulation, regardless of whether hypocretin sticks non-specifically to the cell membrane or filter. Furthermore, the assay is bi-directional, and could assess either the facilitation or the inhibition of hypocretin-stimulated signal transduction by the compounds screened. This method is thus useful for screening for compounds that interact with the hypocretin receptor/effector, as well as functional mapping of hypocretin receptors. The autoradiography of [35S] GTPγS binding is now in progress to further extend this line of experiments.

References:


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Differential Effects of Hypocretin-1, Melanin-Concentrating Hormone and Cocaine- and Amphetamine-Regulated Transcript on Sleep in Rats


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Introduction: The discovery that orexigenic peptides in the hypocretin (orexin) family play a critical role in narcolepsy has bridged the fields of energy metabolism and arousal state regulation. Disruption of the hypocretin (Hcrt) ligand-receptor system produces narcolepsy, and hypocretinergic cell bodies are located exclusively in the lateral hypothalamic/perifornical area (1). A distinct population of neurons that express melanin-concentrating hormone (MCH) is interspersed among these Hcrt neurons. MCH neurons project to many areas that are implicated in arousal state control, including the midbrain tegmentum, parabrachial nucleus, cortex, and thalamus (2). Cocaine- and amphetamine-regulated transcript (CART) colocalizes with MCH, and suppresses feeding when injected intracerebroventricularly (3). By contrast, MCH stimulates food intake. The aim of this study was to compare the effects of the feeding-related peptides Hcrt-1, MCH, and CART on arousal state in the rat.

Methods: Sixteen male Wistar rats were surgically prepared for chronic EEG, EMG and body temperature recording and lateral ventricle cannulation. After at least two weeks surgical recovery and recording cable adaptation, the rats were administered intracerebroventricular microinjections once per week in an unbalanced crossover design. Experimental compounds, supplied by Neurocrine Inc. and American Peptide Co., were Hcrt-1 (8 nM, n=13), MCH (24 nM, n=9), and CART (10 nM, n=7). The vehicle control was artificial cerebrospinal fluid (aCSF; n=16). Compounds were prepared and delivered under sterile conditions in a volume of 10 microliters, five hours after lights-on. Arousal states were monitored for 29 h before and 31 h after treatment using SCORE™. Sleep latency was defined as the minutes post-treatment that passed until one minute of sleep occurred. Minutes of NREM and REM lost were calculated as the maximum accumulated negative change from baseline post-treatment. Minutes of NREM and REM recovered were calculated as the maximum accumulated positive change from baseline post-treatment. Differences between treatments were assessed by one-way ANOVA.

Results: Table 1 shows Hcrt-1 induced more wakefulness than MCH and CART. Sleep latency was longer and more NREM was lost after administration of Hcrt-1 than the other peptides. MCH and CART did not reduce NREM more than the vehicle controls. However, MCH suppressed REM well below controls, similar to the effect of Hcrt-1 on REM. During recovery after MCH, REM remained below baseline, whereas after Hcrt-1, REM was gained beyond the amount lost and above baseline levels. CART was similar to MCH on reducing REM below baseline, but the trend was more mild.
Conclusions: These results suggest Hcrt-1, MCH, and CART exert distinct influences on arousal state. These peptides may have specific functions in mediating energy homeostasis through the coordination of feeding and sleeping behavior.

References:

Research supported by NIH Grants NS27710, NS23724

258.A

Co-localization of c-Fos Protein and GABA in Preoptic Area Neurons Following Sleep

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Introduction: Increased c-Fos gene expression is a marker of neuronal activation in most brain sites (1). Neurons that exhibit c-Fos protein immunostaining following sustained sleep have been described in the ventrolateral preoptic area (VLPO) of rats (2). These VLPO neurons contain the neurotransmitters gallamin and gamma aminobutyric acid (GABA). In a previous study, we found that the number of c-Fos immunoreactive neurons (IRNs) in both the rostral and caudal parts of the median preoptic nucleus (MnPN) also increased after sustained sleep (3). We hypothesize that MnPN neurons exhibiting sleep-related c-Fos protein immunoreactivity (IR) are GABAergic.

Methods: Four male Sprague-Dawley rats (280-320g) were surgically prepared with chronic cortical EEG, dorsal neck EMG electrodes and a chronic guide cannula targeting the lateral ventricle. Following recovery, rats were lightly anesthetized and given a unilateral intraventricular colchicine injection (30-45ug in 20ul PBS ICV). On day 12, polygraphic recordings were conducted from 9:00 to 11:00am and all animals were allowed undisturbed sleep. Rats were sacrificed at 11:00am. 40um sections were prepared for double-immunostaining for c-Fos protein and Glutamate decarboxylase (GAD). GAD is an established marker of GABAergic neurons. Stained cells were identified by direct visualiza-
deeply anesthetized and perfused for immunocytochemistry. In two cats, cholera toxin subunit b (CTb) was applied by iontophoresis before euthanasia (6 and 12 days, respectively; +2 microamperes, 7s on and 7s off, 40 min) into the same area where carbachol microinjection produced the state of AS-carbachol. Double immunostaining for Fos and hypocretin 2, as well as for CTb and hypocretin 2, were performed. The distribution of hypocretin+, hypocretin+ Fos+, CTb+ and CTb+ hypocretin+ neurons were analyzed.

Results: The greatest number of hypocretinergic neurons expressed c-fos during AW (186 ± 18.5, 80 %, P < 0.005). In addition, there were more Fos-immunoreactive hypocretinergic neurons during AS-carbachol (54.7 ± 15.6, 33%) than there were during AW (4.5 ± 4.5, 3%). In addition, immunocytochemical analysis revealed that single labeled neurons (CTb+) were surrounded by hypocretinergic neurons in the perifornical hypothalamic area. Double-labeled neurons (CTb+ and hypocretin+) were also observed in this area.

Conclusions: The significant difference in the number of c-fos-expressing hypocretinergic neurons between QW and AW indicates that these neurons may not be responsible for maintaining wakefulness, per se, but may be involved with processes underlying arousal that is accompanied by locomotor-explorative activity. In addition, the intriguing finding that a significant portion of hypocretinergic neurons express c-fos during AS-carbachol indicates that a sub-population of these cells may carry out functions during AS. In addition, a subpopulation of hypothalamic hypocretinergic neurons as well as non-hypocretinergic neurons were found to project to the NPO. These data suggest that the activity of neurons in the NPO, which are involved in the generation of active sleep (2), may be modulated by hypocretin.

References:

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260.A

Genetic Ablation of Orexin Neurons in Mice: A Mouse Model of Narcolepsy

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Introduction: Orexins (hypocretins) are recently identified neuropeptides that are derived from the same precursor peptide, and are specifically localized in the lateral hypothalamic area (LHA) 1. Recent studies suggest that specific degeneration of orexin-containing neurons occurs in brains of human narcolepsy patients 2. Here, we generated transgenic mice in which orexin-containing neurons are ablated by expression of a truncated Machado-Joseph disease gene product (ataxin-3) with expanded polyglutamine repeats.

Methods: We constructed a transgene with the 3.2-kb fragment of the 5’-upstream region of the human prepro-orexin gene as a promoter 3, which was ligated to the N-terminally truncated cDNA for human ataxin-3 with abnormally expanded polyglutamine repeats. We myc-tagged the C-terminus of the transgene for histological examination. The transgene was injected into fertilized mouse eggs to generate founder animals, which were bred to produce orexin/ataxin-3 transgenic lines. Transgenic mice were genetically and histologically characterized by standard procedures.

Results: Double-immunofluorescence histochemistry using an anti-myc monoclonal antibody and anti-orexin antiserum showed expression of myc-like immunoreactivity exclusively in the hypothalamic orexin-containing neurons in 2-week-old orexin/ataxin-3 mice of all lines. Brains of older orexin/ataxin-3 mice showed an apparent loss of orexin neurons. Anti-orexin immunostaining revealed that 75± 5% and 90± 8% of orexin neurons were eliminated by 4 and 8 weeks of age, respectively (n=4). By 12 weeks of age, over 99% of orexin neurons were lost in the hypothalamic regions of all lines. In situ hybridization of coronal sections also revealed that prepro-orexin mRNA expression in the LHA was markedly reduced in the transgenic mice. Orexin-immunoreactive fibers in the locus coeruleus, a region of the brain normally receiving the densest orexin neuronal projections, were markedly reduced in the transgenic mice. Gross anatomical and histological studies, using hematoxylineosin and Nissl staining, failed to detect any structural abnormality in the brains of the transgenic mice at 12 weeks of age. Immunostaining for other hypothalamic peptides including MCH, NPY and aMSH) also failed to detect any abnormality in the brains of the transgenic mice. These observations suggest that orexin neurons are postnatally and specifically removed in orexin/ataxin-3 transgenic mice.

Conclusions: We generated transgenic mice in which orexin-containing neurons are ablated by expression of a truncated Machado-Joseph disease gene product (ataxin-3). Orexin-containing neurons were highly specifically ablated in these transgenic mice. These mice showed a phenotype strikingly similar to human narcolepsy, including behavioral arrests, premature entry into rapid eye movement (REM) sleep and poorly consolidated sleep patterns (Beuckmann et al.; companion abstract). These mice will be useful for understanding the pathophysiology of narcolepsy and for investigating possible treatment of this disorder.

References:

261.A

The Dynamics of Sleep and Waking in a Large-scale Computer Model of the Thalamocortical System

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Introduction: A number of experimental studies have investigated spatial and temporal properties of neural activity patterns in the thalamocortical system during the sleep-waking cycle. In-vitro studies have revealed how intrinsic properties of thalamocortical and cortical neurons can produce burst- and tonic firing. These intrinsic properties combined with network interactions between thalamic and reticular neurons produce the firing patterns that characterize different arousal states. Large-
scale computer models of the thalamocortical system can usefully complement in-vivo experiments in investigating anatomical and physiological factors that contribute to network dynamics by providing detailed access to the interactions among thousands of neurons in parallel. We have developed such a large-scale model to explore the dynamics of simulated activity patterns during conditions resembling spontaneous waking and sleep.

Methods: An anatomically realistic large-scale model of the cat thalamocortical system (~65,000 neurons and 5 million connections), previously used to investigate neural responses to visual stimuli (Lumer et al. 1997a, 1997b), was modified to incorporate experimentally observed intrinsic currents. The cellular properties of the model neurons were augmented by several additional ionic currents: a depolarizing cation current, commonly called $I_{K}$; a depolarizing Ca$^{2+}$ current, called $I_{T}$; a hyperpolarizing K$^{+}$ current, called $I_{K}$; a Ca$^{2+}$ activated potassium current, $I_{K(SLOW)}$; and a persistent sodium current, $I_{Na(P)}$. $I_{K(SLOW)}$ and $I_{Na(P)}$ were activated (spontaneously) or inactivated (in response to visual stimuli) to mimic the action of neuromodulatory systems that regulate the sleep-waking cycle.

Results: Depending on the magnitude of $I_{K}$ and $I_{K(SLOW)}$, the model evolved from a state of low-voltage fast activity to a state of coherent firing in which spindle and delta waves coexisted with the slow oscillation. The interplay of $I_{K}$ and $I_{K(SLOW)}$ caused thalamocortical cells to shift from a state of tonic firing (corresponding to waking) to a state of burst-pause firing (corresponding to the spindles and slow waves of sleep). As in physiological observations, this occurred when $I_{K}$ was increased, mimicking the reduced depolarizing influence of modulatory diffuse ascending systems during sleep. These modifications at the single cell level resulted in global dynamics that resembled those observed with electroencephalography during different behavioral states. The spatial and temporal coherence of firing was analyzed by computing crosscorrelations between many individual neurons as well as population-averaged activities of groups of neurons. During slow-wave and spindle sleep spatiotemporal coherence was high, with the crosscorrelations showing essentially zero phase lag as well as infinite correlation length in their maxima. Random permutation tests, used to compare the network with intact and lesioned network pathways, show that the cortex and reticular thalamic nucleus are both important in maintaining synchronous oscillations. Corticothalamic projections onto thalamic interneurons also contribute significantly to the maintenance of synchronous activity. The $I_{K(SLOW)}$ and $I_{Na(P)}$ currents in cortical cells were shown to be sufficient to produce a slow cortical oscillation with network interactions influencing the synchronization of the oscillation. The presentation of simulated visual stimuli in different arousal states demonstrates that, although excitation from the periphery can still influence cortical firing, the specificity of neural responses is considerably reduced during sleep.

Conclusions: A large-scale computer model of the cat thalamocortical system was used to investigate anatomical and physiological factors influencing the dynamics of spontaneous and evoked neural activity in different arousal states.

References:

2. Lumer ED, Edelman GM, Tononi, G: Neural dynamics in a model of the thalamocortical system. II The role of neural synchrony tested through perturbation of spike timing. Cerebral Cortex 7(3):228-236, 1997b.

Supported by Neurosciences Research Foundation
On the Role of Posterior Hypothalamus Neurons in the Paradoxical Sleep Control

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Introduction: According to our previous studies posterior hypothalamus takes part in the inhibitory control of paradoxical sleep. In particular, it was shown that high-frequency electrical stimulation of the posterior hypothalamus resulted in the reduction of the REM sleep duration and phasic events. In order to further test this hypothesis the sleep-waking discharge patterns of neurons in the posterior hypothalamus have been studied.

Methods: Chronic experiments were conducted on 7 adult unanesthetized cats. Under nembutal anesthesia (40 mg/kg) electrodes for polygraphic sleep monitoring and special appliance for indolent head fixation were implanted. Single-unit neuronal activity was recorded in the posterior hypothalamus (F=+10, ML=1,5-2, H=4) with glassinsulated tungsten microwires. At the end of the recording sessions histological verification of electrodes localization was performed. Results. Neurons recorded during the each stage of sleep-waking cycle (n=72) were subdivided into three populations. The neurons of the first one (39%,) discharged with the high frequencies both during waking and PS and decreased their discharge rates during slow-wave sleep. The firing frequencies of neurons belonging to the second population (47%) were at their maximum during waking, decreased in slow-wave sleep and reached their minimum during paradoxical sleep. The firing rates of these neurons were higher in tonic stage of paradoxical sleep than in phasic one. The neurons of the third population (14%) discharged tonically at a very low rates during waking, decreased their firing rates in slow wave sleep and nearly ceased discharging during PS. According to literature data, neurons with such firing properties are histaminergic.

Results: NA

Conclusions: Our results suggest that the neurons both of the second and the third populations are waking-related and their functional activity is at its minimum during paradoxical sleep We suppose that these neuronal populations play an important role in waking maintenance and participate in the inhibitory control of brain stem paradoxical sleep centers.

References:

Acoustic fMRI During Sleep: Negative BOLD Response in the Visual Cortex

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Introduction: Brain activity during the sleep-wake cycle has been studied using SPECT and PET methods showing a deactivation of the frontal cortex and a significant decrease of the cerebral metabolic rate during slow wave sleep (SWS) in specific brain regions (1). Recently, functional magnetic resonance imaging (fMRI) studies in sleeping subjects combined with MR compatible EEG recording have been performed (2, 3). Here, we report the effects of acoustic stimulation on blood oxygenation level-dependent (BOLD) response in the auditory and visual cortex across the sleep-wake cycle.

Methods: Fourteen healthy subjects (6 m, 8 f; mean age 24.7 years) were studied following 36 hours of sleep deprivation. Polysonomographic recordings including the EEG (according to the 10-20 system), EOG, and EMG using a system adapted for the MR environment were performed. Sleep stages were visually scored online and re-evaluated following post processing including frequency filtering and pulse-artifact correction. The study was performed on a GE Echospeed at 1.5 T. During a baseline session, a standard acoustic fMRI using echo planar imaging was measured. For the functional imaging during sleep, a silent gradient echo sequence was used (TE = 50ms, TR = 102ms, flip angle 30 degree, noise reduction of 30 dB by lowering the slope of gradient flanks). A single slice of 5 mm thickness was acquired and positioned such that the maximal activation in the auditory cortex and parts of the visual cortex were covered. The fMRI text paradigm was repeated during wakefulness and different sleep stages as determined by online EEG recordings.

Results: Ten subjects were able to fall asleep, 5 of them had SWS. There was a distinct activation pattern depending on the sleep-wake state. During wakefulness, a regular positive response was detected in the auditory cortex, but no consistent BOLD responses were seen in the visual cortex (Figure 1, top left). During sleep, the BOLD response was clearly reduced in the auditory cortex. Furthermore, a marked negative correlation was observed in all subjects in the visual cortex predominantly during sleep stages 1 and 2, but not during wakefulness (Figure 1, top right). During SWS, BOLD responses were diminished in both regions.

Conclusions: Reduced BOLD responses in the auditory cortex during sleep probably reflects reduced processing of external stimuli. The effect of a negative transmodal BOLD response of the visual cortex during sleep stages 1 and 2 is similar to the previously reported negative BOLD response upon visual stimulation in sleep (3) and may reflect a deactivation through thalamic filtering processes. However, the mechanisms of negative BOLD responses are not fully understood. The neurovascular coupling may also be altered during sleep which need to be clarified.
References:

265.B

Frequency Analysis of Slow Wave Sleep During and After Prolonged Spaceflight

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Introduction: Because cosmonauts are reported to experience postflight “Asthenic Syndrome”, we hypothesized that there would be a reduction in slow wave delta EEG sleep and increase in alpha EEG sleep during and after prolonged spaceflight, comparable to patients with fibromyalgia/chronic fatigue syndrome.

Methods: Pre-flight (baseline, liftoff day-55, -56), inflight (days 81, 82, 143, 144), and post-flight (approx. 1 week, 3 mon. later) recordings of standard sleep-wake physiological assessment for five crew members on the Mir Space Station (flight designations NASA 4/Mir 23 & 24) were analyzed for each quarter of the sleep time using a period amplitude analysis (PAA) method.

Results: We found increases in alpha-delta duration ratio (p=0.044) and alpha-delta integrated amplitude ratio (p=0.029) in the second quarter of the night for early postflight compared to preflight data, with rises of 15.7±9.3% and 18.2±19.2% respectively. Mean delta wave amplitude decreased over the course of inflight (approx. days 81 and 82, p=0.045), early postflight (p=0.021) and late postflight (p=0.063), compared with preflight, with decreases of 17.5±9.7%, 29.0±18.6%, and 39.3± respectively. Mean delta wave duration, alpha wave amplitude, and alpha wave duration did not differ significantly for any time period.

Conclusions: 1) Sleep disturbances that occur inflight continue post-flight for up to three months in a group of cosmonauts/astronaut. 2) Sleep disturbances result from decreased delta wave activity rather than increased alpha wave intrusion, in contrast to that reported for terrestrial patients with fibromyalgia. 3) These sleep changes during extended stays in microgravity may contribute to skeletal and fatigue problems.

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266.B

Effects of Music and Tones on Sleep Neurophysiology

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Introduction: There are currently a number of musical selections on the market that claim to help people sleep. Thompson(1) has created a commercially available CD that purports to ‘improve sleep by entraining EEG rhythms in the delta frequency.’ Since it is possible to entrain EEG using visual stimulation—as in the phenomena of photic driving—could it also be possible to entrain EEG in the delta frequency via auditory stimulation? And if so, would this improve sleep. This study used both objective and subjective measures to compare sleep parameters between the music of the Delta Sleep System, with a control condition and a tones condition. Sleep onset latency, sleep efficiency, and WASO were used as indicators of sleep quality, and percent SWS (stage 3 + 4) and power spectral analysis were used as indicators of the amount of delta activity. It was hypothesized that sleep quality and the amount of delta activity would be greatest in the music condition.

Methods: 10 female students—with no sleep difficulties—between the ages of 17 and 24 (M = 19.90, SD = 1.91) participated. Each completed the Pittsburgh Sleep Quality Index, Personality Assessment Inventory, and a weekly sleep log prior to PSG recordings. Subjects spent 4 consecutive nights in the lab. The first served as an adaptation night, and the other nights had music, tones, and the control condition in counterbalanced order. The ‘music’ was derived from the first of 2 CD’s of the Delta Sleep System, and 300 Hz tones were 1 sec in duration, with 1.5 sec between tones. Both stimuli commenced at ‘lights off’ and were discontinued 5 min after the first spindle or K-complex.

Results: The results indicate that there was no significant difference in any of the objective sleep measures between the music, tones, and con-
trol conditions. That is, sleep onset latency (F(2,18) = 1.15, p = .339), sleep efficiency (F(2,18) = .59, p = .547), WASO (F(2,18) = .10, p = .800), and percent Stage 3 and 4 combined (F(2,18) = .20, p = .780) were all non-significant. Also, 95 of 96 power spectral analyses were not significant. However, for the subjective measures, participants rated the music as being more soothing (t = 4.27, p = .002), comforting (t = 2.77, p = .022), pleasant (t = 4.59, p = .001), and relaxing (t = 3.132, p = .012) than the tones.

Conclusions: While participants found the music more enjoyable to listen to than the tones, there was no evidence that the music had any influence on subjects’ neurophysiology during sleep compared to either the control or tones condition. That is, when listening to the music, participants did not sleep better, nor did they show any increases in delta activity. It appears that in a sample of normal sleepers, the claims of the manufacturer are unsubstantiated.

References:

Research supported by Grant from the Natural Sciences and Engineering Research Council of Canada

267.B

The Relationship Between Stage 2 Sleep Spindles and Intelligence

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Introduction: A number of studies have been done to examine the relationship between Stage 2 sleep and intelligence. One such study has reported that the number of sleep spindles was related to learning efficiency(1). Expanding on this idea, we predicted that the number of spindles and the mean amount of sigma power during Stage 2 would be related to the subjects’ intelligence scores on the MAB-II IQ test.

Methods: Ten subjects (age range: 18 - 29) were used in the study. Subjects were screened for abnormal sleep patterns and excessive drinking/drug use. Subjects completed the MAB-II(2) IQ test and spent the subsequent two nights (acclimatization and baseline) in the laboratory. The number of sleep spindles (12-16Hz) and the mean Sigma Power (12-14Hz) was assessed for each page of Stage 2 sleep on the baseline night. Epochs with large body movements or major artifacts were excluded. Spindle activity and sigma power were assessed for both the C3 and C4 derivations.

Results: The total number of spindles (C3+C4) for the night was highly correlated with Performance IQ (r = .71, p = .022), and with Full Scale IQ (r = .76, p = .010), but not with Verbal IQ (r = .56, p = .094). The mean sigma power of both C3 and C4 for the entire night was highly correlated with Performance IQ (r = .76, p = .011) and Full Scale IQ (r = .77, p = .009). When the night was divided into thirds, the mean sigma power in the last third of the night showed the strongest correlation with both Performance IQ and Full Scale IQ (r = .87, p = .001, and r = .84, p = .002 respectively). None of the correlations with Verbal IQ were significant. Sigma power was found to be the most highly correlated with two of the sub-tests of the Performance IQ scale: Picture Completion and Object Assembly. Both tasks require perceptual and analytical skills for successful completion. A forward stepwise multiple regression was conducted with mean sigma for the second and last thirds of the night as the independent variables and Performance IQ as the dependent variable (R2 = .85, F2.7 = 20.06, p = .001).

Conclusions: We suggest that sigma power is a powerful indicator of how an individual will perform on the Performance portion of an IQ test, particularly with respect to tasks that require perceptual and analytical skills. While a high level of sigma power is correlated with a high aptitude for these skills, the longitudinal nature of this relationship is not yet understood. Whether sigma power influences an individual’s Performance IQ or whether the skills required affect the amount of sigma power a person exhibits is not yet clear.

References:

Research supported by Canadian Institutes of Health Research (CIHR).

268.B

The Effects of Bright Light and Nighttime Melatonin Administration on Cardiac Autonomic Activity

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Introduction: The administration of exogenous melatonin increases sleepiness, decreases core body temperature and increases peripheral body temperature. Melatonin receptors have been identified in animal peripheral vasculature, suggesting that melatonin produces these effects via its action on the periphery (1). Melatonin may also directly alter autonomic activity.

Methods: We investigated this hypothesis in 16 healthy supine and awake subjects (8m, 8f) by systematically altering melatonin levels and observing concurrent changes in cardiac autonomic activity. We suppressed melatonin secretion with bright light. There were 3 conditions: NORMAL MELATONIN (dim light <10 lux), LOW MELATONIN (bright light >3000 lux and placebo), and HIGH MELATONIN (bright light and exogenous 5 mg melatonin). See Figure. The placebo and melatonin were administered at each subjects estimated melatonin onset time (wake time + 14 hrs) and all measurements were taken from 3 hours before each subjects estimated melatonin onset to 2 hours after their normal sleep time.

Results: Salivary melatonin concentrations indicated that the interventions were successful in producing three conditions of significantly different low, normal and high melatonin levels (p<0.001). In the low melatonin condition as compared to the other conditions, sleep onset latency to stage 2 NREM sleep was significantly longer (mean 5.53±1.87 mins), rectal temperature was significantly higher (mean maximal difference of 0.27±0.06 deg C) and foot temperature was significantly lower (mean maximal difference of 1.98±0.70 deg C). There were no observed differences in respiratory sinus arrhythmia (measure of cardiac parasympathetic activity) or pre-ejection period (measure of cardiac sympathetic activity). However, in the high melatonin condition as compared to the low melatonin condition, there was a close to significant decrease in heart rate (3.80±1.95 beats/min, p=0.052) and significant decrease in systolic blood pressure (5.75±1.65 mmHg).
Conclusions: These results, together with the results from daytime administration studies, provide conclusive evidence that melatonin administration, whether administered during the day or at night, does not significantly alter cardiac autonomic activity. Thus presleep increases in cardiac parasympathetic activity (1) cannot be attributed to melatonin. Importantly, the observed changes in heart rate and blood pressure (here and elsewhere) do support the notion that melatonin binds directly to peripheral receptors in the vasculature (2) and maybe in the heart itself (3).

References:

Research supported by Australian Research Council

269.B

The Relationship Between REM Sleep and Intensive Piano Learning

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Introduction: Studies using human participants have shown a relationship between REM sleep and learning processes and/or consolidation of a non-declarative type of procedural memory(1-3). Furthermore, SWS also appears to be important for memory consolidation(3). To seek further evidence of sleep-related learning requiring this type of memory, we examined the relationship between sleep processes and learning new piano pieces using music students under a natural non-laboratory setting.

Methods: Ten healthy adolescents (grades 7-10, Royal Conservatory of Music) were selected for this study (The current report is based on 6 participants who already completed the study). The experimental period was 15 consecutive days consisting of Baseline (B), Intensive Practice (IP), and Recovery (R) phases (5 days each). Participants were to light-practice familiar pieces during the B and R-phases. They were given difficult new piece(s) to practice intently during the IP-phase. Performance of the new pieces was evaluated by their piano instructor. A sleep log, questionnaires and dream reports were filled out daily to measure sleep patterns, daytime activity levels, and mental condition. Nocturnal sleep (EEG, EOG, EMG) was recorded on 9 nights (B4-5, IP1-5, R4-5) in each participant’s house using a portable EEG system (Biosaca(TM), Stellate Systems) and converted to the Stellate Systems file format for further analyses with Harmonie(TM). Mean amounts and percentages of sleep stages per night as well as per each NREM-REM cycle, initial sleep and REM latencies were analyzed. REM densities within the 4th REM period were calculated based on the proportion of 3-second epochs containing REMs. One participant’s data was discarded for the REM density analysis due to a recording problem. These parameters were compared on the B5, IP2, R5 nights.

Results: All participants achieved or surpassed expected performance levels as evaluated by their instructor. There was no significant effect of phases on sleep stages and latencies. However, there was a quadratic trend in REM density among the 3 phases (F(1,4)=6.014, p=.07; Fig.1). Visual inspection indicated that 4 of the 5 participants clearly showed an increased REM density in the IP-phase which returned to baseline level during the R-phase.

Conclusions: REM densities tended to increase during intensive practice of new piano pieces although overall sleep stage structures did not change. These findings support previous research suggesting a relationship between phasic REM activities and learning processes. Further investigation including practice time suggestive of "paradoxical sleep windows(2)" or time course of SWS and REM sleep to test "the multistep process of memory formation(3)" may give us more evidence to support sleep-related learning.

References:

Research supported by Grant from the Natural Sciences and Engineering Research Council of Canada
Effects of Task Difficulty and Invested Mental Effort on Peripheral Vasoconstriction

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Introduction: Mental effort was shown to be associated with tonic activation of the sympathetic nervous system. One result of this activation is peripheral vasoconstriction. As blood flow in peripheral vascular beds is reduced possibly more blood is preferentially directed from the periphery to the brain and heart. Because the finger is densely innervated with sympathetic vasoconstrictor efferents and because vasoconstriction at this site reflects solely the activity of the sympathetic nervous system, peripheral vasoconstriction may constitute a reliable index of mental effort. We conducted four experiments to test the effects of task difficulty and invested mental effort on peripheral vasoconstriction.

Methods: Finger pulse wave amplitude (PAT) was measured from male undergraduate students by means of a newly developed finger plethysmograph that measures peripheral arterial tone (PAT) during both rest and cognitive performance. In the first two experiments, subjects performed a visuomotor task. In Experiment 1, subjects were instructed to perform the task without investing effort, subjects were instructed to perform the task with varying amounts of effort. In Experiment 2, subjects were instructed to perform the task with varying memory loads, whereas in Experiment 3, subjects were instructed to vary the amount of effort invested. In Experiment 4, subjects were instructed to vary the amount of memory load. The last two experiments used the same two types of effort manipulation and the Sternberg memory set size of 4 letters.

Results: We computed a change score for the PAT amplitude by subtracting average values for the baseline from the average values of the task periods and dividing it by the baseline. As expected,PAT amplitude was lower during the task period than during the baseline rest period (p<0.05) in all four experiments. In Experiment 1, although performance decreased significantly as difficulty levels increased, PAT amplitude did not differ significantly across levels. In Experiment 2, PAT amplitude decreased significantly only when subjects were instructed to invest effort in the task (p<0.05). In Experiment 3, performance decreased linearly as task difficulty increased. PAT amplitude did not differ under 4 or 7 letter loads, but it was lower in both conditions compared to the 2 letter load condition (p<0.05). Performance was higher and PAT amplitude lower when subjects were instructed to perform well and invest effort compared to when they were instructed to perform the task without investing effort (p<0.05). These results were significant only for those subjects presented with the memory set size of 4 letters.

Conclusions: The difference in PAT amplitude between rest and task periods suggests that PAT amplitude reflects changes in sympathetic activity due to task engagement. The demands of the task increase, PAT amplitude tends to decrease. Our results seem to suggest that peripheral vasoconstriction may be more sensitive to the amount of voluntary effort invested in task performance rather than to the objective task demands.

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Electromagnetic Radiation and Sleep

Kovalzon VM, Rozhnov YV, Titorov SF

Introduction: From the neurobiological point of view, +1Bw-resonance +IBw- effects of rare, short and strong pulsatile electromagnetic radiation (possessing negligible total energy) upon nervous tissue are of special interest. We firstly studied low frequency (6 Hz, basic theta-rhythm predominated in both active wakefulness and paradoxical sleep of the rodents), super-broad band, ultra-short (1-2 ns), powerful (field intensity 100-130 V/cm) impulses on EEG and sleep-waking cycle in laboratory rabbits.

Methods: During 1 hr exposure 4 animals (preliminary implanted under local procaun anesthesia with conventional electrodes for polygraphic recordings) were placed simultaneously into individual narrow wooden boxes with their heads directed to the side of a parabolic antenna of the electromagnetic wave radiator at the distance of 1 m from it. The same animals exposed in front of the switched off radiator were used as controls. Exposition took place between 8:00-9:00 PM. Then the animals were transferred to their habitual individual chambers and a 22-hr continuous paperless recording was started in 9:30 PM simultaneously with the beginning of a 12 hr dark period. The recordings were scored visually, and hourly percentage of W, SWS and PS for both experimental and control conditions was averaged, compared and analyzed statistically using Mann-Whitney U-test.

Results: Electromagnetic radiation evoked no clear disturbances in general appearance, behavior and body temperature of the animals. As it can be seen from the Fig. 1, hourly SWS percentage was not changed too either during the initial 12-hr dark or the following 10-hr light period in the chamber. However, a total sleep time (Fig. 2) has demonstrated a non-significant tendency to decrease in SWS during the dark period followed by a correspondent rebound, so the difference between total amount of SWS in the dark and light periods increased and reached the significance level (+BEA<-0.05; N=8). The most important effect was a pronounced increase in PS delayed for up to 16 hr from the end of the exposition. The tendency to increase in PS percentage was clearly seen within 17-19th and 21-22nd hrs which reached significance level at the 18th and 19th hrs (Fig.1). Generally, despite a weak tendency to decrease in PS at the beginning of the light period (12th-16th hrs), its summary duration for the entire 10-hr period (Fig. 2) was significantly higher (increment more than 40%, p<0.05) as compared to the control value (100%).

Conclusions: The above mentioned influence of electromagnetic radiation on sleep seems to be surprising: we could not find similar descriptions in the literature. If the effect on SWS could be explained by a slight homeostatic disbalance (radiation stress evokes a slight suppression of sleep followed by a restoratory rebound), the pronounced and delayed increase in PS is an order higher than its precedent negligible loss which might be regarded as a result of radiation exposure. The reason of such an effect is unknown; perhaps, it directly reflects a +IBw-resonance +IBw- effect of low frequency strong electromagnetic impulses upon +IBw-biological clock +IBw-, that is the SCN/pineal system.
Increased Number and Density of Rapid Eye Movements in Individuals of Varying I.Q. Levels Following Acquisition of Two Procedural Tasks

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Introduction: In humans, the changes in REM sleep following successful acquisition of cognitive procedural material have reportedly included increases in REM sleep time as well as increases in number of rapid eye movements (REMs) and REM densities (1). Animal studies have suggested that faster learning subjects show larger changes in these variables than slow learning subjects (2). The present study examined changes in REM sleep parameters in college students of varying I.Q. following training in two cognitive procedural tasks. It was predicted that there would be an increase in both number of REMs and REM densities following training. Further, it was predicted that High I.Q. individuals would exhibit more REMs than those in the Medium or Low I.Q. groups.

Methods: Participants were 20 introductory college students (male and female) from Trent University. Subjects were screened for sleep problems and administered the MAB-II I.Q. scales. They were then assigned to one of three different I.Q. groups - High, Medium or Low. After an acclimatization night (night 1) in the sleep lab, subjects were given a second night of baseline sleep (night 2). On the evening of sleep night 3, subjects were asked to learn the Mirror Trace and Tower of Hanoi tasks. Subjects were all retested one week later to assess levels of learning. A fourth, non-learning control group was also included. Sleep stage scoring was done on all subjects. As well, all eye movements during REM sleep larger than 10 uv were also counted for these two nights.

Results: Learning - All test groups successfully learned the Mirror Trace task [F(1,13) = 29.14, p < .0001] and the Tower of Hanoi task [F(1,13) = 49.58, p < .0000]. Sleep States - The three test and non-learning control groups did not differ in terms of number of minutes of Stage 1, Stage 2, Stage ¾, REM sleep, %REM sleep or Total Sleep. Rapid Eye Movements - The total number of REMs was significantly larger for all groups on post training night 3 compared to baseline night 2 [F(1,16) = 16.05, p < .001]. There were no differences between test groups on this measure, although all test groups had significantly more REMs on post training night 3 than did the non-learning controls [F(3,16) = 4.35, p < .02]. The REM density measure also showed an increase from night 2 to night 3 [F(1,16) = 22.69, p < .0002]. The three test groups were superior to the non-trained control group [F(3,16) = 4.46, p < .02]. While the High I.Q. group did not differ initially from the other test groups (Low and Medium I.Q.), on this measure, there was a marginal difference (p < .06). The High I.Q. group had significantly higher densities than the control group on baseline night 2 (p < .05). On post training night 3, the High I.Q. group had higher REM densities than all other groups (p < .004).

Conclusions: As predicted, the total number of REMs was increased in all groups (Low, Medium and High I.Q) following learning. Further, the REM densities were also increased in all test groups following task acquisition. The High I.Q. group had the largest increase in REM densities, with values significantly greater than the Medium and Low I.Q. groups as well as the controls. The Medium and Low I.Q. groups did not differ from each other in terms of REM densities. Results support the hypothesis that REM sleep, particularly the phasic component is involved with consolidation of cognitive procedural material.

References:

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Sexual Dimorphism in REM Sleep Rebound After Stress in C57BL/6J Mice

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Introduction: Although research on sleep regulation has been mainly conducted in males, several studies have reported sexual dimorphism in sleep patterns in both humans and animals. Studies in humans indicate that although sex differences are subtle under baseline conditions, they increase in magnitude under biological or environmental challenges, and rodent studies have highlighted important differences in REM sleep (REMS)1. The present experiments were undertaken to examine whether the sexual dimorphism in REMS reported in mice2 is influenced by two different challenges, restraint stress and enforced wakefulness, known to affect sleep patterns in both humans and animals.

Methods: Data from adult female (n=7) and male (n=6) C57BL/6J mice bred in our laboratory were collected. After EEG and EMG electrode implantation, animals were allowed a minimum of 10 days of recovery plus four days of adaptation to the sleep recording chambers and head tethers. After a 24-hour baseline recording, animals were subjected at lights on to either a 1-hour restraint stress period or a 6-hour sleep deprivation period using the platform over water method. Data were subsequently collected until the beginning of the next lights on phase. Seven to 10 days later, all animals were submitted to the other manipulation. Vaginal rinsings were performed daily at lights on in females in order to determine cycle staging, and only females in diestrus for baseline and recovery recordings were kept in the study. All EEG data were hand-scored for wake, NREMS, or REMS in 10-second epochs.

Figure 1

Variations in REM sleep after a 1-hr restraint stress in male and female C57BL/6J mice.

Results: Baseline sleep pattern: No differences were observed in the amounts of wake and NREM sleep (NREMS) between males and females. However, females showed increased REMS during the 12-hour daylight period. Stress-induced sleep changes: Restraint stress at lights on induced an increase in NREMS during the first 6 hours of the dark phase in both male and female mice. REMS was significantly increased in females during the daylight period and went back to baseline during the dark phase. Conversely, males displayed no overall changes in REMS during the light phase but a 3 fold increase during the dark phase.
Sleep-deprivation induced sleep changes: Both males and females recovered from sleep deprivation with an increase in NREMS and REMS during the dark phase, which was not different between the sexes (fig. 2).

**Figure 2**

![Variations in REM sleep after a 6-h sleep deprivation in male and female C57BL/6J mice.](image)

Conclusions: These data confirm previous reports indicating that sleep patterns are sexually dimorphic, and that REMS is differentially regulated in male and female mice. Furthermore, we report here that this REMS dimorphism is differentially influenced by environmental challenges: it is abolished after enforced waking but magnified after restraint stress, thus suggesting a complex interaction between stress and sex hormones in sleep regulation.

References:

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**274.B**

Sleep Physiology and Ethnicity

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Introduction: Although there has been an increased recognition of ethnic differences in health, the possibility that there may also be ethnic differences in sleep physiology has been curiously understudied. We initially examined the possibility of ethnic differences in sleep physiology in conjunction with our studies of sleep apnea (Study 1). In light of these initial results, we examined this possibility in a second cohort of patients in order to determine whether these results might generalize (Study 2).

Methods: These analyses include 61 participants from Study 1 (46 whites and 15 blacks) and 35 participants from Study 2 (15 whites and 20 blacks). Ethnicity in both cohorts was determined by self-report. Participants in both studies were monitored during sleep with traditional polysomnography including EEG, EMG, EOG, and oximetry. Data from each study were analyzed separately using analysis of variance procedures.

Results: In Study 1, blacks had longer total sleep time (TST) (p<.01), and more rapid eye movement (REM) sleep than whites (p<.05). Blacks also had less wake time after sleep onset (WASO) than whites (p<.05). After controlling for respiratory disturbance index (RDI), while the difference in REM sleep dropped out, the difference in TST remained significant (p<.05). In addition, a difference in percent deep sleep emerged, with blacks spending a smaller percentage of their total sleep time in deep sleep (p<.05). In Study 2, blacks had longer TST and REM sleep minutes (p's <.05). Blacks also spent a smaller percentage of their total sleep time in deep sleep, and this difference in percent deep sleep remained significant after controlling for RDI (p'<.05).

Conclusions: In two separate studies, blacks had longer TST, more minutes of REM sleep, and spent a lower percentage of their total sleep time in deep sleep after controlling for differences in RDI. These findings suggest possible ethnic differences in sleep physiology.

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**275.B**

Protein-Rich Diet Suppresses NREM Sleep Intensity in Rats

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Introduction: There is a well-established relationship between feeding and sleep. Excessive eating by cafeteria diet (1) or refeeding after starvation (2) increases sleep in rats. Sleep has also been shown to affect levels of protein metabolism on a 24-hour cycle (3). Although the metabolic determinants of feeding and sleep have been investigated, the effect of a protein-rich diet on sleep has not yet been studied. The aim of the present experiment was to examine the effects of various protein-rich diets on sleep in rats.

Methods: Male Sprague-Dawley rats (380-490 g) were implanted with EEG and EMG electrodes. The rats were kept on a 12:12 h light-dark cycle, light onset at 1000 h. On the two control days, rats (n = 8) were fed standard diet (LM-485 Mouse/Rat Diet, Harlan Teklad, Madison, WI), followed by 3 days of a 20% protein diet and 2 consecutive days of a 40% protein diet. At dark onset, all cages were cleaned of leftover food, and fresh food was provided. Recordings were conducted every day, from dark onset to dark onset.

Results: As the diet increased in protein content, there was a strong tendency towards increased dark-phase REM and NREM sleep during the dark phase, but the changes did not reach significance. There were statistically significant decreases in dark-phase NREM sleep intensity on the second and third 20% protein diet days, as well as both 40% protein diet days. On the baseline days, food intake averaged 7.17 ± 0.33 g/100 g bw. On the first 20% protein day, rats had significantly increased food intake, and on both 40% protein days, food intake was significantly lower than baseline. The average daily food intake on the 3 days of 20% protein diet was 7.54 ± 0.22 g/100 g bw, significantly below the food intake on both 20% protein diet days. The average daily food intake on the two 40% protein diet days was 6.21 ± 0.22 g/100 g bw (not significant difference from baseline). The average daily food intake on the 3 days of 20% protein diet was 7.54 ± 0.22 g/100 g bw, significantly below the food intake on both baseline and 20% protein days. Although the rats’ net intake of 40% protein diet was lower than the 20% protein diet, a daily average of 69.8% more protein was consumed on 40% protein days than on 20% protein days.
Figure 1

| Figure legend: From top to bottom: NREM sleep, REM sleep, and NREM slow-wave activity in the dark phase, and 24-h food intake. B: average of two baseline days. L1, L2, L3: first, second, and third 20% protein diet days, respectively. H1, H2: first and second 40% protein diet days. Asterisks: significant difference from baseline (p < 0.05).

Conclusions: All of the experimental diets were equal in calorie count. The variations in protein significantly match trends in food intake and NREM sleep intensity, suggesting that the suppressed slow-wave activity could be due to higher levels of consumed protein. The changes in NREM and REM sleep amounts are only tendencies. Possibly further increases in protein intake could elicit more pronounced sleep changes. The slight increases in NREMS after 20% and 40% diet likely do not serve a homeostatic need. It is possible that decreases in SWA are due to a homeostatic compensatory mechanism caused by the excess amount of ‘luxury’ NREMS.

References:

This work was funded by NIH (NS-30514).

276.B

Thermoregulatory Changes begin after Lights off and not after Onset of Sleep Stage 2

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Introduction: The parallel evolution of endothermy and sleep in mammals and birds implies an energy-conserving function of sleep by reducing metabolic rate, and hence, core body temperature (CBT). In all species, rest and sleep occur during the the circadian trough of the CBT. A major problem in studying this relationship between thermoregulation and sleep is “masking” (e.g. food intake, posture changes, motor activity), which only in humans can be reduced and controlled by using a constant routine (CR) protocol. The aim of the analysis was to show whether the transition to nocturnal sleep induces thermoregulatory changes in a CR protocol.

Methods: In total 36 healthy young men (age: 26y ±1, sem; BMI: 22.8 ±0.3) participated in 4 separate constant routine (CR) studies (<8 lux, 22°C ambient temperature) followed by a nocturnal sleep episode (habitual bedtime). Thermometry [rectal (CBT), distal (averaged hands and feet) and proximal (weighted mean of forehead, thigh, infracavicular and stomach) skin temperatures], heart rate and sleep-EEG were continuously recorded. Only data of the baseline and placebo conditions were included in this analysis (data were individually averaged; total of 124 nights). The results are depicted in 10min-mean bins adjusted to 2 hours before and after lights off (±0) or to sleep onset latency (SOL, time between lights off and the first occurrence of sleep stage 2; ±0), respectively. Statistical analysis was calculated by one-way repeated-measures ANOVA and reversed Helmert contrasts (*, p<0.01) to localize the time point of appearance of the first significant change.

Figure 1

Results: Before lights off, proximal skin temperature and CBT declined, whereas distal skin temperature increased (see Figure). These differences arise because distal skin regions contain artereovenous shunts, which control heat loss very efficiently when they are open, via fast blood flow (convection) from the core to the periphery. In contrast, proximal skin regions contain only capillaries with mainly nutritional functions and slow blood flow. At lights off (without any postural change), very rapid changes were induced (significant changes in the first 10min-bin): heart rate decreased, distal and proximal skin temperatures increased concomitantly, followed by a decrease in CBT (significant changes in the second 10min-bin). This indicates a general precapillary skin vasodilatation after lights off with minor changes in total body heat loss (redistribution of heat from the core to the shell). SOL adjusted data revealed no additional thermoregulatory changes after onset of sleep stage 2.

Conclusions: This analysis indicates that a long lasting redistribution of heat from the core to the shell begins after lights off before the onset of sleep. In contrast to a previously claimed hypothesis (1), slow wave sleep has minor, if any, thermoregulatory functions.
References:

277.B

Spindle Frequency Is Related To Sleep Depth

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Introduction: In the course of night sigma activity exhibits a rising trend showing U-patterns within NREM sleep cycles (1). Slower sigma activity has been noticed to dominate at 2-5 am, while faster frequencies are more abundant in the morning hours (2). The aim of this pilot study was to examine spindle frequencies within sleep cycles.

Methods: Seven healthy, drug-free subjects were studied. Five were female and two male. Their median age was 31 years (range 25-41). Whole-night polygraphies were recorded by an Embla sleep recorder (Flaga). The recordings were scored by the method of Rechtschaffen and Kales (1968). In three subjects sleep spindles were detected by a previously validated fuzzy detector. The frequency of each spindle was determined. In four subjects spindles were visually scored by two independent raters. The EEG derivation C3-A2 was used. The frequency of five spindles from the beginning, middle and end of each of the first five sleep cycles were measured. Only those spindles marked by both scorers were taken into account.

Results: By fuzzy detector the spindle frequency was higher (13-13.5 Hz) in all subjects at the beginning of the sleep cycles, declined by 0.5-2 Hz towards the middle of the cycles and increased to initial levels before stage REM (Figure 1). The magnitude of the decline was higher when slow wave sleep was present. By visual spindle scoring the median spindle frequency of the pooled data was 13.5 Hz in the beginning of the first cycle declining to 12.5 Hz and increasing to 12.9 Hz (Figure 2). In the subsequent three sleep cycles the pattern was similar. In the fifth cycle, consisting of only S2, no frequency decrease was observed.

Conclusions: This pilot study shows slower spindles to be present in the first four sleep cycles. The frequency of spindles seems to be related to sleep stage. According to Steriade and Amzica (3) spindle frequency is connected to hyperpolarization of the thalamocortical cells. With longer hyperpolarization the spindle frequency is lower. Thus in the beginning of sleep cycles with fast spindles the hyperpolarization of the thalamocortical cells would be shorter, lengthening along with deepening of sleep, slowing slower spindles. In transition phase to REM sleep the spindle frequencies fasten thus indicating the hyperpolarization to shorten. This strengthens the view that the spindle process is regulated by slow oscillation. As slow oscillation with increasing hyperpolarization is responsible for deepening of non-REM sleep the lengthening of hyperpolarization also seems to be related to sleep microstructure within cycles.

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278.B

Predicting the Occurrence of the Auditory Evoked K-complex in non-REM Sleep

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Introduction: The evoked K-complex (KC) is a large bi-phasic negative wave (peaking at 350 and 550ms), followed by a large positive wave (900ms). It will be elicited on 25-50% of stimulus presentations in non-REM sleep. It is unknown why the same stimulus will elicit KCs on some trials but not others. The function of the KC itself is still a topic of considerable debate. The precursors of the KC have been investigated in an attempt to predict the conditions under which a KC will be elicited (1,2). We reported that the amplitude of the N350 wave on trials preceding the KC predicts its subsequent occurrence (2). In this report, we attempt to replicate this finding in three separate studies.

Methods: Twenty-one subjects (mean age 23.2) were randomly assigned...
to one of three groups in which auditory stimuli were delivered during sleep. Standard 1000Hz (80dB) tone pips were delivered via an earphone every 1.5s. On rare and random occasions, the stimulus was changed to either a higher pitch (2000Hz) or a louder intensity deviant (100dB). These deviant stimuli were delivered on either 20%, 10%, or 5% of trials (Groups 1-3). The EEG was recorded from midline frontal, central, parietal, and occipital sites. Trials were sorted and averaged on the basis of the presence or absence of K-Complexes (KC+, KC-), sleep stage (stage 2, SWS), stimulus type (pitch, intensity), and deviant probability (.20, .10, .05). Data were reconstructed off-line into discrete trials consisting of 256 data points beginning 100ms prior to the stimulus and continuing for 900ms. Repeated measures ANOVAs were run as the main analysis.

Results: Table 1 presents the percentage of KCs elicited in the various conditions. For the pitch stimulus in stage 2 sleep only, consistent findings were noted across all probability conditions - N350 was larger on the trials that preceded a KC compared to those in which no KC followed. The difference was statistically significant only in the .20 probability condition, F(1,18)=7.407, p<.05 (See Figure 1). The effect size is quite small possibly as a result of the small sample size and large inter-subject variability in the event-related potential waveforms.

Table 1

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Figure 1

Conclusions: The larger amplitude N350 on trials preceding the KC appears consistent in the grand average event-related potentials and has been replicated across several studies. The N350 is thus a reliable predictor of KCs. It now remains to be determined whether the N350 signifies a state of inhibition or arousal prior to the KC. Understanding the antecedent conditions of the KC may elucidate its function.

References:

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279.B

Alterations in Sleep after Fear Conditioning

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Introduction: We are interested in examining the neural mechanisms underlying the role of sleep in the consolidation of hippocampus-dependent long-term memory. Physiological data demonstrates that sleep after training for hippocampal dependent tasks is altered (1,2,3). REM sleep deprivation after hippocampal dependent spatial task training impairs memory consolidation (2). Previously, we have found that total sleep deprivation after fear conditioning (a hippocampus dependent task) impairs memory consolidation (LAG, AP, and TA unpublished observation). Therefore, we have begun to examine sleep parameters after training for fear conditioning in order to investigate whether alterations in these parameters may contribute to memory consolidation.

Methods: We surgically implanted EEG and EMG electrodes in adult C57BL/6J mice and allowed 2 weeks for recovery. After recording 1 week of baseline EEG activity, mice were placed in a fear conditioning chamber for two minutes and presented either one or three pairs of a thirty second tone ending with a 2 second 1.5 mA shock with a two minute interval for three pairs. Afterwards, mice were returned to their home cage. Ten second epochs were scored offline as wake, non-REM, or REM. We performed spectral analysis by averaging half hour blocks of fast fourier transforms performed on every 10 second epoch.

Results: Preliminary data shows that training increased wakefulness immediately following training for one hour and increased sleep two and three hours after training. Training with 3 shocks produces a greater percentage of wake in the first hour, and a greater percentage sleep in the second and third hour. During the second and third hours there is more delta, theta and spindle activity following training for both 1 and 3 shocks.

Conclusions: Fear conditioning training with both 1 and 3 shocks alters the pattern of sleep and cortical oscillations for three hours after training. Alterations in sleep states after training may regulate memory consolidation for this task because the lack of sleep is known to impair memory consolidation. Alterations in sleep states are known to affect gene expression and changes in sleep after fear conditioning may allow transcription and synthesis of proteins essential for memory consolidation. Future studies will determine if alterations in sleep states after training are important for memory consolidation, by analyzing sleep after training in genetically modified mice with memory defects.

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Supported by NIH, John Merck Fund, and Whitehall Fund.

280.B

The Relationship Between Stage 2 Delta Amplitude and Evoked K-complex Production: The Effect of Sleep Fragmentation

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Introduction: Recent studies have shown that there is a relationship between K-complexes and delta frequency in cats and possibly humans(1). Delta activity shows maximal power, and is thought to be generated, in frontal regions of the brain. This is also the region over which K-complexes have been shown to be maximal(2). This study looked at the effect of increasing sleep drive by one night of sleep fragmentation on the relationship between the probability of evoking a K-complex and delta activity amplitude. It was hypothesized that the increase in sleep drive should produce an increase in both the probability of eliciting a K-complex and delta activity amplitude.

Methods: Six young healthy subjects participated in the study (mean age = 22.33 yrs., SD = 1.03 yrs.). Each subject spent three consecutive nights in the laboratory. EEG was recorded from 29 scalp sites adapted from the international 10/20 system using an ECI electrocap and referenced to linked ears. EOG and EMG were also recorded. The first and third nights involved the measurement of auditory tone (50msec, 80dB) evoked K-complexes. The second night involved approximately eight hours of sleep fragmentation using long, 5-10sec, auditory tones, (70-110dB). Stimulus and evoked K-complex free 16.384sec EEG epochs were chosen from stage 2 sleep periods on nights one and three for period amplitude and FFT analysis. Responses to the auditory stimuli on nights one and three were analyzed to determine the probability of evoking a K-complex whether or not it was associated with a Vertex Sharp Wave and the probability of evoking a K-complex as the sole response to the stimulus (KC only). Difference scores were calculated for delta activity amplitude at the Fz Scalp site and K-complex probabilities. Pearson correlations were calculated for the change in delta activity amplitude verses change in probability of evoking a K-complex (both KC only and all K-complexes).

Results: Mean Delta amplitude increased from 19.85mV (± 9.6) to 23.53mV (± 6.1), t(5)=2.10, p<.05. The proportion of isolated evoked K-complexes (KC only) increased from 0.66 (± 0.12) to 0.75 (± 0.08) t(5)=2.81, p<.01. The proportion of total evoked K-complexes increased from 0.62 (± 0.11) to 0.70 (± 0.09) t(5)=3.46, p<.01. The increase in delta activity amplitude was significantly positively correlated with both increasing KC only values, r(5)=0.78, p<.05 and KC all values, r(5)=0.81, p<.05.

Conclusions: There is a strong positive relationship between changes in the probability of eliciting a K-complex and stage 2 delta activity amplitude (as measured by period amplitude analysis) caused by increases in sleep drive. This supports the notion that K-complexes and delta activity are indeed related. A parsimonious explanation of the data is that K-complexes are easier to elicit when the cortex is in a more synchronized state, as indicated by the increase in delta activity amplitude.

References:

Supported in part by: National Institutes of Alcohol Abuse & Alcoholism grants - AA-05965, AA-12388.

281.B

Measures of Cardiac Autonomic Activity During Sleep: Comparison of Impedance Cardiography, Spectral Analysis and Poincare Plots

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Introduction: The relationship between cardiac autonomic activity and sleep quality and quantity is emerging as an area of considerable research interest. Respiratory sinus arrhythmia, defined as power in the 0.15-0.40 Hz band derived from the spectral analysis of RR intervals (HF component), and the pre-ejection period (PEP), determined by impedance cardiography (ICG), are two of the best-validated measures of cardiac parasympathetic and sympathetic activity, respectively (1). The autocorrelation of interbeat intervals (rRR) was recently proposed as a novel index of cardiac sympathovagal balance, based on comparisons with spectral (low/high frequency ratio, LF/HF) and time-domain measures of heart rate variability (2). The present study examined the relationship between PEP, rRR, HF, LF and LF/HF during normal sleep in humans.

Methods: Twelve healthy male subjects (ages 18-36, BMI < 27 kg/m2) spent one night in the sleep laboratory with habitual bedtimes and wake-up times. Sleep was recorded with a computer-based polysomnography system (Alice-3, Respiromics) and scored manually using standard criteria. Portable ambulatory equipment was used to simultaneously monitor continuous heart rate and interbeat intervals (Mini-logger, Mini-Mitter Co.), systolic and diastolic blood pressure at 10-minute intervals (Accutrack II, Suntech Medical Instruments) and ICG profiles averaged every 30 seconds (AMS46, Vrije Universiteit, Netherlands). Correlations between ICG, spectral and Poincare plot measures (in 2-minute epochs) were calculated within each subject.

Results: The non-invasive monitoring of cardiac function, using ambulatory devices, produced reliable results with rare technical problems and data loss. There were significant changes in PEP, LF, HF, LH/HF and rRR during REM vs NREM sleep in all subjects. In addition, there was a clear increase of PEP length from sleep onset to morning awakening. Preliminary analysis showed correlations between rRR and LF (r=0.34), HF (r=-0.34) and LF/HF (r=0.33). Correlations of PEP with both HF (r=0.41) and LF (r=-0.42) were also detected. PEP and rRR were not strongly related (r=-0.15). All identified correlations between ICG, spectral and Poincare plot measures were in the expected direction. Ongoing analyses will examine the relationship of cardiac autonomic activity with sleep architecture and spectral EEG characteristics.

Conclusions: The results suggest that parasympathetic cardiac activity is a significant determinant of rRR, LF and LF/HF indices. Sympathetic cardiac activity was partially reflected by LF (but not rRR), however only PEP provided unique information on the global trend of the sympathetic input to the heart during overnight sleep. The use of more selec-
Free-Running Sleep Accumulates at a Uniform Rate

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Ohio State University

Introduction: Sleep deprivation induces recovery sleep that is longer and deeper than usual. This is a universal response in animals that are neurally capable of sleep and implies that sleep length is at least crudely regulated (Tobler & Borbely, 1990). Sleep deprivation of the degree imposed by investigators may, however, be uncommon in nature and in any case does not imply that the same recovery process participates in the day-to-day regulation of sleep.

Methods: Eighteen 20-35 year-old men and women lived in the Ohio State University Temporal Isolation Laboratory for 7 days. Polysomnography was conducted continuously, and the data were reduced to two states, sleep and wakefulness. In a space formed by the two variables, cumulative time awake and cumulative time asleep, each 7-day experiment was represented by a staircase-like trajectory or sleep process (Pollak et al, 1994). The stair risers and treads respectively represented circadian sleep and wake periods. To test the sleep processes for overall linearity, each was divided into 2, 3 or 4 equal segments, and a regression line was fitted to each segment.

Results: Apart from the circadian steps, the sleep processes gave the appearance of being linear, and the slopes of the regression lines fitted to segments of the processes showed no significant differences [F(1,16)=0.21, p=0.657 for 2 segments, F(3,48) =2.11, p= 0.111 for 4 segments]. Because the hypothesis that the processes were linear could not be rejected, a single slope or sleep rate could be used to characterize the accumulation of sleep by each subject.

Conclusions: Linearity of sleep processes suggests that the accumulation of sleep relative to wakefulness (sleep rate) is regulated in some way. Two possibilities suggest themselves: 1) A circadian pacemaker. By limiting sleep to specific times of the circadian day, a circadian pacemaker would maintain a relatively constant ratio of time asleep to time awake. As a result, sleep would accumulate at a constant rate. 2) An independent regulatory process that uses feedback. In this case, the more waking time that transpires, the longer that sleep lasts (or vice versa). Additional analyses are in progress that may enable us to ascribe the regulation of sleep rate to one of these mechanisms.

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Research supported by NIA AG11382 & NIH MO1RR00034.

283.C

Randomized, Double-Blind Clinical Trial, Controlled with Placebo, the Toxicology of Chronic Melatonin Treatment

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Introduction: Melatonin (N-acetyl-5-metoxytryptamine) is a secretory product of the pineal gland. The physiological significance of the nocturnal rise of melatonin levels is possibly related to several effects including a reduction of body temperature (Anton-Tay et al., 1971), alterations of brain monoamine levels (Vollbrath et al., 1981), and induction of somnolence (Penev and Zee, 1997). However, the safe therapeutic use of melatonin depends on its pharmacological effects and clinical and toxicological results. Objective: The purpose of the present study was to assess the toxicology of melatonin (10 mg), administered for 28 days.

Methods: 40 volunteers were randomly assigned to groups receiving either melatonin (N = 30) or placebo (N = 10) in a double-blind fashion. The following measurements were performed: polysomnography (PSG), laboratory examinations, including complete blood count, urinalysis, sodium, potassium, calcium and phosphate levels, total protein, albumin, blood glucose, triglycerides, total cholesterol and its fractions HDL, LDL and VLDL, urea, creatinine, uric acid, glutamic-oxaloacetic transaminase (GOT), glutamic-piruvate transaminase (GPT), bilirubin, alcaline phosphatase, gama-glutamic transaminase (GGT), T3, T4, TSH, LH/FSH, cortisol and melatonin serum concentrations. In addition, the Epworth Somnolence Scale (ESS), sleep diary (SD), and side effects (SE), were estimated.

Results: The two-way ANOVA did not reveal any statistical difference in the sleep latency, total sleep time, total time of slow wave sleep, time of stages 0, 2, 3 and 4 (either in min or in percentage of total recording time), latency to and total time of REM sleep, sleep efficiency and number of arousals. Stage 1 of sleep was the only parameter reduced in the melatonin group, compared to placebo [F(1,38) = 4.7; p = 0.037]. The values of laboratory examinations obtained on Visits 1 and 4, did not show any difference in basal levels between the groups (Student’s t test; p = 0.6). Serum melatonin concentrations on the melatonin group were statistically higher than that of placebo group throughout the study. In regard to the adverse effects, somnolence was present in 17, whereas headache was reported by 14 of the 30 volunteers who ingested melatonin.

Conclusions: The present study did not reveal, according to the parameters analyzed, any toxicological effect that might jeopardize the use of melatonin at a dose of 10 mg for the period of time utilized in this study.

References:

Financial support: Associação Fundo de Incentivo à Psicofarmacologia - AFIP
284.C

**Effect of Melatonin on Sleep, Considering Differents Criteria to Sleep Latency**

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**Introduction:** To observe the action of melatonin, it is essential to establish the real sleep start. The Rechtschaffen and Kales criteria, used by many specialists, may not reflect an effective consolidation of sleep, since 1.5 minute in stage 1 can already mean sleep start, even if after this period an awake occurs. Aiming at observing a probably hypnotic action of melatonin, we studied sleep latency in healthy volunteers who were taking melatonin, considering two criteria for sleep start: 10 minutes of uninterrupted sleep after the first stage 2 and 1.5 minute in stage 1.

**Methods:** Thirty healthy male volunteers were recruited (mean age 28.8±5.3 yr). Each volunteer underwent a first polysomnogram (PSG) after an adaptation night. On the follow day, 10 mg melatonin was administered for 28 days, and was ingested 1 h before sleep time. On the 14th day of treatment, it was performed the second PSG. On the 28th day, melatonin treatment ended. On the 35th day another PSG was performed. The sleep latency was defined considering two ways: 10 minutes of uninterrupted sleep, considering the period of sleep starting after the first stage 2, and the second criterion was considering sleep start the first 1.5 minute of stage 1 or the first stage 2, independent of the time of the first stage 1. Statistical analysis was performed using two-way analysis of variance with repeated measure in treatment factor.

**Results:** After the administration of melatonin we observed a significant decrease of sleep latency, considering 10 minutes of uninterrupted sleep, On the other hand we couldn’t observe no differences in sleep latency when we utilize the criterion of 1.5 minute to sleep onset.

**Conclusions:** This effect suggests that melatonin can exerts an hypnotic effect, considering a better sleep consolidation. These differences result has clinical implications, since the criteria of the concept of insomnia inicial depends of the real sleep start.

**References:**

This work was supported by Associacao Fundo de Incentivo a Psicofarmacologia(AFIP) and to Schering-Plough, Brazil.

285.C

**(S)-Zopiclone – An Isomerically Pure Non-Benzodiazepine Hypnotic Without Respiratory Depression**

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**Introduction:** (S)-Zopiclone – currently under development for use as a hypnotic – is the pharmacologically active isomer of racemic zopiclone, a non-benzodiazepine hypnotic. Respiratory depression is an undesired side effect of some sedative hypnotics. In order to establish the safety of (S)-zopiclone with respect to respiratory depression we studied its effects on ventilatory and mouth occlusion response to CO2

**Methods:** Fourteen healthy male volunteers, aged 20 to 43 years, participated in the study. Each subject was randomized to receive 3.0 mg (S)-zopiclone, 7.0 mg (S)-zopiclone, placebo, and 60 mg codeine according to one four sequences in double-blind crossover design. Ventilatory response to CO2 and mouth occlusion pressure (negative pressure generated in the mouthpiece during first 100 msec of occlusion during inspiration) were measured at pre-dose and 2, 4, and 6 hours post-dosing. The primary outcome variables were the slope of ventilatory response to CO2 and slope of mouth occlusion pressure response to CO2 (negative pressure generated in the mouthpiece during the first 100 msec of occlusion during inspiration). The analysis consisted of an ANCOVA with terms for sequence, subject within sequence, period, treatment, and covariate (the predose measurement).

**Results:** As expected, 60 mg of codeine significantly reduced ventilatory response to CO2 two hours post dosing (p<0.05). This effect was absent at 4 and 6 hours. Neither 3.0 mg nor 7.0 mg of (S)-zopiclone affected ventilatory response to CO2. Mouth occlusion pressure was unaffected by all treatments at all time points except for the lower dose of (S)-zopiclone at the 6 hour time point. This effect was small and clinically insignificant. There were no adverse events reported.

**Conclusions:** (S)-Zopiclone, at doses up to 7.0 mg – which represents at least twice the expected therapeutic dose – does not produce respiratory depression.

286.C

**Past-year Opiate Use and Sleep Problems in the General Population**

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**Introduction:** The few laboratory studies of the effects of opiates on sleep in healthy normals or abstinent addicts have found that opiates disrupt sleep and increase daytime sleepiness. Opiates usually are prescribed for pain relief. Since pain is disruptive of sleep, opiates in persons with pain may improve sleep. This report, part of a larger population-based study of daytime sleepiness, sleep, health problems, and drug use, assessed the relation of opiate use, sleep problems, and daytime sleepiness.

**Methods:** A random-digit-dial, computer assisted, survey of a representative sample of adults aged 18-65 yrs is being conducted. The survey assesses sleep habits, sleep problems, daytime sleepiness, health and psychiatric status, alcohol and drug use. The eligible household survey response rate is 70%. A sample of all respondents over a four-month period (7-00 to 10-00) was collected (n=213). Past-year use of vicodin, darvon, demerol, dilaudid, methadone, talwin, morphine, percodan, or tylenol with codeine was reported by 27% (n=57) of respondents, the same percent found in a one-year sample using the same methods. Given that sleep problems and sleepiness increase with age and female sex, an age- and sex-matched sub-sample (n=57) was drawn from the total sample, excluding opiate users, for comparison to the opiate users.

**Results:** Opiate users did not differ from the total sample in age [41.3 (12.8) vs 42.9 (12.7 yrs], sex (49% vs 42% female), race (70% vs 69.1% white), marital status, and education. Opiate users tended to differ (p<.06) in body mass index [29.1 (6.61) vs 27.3 (5.43)], had more total arthritis (21.1% vs 8.5%; X2=6.24, p<.01), and a trend toward more arthritis (p<.07). Compared to age- and sex-matched controls, opiate
users had more lifetime difficulty sleeping lasting more than a month ($X^2 = 5.72, p < 0.02$), took greater than an hour to fall asleep more often ($X^2 = 7.12, p < 0.01$), had more restlessness and twitching in the legs ($X^2 = 12.78, p < 0.001$), and worried more about sleep ($X^2 = 6.27, p < 0.02$). While sleeping similar on weekdays [6.2 (1.55) vs 6.3 (1.25) hrs], unlike controls they did not increase sleep time on weekends [6.7 (1.70) vs 7.5 (1.80) hrs; ($t = 2.13, p < 0.05$)]. They more often used alcohol ($X^2 = 33.68, p < 0.001$) and prescribed hypnotic medications ($X^2 = 7.07, p < 0.01$), but not OTCs, for sleep. They did not differ in use of other CNS-acting drugs, drugs of abuse, or in daily caffeine use. Opiate users also did not differ from controls in daytime sleepiness assessed with two different sleepiness scales, the Epworth Sleepiness Scale validated in clinical populations and the Daytime Sleepiness Scale validated in epidemiological populations.

Conclusions: Past-year opiate use was associated with greater prevalence of medical diseases, specifically migraine and arthritis, also greater insomnia and drug use to treat it, but not greater daytime sleepiness. It remains to determine whether the disease-associated pain or the opiate is the critical causal factor in these individual’s insomnia.

Study supported by NIH, NIAAA grant # R01-AA11264 and NIMH grant # R01-MH59338

287.C

The effect of Hypericum Perforatum (St. John’s Wort) on Salivary Cortisol, Subjective Stress and PSG Recordings.

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Introduction: Previous studies have suggested that oral doses of Hypericum extract have treatment effects rivaling those of classical antidepressants (1). However, aside from possible antidepressant action, Hypericum is gaining popularity as a sleep aid. Only one study to date has investigated the effects of Hypericum on human PSG recordings (2). Sharpley et al. (2) found REM sleep suppression, consistent with antidepressant action, after giving 0.9-1.8mg does to subjects 2hrs before retiring. The aim of the present study was to investigate measures of reported anxiety, salivary cortisol (a physiological stress indicator) and PSG variables after one week of Hypericum treatment compared to a placebo control.

Methods: Design:The design was placebo controlled repeated measures, where subjects participated in both the Hypericum and Placebo conditions. The experiment was also double blind where both the experimenter and subjects were unaware of treatment conditions. Counterbalancing of the order of conditions was conducted by a third party. There was a washout period of one week between conditions. Subjects: 4 males and 8 females aged 18-46 years (2 females did not complete the STAI or attend the PSG session) Apparatus: PSG - La Trobe University Sleep Laboratory. Anxiety Measure - State-trait Anxiety Inventory (STAI).Salivary Cortisol - Collected in Salivettes (Sarstedt, Germany) and analyzed using RIA technique (Ortho- Clinical Diagnostics, UK).Treatment - 2400mg Hypericum/1980mcg Hypercin (Hypericum 1200, Kordel, Australia)Placebo - Crushed placebo tablets in non-transparent gelatin capsules (Fawns & McAllan, Australia) Procedure:During weeks 1 and 3 - Subjects took either Hypericum or Placebo each day before 9am. They also collected their own saliva samples, twice daily (before 9am and after 9pm).On the last week of weeks 1 and 3 - Subjects came to the laboratory for PSG and completed the STAI before lights out.

Results: No significant differences were found between the Hypericum (H) and Placebo (P) conditions for: TAI scores: H (M=28.3, SD=3.9) P (M=27.3, SD=6.3); t(9)=0.69, p>0.05 SAI scores: H (M=25.4, SD=5.1) P (M=28.6, SD=9.7); t(9)=1.12, p>0.05 REM latency: H (M=110.6 min, SD=47.1) P (M=107.2min, SD=60.2); t(9)=1.72, p>0.05 REM time: H (M=85.4 min, SD=54.3) P (M=64.8 min, SD=27.7); t(9)=1.72, p>0.05 Sleep time: H (M=408.6 min, SD=67.6) P (M=401min, SD=73.9); t(9)=0.360, p>0.05 Morning salivary cortisol: H (M=25.5nmol/L, SD=7.3) P (M=23.3nmol/L, SD=8.1); t(11)=0.824, p>0.05 However, significantly lower evening cortisol levels were found in the Hypericum condition (M=3.9nmol/L, SD=1.2) compared to placebo (M=5.7nmol/L, SD=2.8); t(11)=2.15, p<0.05.

Conclusions: Antidepressant effects of Hypericum on anxiety (1) and REM sleep (2) reported previously were not observed in the present study. This suggests that Hypericum is no more effective than placebo on several measures after one week of treatment. The preliminary result regarding evening cortisol levels requires further investigation as it suggests that previously observed antidepressant effects may be due to a regulatory action of Hypericum on the Hypothalamic-Pituitary-Adrenal axis (3).


288.C

Driving 5.5 hours after taking Zolpidem or Temazepam: A Driving Simulator Study

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Introduction: It is not rare to find a situation where a person drives a car in the morning after taking a sleeping pill after midnight on the preceding night. We have started to study in a real life like condition what is the residual effect of zolpidem 10mg and temazepam 20 mg on driving performance in the morning 5.5 hours after drug intake.

Methods: The inclusion criteria are:1) woman, aged 35-60 years, 2) driving licence over 5 years and driving over 5000 km annually, 3) difficulty initiating or maintaining sleep or non-restorative sleep for at least 1 month, 4) sleep disturbance affecting social, occupational or other important areas of daytime functioning 5) subjective total sleep time 3-6 hours per night, and 6) at least one of the following criteria:a. sleep latency > 30 minb. over 3 awakenings per night c. WASO > 30 min on average. The exclusion criteria are. 1) Organic sleep disorder, 2) Abuse of alcohol or drugs, 3) Any chronic illness as well as pregnancy, hypersensitivity to the study drugs, 4) Use of hypnotics over 12 DDD/month, 5) Known history of travel sickness or “ simulator sickness”, 6) SCL-90R test the general symptom index (GSI) score < 70 , 7) Clinically significant abnormalities in the medical examination.The subjects come to the sleep laboratory four times at 9 p.m. and are kept awake until 2 a.m. They are awakened at 07:00 the next morning, i.e. after 5 h of sleep. During the first (baseline) night the subjects receive no medication. On the three other nights a pill of placebo or 10mg zolpidem or 20 mg temazepam is given at 2:00 am with 100 ml water. The interval between each night is 3-14 days. The following morning, at 07:30, a driving simulator test is driven with a STISIM simulator built in a real personal car.
Reaction times (RT), lane position deviation (LPD), speed deviation and number of errors and simulator accidents are computed. The test driving tests consists of a 90km long foggy highway drive. After the drive neuropsychological tests are given (Fepsy, Het Instituut voor Epilepsiebestrijding).

**Results:** In a preliminary study 14 women, suffering from non-organic insomnia, participated in the study. The mean age of the women has been 49.4 years (SD 7.5, range 35 – 58) and the mean BMI 25.1 kgm-2 ( SD 4.2, range 20 – 34). As compared to placebo, neither zolpidem, nor temazepam 20 mg had a statistically significant deteriorant effect on driving performance. There have been some differences in the following measures: A. Mean time to collision (MTTC): MTTC was longest after zolpidem (same as in baseline) and shortest (worst) after temazepam. B. There was a trend towards shorter reaction times after use of zolpidem. The longest reaction time were recorded during baseline and placebo period. C. In the delayed memory recall best results were obtained after taking zolpidem.

**Conclusions:** We are continuing the study and the final results of this study will be reported in the APSS congress in 2001.

289.C

**Daytime Acute Tryptophan Depletion Delays REM Sleep Onset in Healthy Subjects.**

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**Introduction:** Serotonergic neurotransmission is involved in the regulation of sleep. To test the effect of a daytime serotonin deficiency on sleep, an acute deficiency in the serotonin precursor tryptophan was induced in healthy volunteers and their nighttime sleep was studied.

**Methods:** After a 48-h low-protein diet, 17 subjects received either a tryptophan-free mixture of amino acids or a placebo at 10:30 AM, in a randomized double-blind cross-over design. Sleep was recorded from 11:00 PM to 7:30 AM. Mood, plasma free tryptophan levels and urinary excretion of the melatonin metabolite sulfatoxy-melatonin were measured before and after tryptophan depletion (ATD) and placebo.

**Table 1**

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<tbody>
<tr>
<td>Total sleep period (min)</td>
<td>453 ± 8</td>
<td>457 ± 7</td>
</tr>
<tr>
<td></td>
<td>(386-522)</td>
<td>(393-505)</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>426 ± 12</td>
<td>425 ± 10</td>
</tr>
<tr>
<td></td>
<td>(312-510)</td>
<td>(342-492)</td>
</tr>
<tr>
<td>Wakefulness after sleep onset (min)</td>
<td>27 ± 10</td>
<td>31 ± 7</td>
</tr>
<tr>
<td></td>
<td>(0-128)</td>
<td>(1-83)</td>
</tr>
<tr>
<td>Latency (min)</td>
<td>16 ± 3</td>
<td>12 ± 7</td>
</tr>
<tr>
<td></td>
<td>(4-43)</td>
<td>(1-31)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>97 ± 6</td>
<td>123 ± 9**</td>
</tr>
<tr>
<td></td>
<td>(69-150)</td>
<td>(70-184)</td>
</tr>
<tr>
<td>Sleep duration (min)</td>
<td>288 ± 12</td>
<td>234 ± 12</td>
</tr>
<tr>
<td></td>
<td>(141-367)</td>
<td>(151-310)</td>
</tr>
<tr>
<td>Stages 3-4</td>
<td>96 ± 9</td>
<td>96 ± 10</td>
</tr>
<tr>
<td></td>
<td>(15-157)</td>
<td>(22-160)</td>
</tr>
<tr>
<td>REM sleep</td>
<td>104 ± 7</td>
<td>95 ± 6</td>
</tr>
<tr>
<td></td>
<td>(41-158)</td>
<td>(44-143)</td>
</tr>
<tr>
<td>Arousal index (events/h)</td>
<td>4.2 ± 0.4</td>
<td>6.3 ± 0.9*</td>
</tr>
<tr>
<td></td>
<td>(1.4-7.5)</td>
<td>(2-18)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; the range is indicated in italics; *p<0.05, ** p=0.007.

**Results:** Five hours after intake of the amino acid mixture, free plasma tryptophan levels were 77 % of the control levels, and were still 41 %, after 11 hours. Urinary sulfatoxy-melatonin excretion and mood were unaffected by ATD, but REM sleep latency increased by 26 min, sleep fragmentation 58%, and REM density of the first REM sleep period doubled.

**Conclusions:** The results suggest that the serotonin control of REM sleep latency is time-dependent.

Research supported by Grant from PHRC AOA 94057 and EMUL 930902

290.C

**Effect of Sustained Caffeine on Core Body Temperature During 88 Hours of Sustained Wakefulness.**

Rogers NL, Price NJ, Szuba MP, Van Dongen HP, Dinges DF
Division of Sleep and Chronobiology, Department of Psychiatry; and Center for Sleep and Respiratory Neurobiology, University of Pennsylvania School of Medicine, Philadelphia, PA

**Introduction:** Several studies have examined the effectiveness of caffeine administration as a countermeasure for the increased fatigue and decreased performance associated with extended periods of sustained wakefulness [1, 2]. Acute administration of caffeine during these protocols has been reported to increase performance and alertness levels. In addition, significant hyperthermic effects associated with acute caffeine administration have also been reported [1, 2]. The aim of this analysis was to understand the dynamics of the temporal relationship between elevated plasma caffeine levels, following sustained administration of oral caffeine, and the subsequent changes on core body temperature and neurobehavioral functioning.

**Methods:** Twenty-one male subjects (aged 21-47) lived in the sleep laboratory, with light levels <50 lux, for 10 days (9 nights). Following 3 baseline days, subjects were required to remain awake for 88 hours, followed by 3 recovery nights. During the final 66 hours of sustained wakefulness subjects were assigned to receive either oral caffeine (0.3mg/kg/hr; N=12) or placebo (N=9) at hourly intervals, in a randomized, double-blind fashion. The initial administration occurred 22 hours after the commencement of the sustained wakefulness period. During the wake period core (rectal) body temperature was measured continuously, and blood samples were collected at 90-minute intervals via an indwelling canula.

**Results:** In the caffeine group a steady increase in plasma caffeine levels was evident from within 3.25 hours of the first administration, and continued increasing until reaching a plateau after approximately 29 hours of administration. In addition, a coincident elevation in core body temperature was observed in the caffeine group, relative to the placebo group (p<0.001). The magnitude of the temperature elevation was greatest during the first few hours of elevated plasma caffeine levels (mean = 0.51 ± 0.02°C). This hyperthermic effect endured for approximately 24 hours (i.e. from approximately 0800h). Corresponding with the increase in core temperature was an improvement in neurobehavioral performance, corresponding with the rising portion of the plasma caffeine profile [3].

**Conclusions:** The activating effects of caffeine, including increased alertness and physical activity, may underlie this elevation in core temperature. Alternatively, this hyperthermic effect may represent a possible mechanism mediating the increased alertness and performance levels associated with the ingestion of caffeine. Further analyses are currently underway to investigate a potential causal relationship between enhanced performance capabilities in the caffeine group relative to the
References:

Research supported by AFOSR grant F49620-1-0388 and NIH grants M01-RR00040 and K23-AG-00867-03

291.C

Habitual Moderate Caffeine Use: MSLT and Vigilance Performance

Burdvali E, Richardson G, Roehrs T, Roth T

Henry Ford Hospital Sleep Center, Detroit, MI

Introduction: Laboratory studies of acute administration of caffeine have clearly shown that low doses of caffeine increase MSLT scores and improve performance, particularly sustained vigilance performance. The question arises as to how habitual moderate caffeine use affects MSLT scores and vigilance performance.

Methods: One hundred and four healthy men, aged 18-40 yrs, being screened for entry to a pharmaceutical study, formed the study population. Three groups were designated according to their self-reported caffeine use: group 1: 0-4 caffeine drinks per week, group 2: 5-9 caffeine drinks per week, group 3: 10 or more caffeine drinks per week. The mean age of the groups was not significantly different: group 1: 25 (5.8), group 2: 23 (3.9), and group 3: 25 (4.8) yrs. Participants reported being normal sleepers with consistent sleep schedules and no complaints of daytime sleepiness. They were free of medical and psychiatric diseases, had no history of alcohol or drug abuse, and no current use of central nervous system medications. Caffeine consumption was prohibited within 24 hrs before the MSLT. Participants viewed 6-minute dream-like segments (Heaven Can Wait) following REMS awakenings. Subsequent data collection and treatment was the same as that of the companion abstract (deriving distinct storyboard components from REMS). Results from Real Dreams) shows recall of components of a dream to be a) incomplete following REMS awakening and b) changed when recalled again over the course of a month. However in that research the experimenters had no direct access to the various original dreams of the subjects.

Methods: To compensate for this, 15 (11 usable) subjects viewed a 6-minute dream-like segment of Heaven Can Wait following awakening from REMS. Subsequent data collection and treatment was the same as that of the companion abstract (deriving distinct storyboard components resulted in 87.1% agreement between two of us) with the addition of deriving a storyboard from the original “dream” (86.4% agreement).

Results: Significant values (p< .05) indicated by *. The mean recall was 64.3% (± one standard deviation of 12.7%) of the composite (F(3,30)=.32, p=.617). The REM awakening recall intervals contained a mean of 67.3% (±22.2%) of the composite components (t=-.889* compared to perfect recall). REM awakening recall intervals contained a mean of 67.3% (±22.2%) of the composite components (t=-.889* compared to perfect recall). REM awakening recall intervals contained a mean of 67.3% (±22.2%) of the composite components (t=-.889* compared to perfect recall). REM awakening recall intervals contained a mean of 67.3% (±22.2%) of the composite components (t=-.889* compared to perfect recall).

Table 1

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>1:0-4 caffeine drinks/week</th>
<th>2: 5-9 caffeine drinks/week</th>
<th>3: 10 or more caffeine drinks/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSLT</td>
<td>8.9 (4.5)</td>
<td>10.5 (4.9)</td>
<td>14.0 (2.8)</td>
</tr>
<tr>
<td>VIG. MSTM</td>
<td>2.25 (2.98)</td>
<td>1.43 (1.77)</td>
<td>0.80 (0.83)</td>
</tr>
<tr>
<td>VIG. RT</td>
<td>331.3 (185.3)</td>
<td>285.2 (107.3)</td>
<td>342.0 (189.1)</td>
</tr>
</tbody>
</table>

Mean (SD)
VIG. MSTM: vigilance missed stimuli
VIG. RT: vigilance reaction time

Conclusions: Habitual moderate caffeine use was associated with increased MSLT sleep latencies and improved vigilance performance. The acute 24 hr caffeine abstinence during the day of the MSLT and performance assessment did not impair the MSLT and performance of the higher intake group relative to the low intake group. It remains to be determined what other factors might contribute to the alertness and vigilance of the habitual moderate caffeine users.

Research supported by NIH, NIDA grant # R01-DA11448 and NIMH grant # R01-MH59338

292.D

Deficiencies of Dream Recall: II. Results from a “Synthetic Dream”

Moorcroft WH, Cenefelt E, Wronekiewicz C, Ondrashek S, Hill J, Backstrom E, Stage N, Koening L, Whitehead D, Sweeney A

Luther College

Introduction: A companion abstract (Deficiencies of Dream Recall: I. Results from Real Dreams) shows recall of components of a dream to be a) incomplete following REMS awakening and b) changed when recalled again over the course of a month. However in that research the experimenters had no direct access to the various original dreams of the subjects.

Methods: To compensate for this, 15 (11 usable) subjects viewed a 6-minute dream-like segment of Heaven Can Wait following awakening from REMS. Subsequent data collection and treatment was the same as that of the companion abstract (deriving distinct storyboard components resulted in 87.1% agreement between two of us) with the addition of deriving a storyboard from the original “dream” (86.4% agreement).
a subsequent recall (F(1,8)=1.058; t=-4.719* compared to perfect retention and t=11.097* compared to no retention). A mean of 10.3% (±10.8%) the composite recall did not come from the original dream (t=3.148* compared to 0%) and the average recall of each subject was missing at least 61.9% (±13.3%) of the original “dream” (F(3,40)=1.903; t=14.718* compared to nothing missing). Of the elements added to later recalls, an average of 21.6% (±32.2%) did not come from the original “dream” (F(2,21)=2.22; t=2.06* compared to nothing from the original).

Conclusions: These results resemble those presented in the companion abstract in showing: a) it is unlikely that most dream components are recalled, even following REMS awakening; b) additionally there are significant changes in the recall of a dream with the passage of time; c) there is a great deal of individual difference in overall dream recall accuracy. Finally, these results show that some components in a dream recall are not from the actual dream.

References:

293.D

Dreams: Correlates of the Contextualizing Image

Hartmann EL,1,2 Zborowski M1
(1) Tufts University School of Medicine, (2) Newton-Wellesley Hospital, (3) State University of New York College at Buffalo

Introduction: The contextualizing Image or Central Image (CI) is a powerful central image in a dream which may “contextualize” or picture the dominant emotion of the dreamer. Thus, the dream image “I was overwhelmed by a tidal wave” contextualizes the emotions of terror and helplessness in people who have recently experienced severe trauma. A reliable scoring system for CI intensity - the CI score - has been developed. Raters assign as score from 0 to 3 (half points are allowed), where 0 is no CI and 3 is an unusually powerful or intense CI. The scorer is then asked to choose the emotion most likely to be pictured by the CI from a list of 18 emotions. The CI score is significantly higher in dreams than in daydreams (1), in content from REM sleep than in content from NREM sleep or waking (2), and in periods immediately after trauma than other times (3). This study relates CI scores to a history of abuse and to personality measures.

Methods: Sample 1 consisted of 286 undergraduate students (66 M, 214 F; 6 gender unknown) age 20.5 ± 4.4 years. Sample 2 consisted of 205 students (47M, 158F) age 21.6 ± 5.0. Each student wrote down a “most recent dream” and in addition filled out a demographic questionnaire, the Boundary Questionnaire, and the Bell Object Relations and Reality Testing Inventory. Dreams were rated for CI scores by several independent sets of scorers, blind as to any knowledge about the students. Inter-rater reliabilities were between r = .60 and r = .80.

Results: Among many significant correlations, only a few especially interesting ones replicable between samples are reported here. CI scores were significantly higher in students who reported any abuse than in students who did not (Table 1). In both samples this involved a comparison between students who had checked off one or more of six questions asking about any physical or sexual abuse in childhood, in adolescence, or more recently. In both samples higher CI scores were found in subjects with higher SumBound scores indicating thin boundaries (Table 2). CI scores were positively correlated in both samples with “insecure attachment” on the Bell Object Relations scale. Sample 1: r = .12 (p < .05) Sample 2: r = .17 (p < .05).

Conclusions: These results, demonstrating increased CI scores in students reporting any abuse, together with previous results finding higher CI scores after trauma, suggest that the CI score in the dream is related to emotional activation or arousal. Higher CI scores in students with thin boundaries are consistent with this since in people with thin boundaries “everything gets through,” and these people are more in touch with their emotions. The higher CI scores related to “insecure attachment” suggests that interpersonal vulnerability may also contribute to the emotional arousal.

References:
(2) 2. Hartmann E, Stickgold R. Contextualizing images in content obtained from different sleep and waking states. Sleep 2000; 23S:A172.

294.D

Emotions Pictured by the Dream: an Examination of Emotions Contextualized in Dreams

Hartmann EL,1,2 Zborowski M1, Kunzendorf R1
(1) Tufts University School of Medicine, (2) Newton-Wellesley Hospital, (3) State University of New York College at Buffalo, (4) University of Massachusetts at Lowell

Introduction: We have proposed that a dream - especially the central image of a dream - pictures or “contextualizes” the dominant emotion of the dreamer. For instance, the dream “I was overwhelmed by a tidal wave” pictures the emotions of terror and helplessness in someone who

References:
(2) 2. Hartmann E, Stickgold R. Contextualizing images in content obtained from different sleep and waking states. Sleep 2000; 23S:A172.

Table 1

| CI Scores Related to Reports of Abuse |
| Students Reporting Abuse | Students Reporting no Abuse | t  | p    |
| Sample 1 (N=52) | (N=228) | 1.12 ± 1.18 | 0.65 ± 0.97 | 2.97 < .01 |
| Sample 2 (N=50) | (N=155) | 1.12 ± 1.25 | 0.61 ± 1.03 | 2.11 < .05 |

Table 2

| CI Scores and SumBound (SB) |
| Subjects with CIs ≥ 2.0 | Subjects with CIs < 2.0 | t  | p    |
| Sample 1 (N=52) | (N=224) | SB = 306 ± 46 | SB = 275 ± 41 | 4.87 < .001 |
| Sample 2 (N=50) | (N=155) | SB = 288 ± 43 | SB = 273 ± 42 | 2.08 < .05 |
has just experienced a traumatic event. The tidal wave is called the central or contextualizing image (CI) (1). A number of studies suggest that the CI score - measuring the intensity of the CI - is related to the emotional activation or arousal of the dreamer (2). The present report deals with the specific emotions judged to be pictured by the dream.

Methods: Groups 1-5 were five different groups of students (total N = 639). Each student among other things wrote down one “most recent dream.” Group 6 consisted of 14 students wearing a “Nightcap device” (2) Hartmann E, Zborowski M. Dreams: correlates of the contextualizing image. Sleep 2001; 24S (this volume).

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>N (Ss)</th>
<th>Emos 1-2</th>
<th>Emos 3-10</th>
<th>Emos 11-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student group 1</td>
<td>286</td>
<td>41 (37%)</td>
<td>39 (35%)</td>
<td>32 (29%)</td>
</tr>
<tr>
<td>Student group 2</td>
<td>64</td>
<td>17 (53%)</td>
<td>14 (44%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Student group 3</td>
<td>205</td>
<td>43 (68%)</td>
<td>14 (22%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Student group 4</td>
<td>40</td>
<td>7 (32%)</td>
<td>8 (36%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Student group 5</td>
<td>44</td>
<td>14 (52%)</td>
<td>6 (22%)</td>
<td>7 (26%)</td>
</tr>
<tr>
<td>All students</td>
<td>639</td>
<td>111 (47%)</td>
<td>77 (32%)</td>
<td>49 (21%)</td>
</tr>
</tbody>
</table>

Results: Tables 1 and 2 present a summary of results. First of all, the two powerful negative emotions (group 1) are the most common - found in 47% of students’ most recent dreams. Subjects after trauma have a very similar distribution of emotions. There was a strong shift only in two subjects judged to have had the most severe trauma; in these cases group 1 emotions accounted for 77% of the total. The recent dreams of the “artists and professionals” were judged as picturing more positive and less negative emotions than typical students. Content obtained from REM and NREM sleep (group 6, not in table 1) showed much less of the strong negative emotions than the “most recent dream” reports.

Conclusions: This preliminary study is the first look at what emotions are judged as contextualized (pictured) by dreams, allowing a broad survey of a great deal of data. The clearest overall conclusion is that the negative emotions and especially the strong negative emotions fear/terror and helplessness/vulnerability are judged to be pictured more frequently than other emotions. Comparing this study with previous ones, it is also of interest that the CI score - measuring the frequency or intensity of the CI - differentiates groups such as trauma vs. no trauma, and abuse vs. no abuse more clearly than does the type of emotion judged to be pictured by the dream.

References:
(2) Hartmann E, Zborowski M. Dreams: correlates of the contextualizing image. Sleep 2001; 24S (this volume).

295.D

The Biology of Dream Formation: A Review and Critique

Kramer M
Dept. of Psychiatry, NYU, School of Medicine

Introduction: Two biological views of the formation of dreams have been presented and will be reviewed and critiqued. One, by Hobson, is a bottom up view in which stimulation initiated in the brain stem (Pons) during REM Sleep transmits, via ponto-geniculo-occipital (P.G.O.) spikes, random stimuli to the cortex which passively elaborates it as the dream. An isomorphic relationship is said to exist between the P.G.O. spikes, random stimuli to the cortex which passively elaborates it as the dream. An isomorphic relationship is said to exist between the P.G.O. spikes and the content of the dream. There is during REM sleep a shift from amine dominance (N.E. AND 5-H.T) to a holinergic dominance (A2). The model for dreaming is dementia i.e., poor memory, hallucinations, delusions, and disorientation and disorganization. Solms offers a top down view of dream formation. In response to any arousing stimuli, the ventral-temporal Nuclei of Tsai, an appetitive, seeking, desiring and sometimes two trained scorers, who assigned a CI score, and then whenever a CI was scored were asked to choose one emotion from a list of 18, which they thought might be pictured or contextualized by the image. For this report the emotions are divided into three groups: Emotions 1 and 2 (fear/terror and helplessness/vulnerability), emotions 3-10 (other negative emotions) and emotions 11-18 (positive emotions). In one study where inter-rater agreement could be examined, there was exact agreement as to which one of the 18 emotions was involved in 45% of cases. When the emotions were classified into three groups there was agreement between scorers in 80% of cases.

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>N (Ss)</th>
<th>Emos 1-2</th>
<th>Emos 3-10</th>
<th>Emos 11-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma Group: First five d’s w/CIs for each S</td>
<td>10</td>
<td>50 (40%)</td>
<td>17 (34%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Two most severe Ss</td>
<td>2</td>
<td>13 (77%)</td>
<td>3 (23%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Artists and Professionals</td>
<td>76</td>
<td>76 (100%)</td>
<td>10 (22%)</td>
<td>25 (55%)</td>
</tr>
<tr>
<td>All Ds, all groups</td>
<td>738</td>
<td>1401 (100%)</td>
<td>217.5 (28%)</td>
<td>301 (39%)</td>
</tr>
</tbody>
</table>
dreaming which is not directly measurable in humans. And they do not account for the narrative aspects of dreaming. The specific critique of the Activation-Synthesis hypothesis of dreaming includes: 1) the recognition of a limited definition of dreaming; 2) doubt that dementia is an appropriate model for dreaming; 3) recognition that REM sleep and the dream experience are not co-extensive; and 4) the work showing that dreaming is not isomorphic with REM sleep. The critique of the Neuropsychological brain lesion theory (see Hobson and Pace-Schott) includes that 1) not all frontal leucotomies caused dream cessation; 2) retrospective failure in dream recall is not an adequate test of non-dreaming, while REM awakening is; 3) lesion analysis is a limited technique as function returns; 4) Dopamine does not change across non-REM and REM. Dopamine drugs are both dream inhibitors and enhancers.

Conclusions: Biological theories of dreaming do not address the content, meaning, or function of dreaming. They remain incomplete, speculative, and reductive.

References:

296.D

The Relation Between Trait Anxiety and Dream Patterns of Healthy Volunteers.

Sartori VA, Leite JR, Pinto J Jr LR, Taflak S
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Introduction: Since earliest historical records, humans have considered their dreams to be a significance source of self-awareness. Initially came the metaphysical theories that tried to give meaning to dreams, and hence considered them as premonitions or prophecies. However, it was at the turning of the century, with the works of Freud which defined dreams as a manifestation of unconscious desires (1), that dreams became an important issue for science, thereby opening up the way for other scientists to point out that there was a continuity between dreams and waking life. Such facts have been found frequently in anxiety dreams of individuals with anxiety disorders (2). So, taking in consideration the importance that dreams represent for an individual’s life, as well as their use for the psychotherapeutic process, this study has been conducted to verify the relationship between traits anxiety and the dream patterns of healthy volunteers.

Methods: Thirty-two healthy volunteers of both sexes were selected and submitted to the following evaluation instruments: a Dream Questionnaire to evaluate emerging dream patterns; the State Trait Anxiety Inventory (STAI) to verify the degree of trait anxiety and a Dream Diary to compare findings with the Dream Questionnaire.

Results: The volunteers with high trait anxiety reported bad and frightening dreams as well bizarre ones. On the other hand, volunteers with low trait anxiety described good and joyful dreams which were also meaningful in essence. Such findings corroborated the data found in the Dream Diary.

Conclusions: The Dream Questionnaire used for this study enabled the researcher to define a dream profile, which by itself was related to degree of trait anxiety of the sample studied, and that such practice could be directed for evaluation in the psychotherapeutic process and for the treatment of anxiety.

References:

Financial support: Associacao Fundo de Incentivo a Psicofarmacologia (AFIP) and CAPES.

297.D

Middle Ear Muscle Activity (MEMA) during sleep: A relationship with EEG arousal rather than sleep mentation?

Brooks JL, Coleman GJ, Sasse A, Conduit R
(1) Department of Psychology, Monash University, Victoria, Australia, (2) Sleep Disordered Breathing Unit, South Eastern Private Hospital, Victoria, Australia, (3) School of Psychological Science, La Trobe University, Victoria, Australia

Introduction: Ponto-Geniculo-Occipital (PGO) waves are claimed to provide pseudosensory stimulation of the cortex during sleep producing the subjective experience of dreaming (1). However, the direct measurement of PGO waves in humans is not yet possible. This has led to the investigation of non-invasive analogue measures of PGO activity such as MEMA (2). MEMA was initially related to greater recall of auditory imagery (2). However, later work failed to replicate this result, but did find a relationship with dream bizarreness (2). Such findings have been cited as evidence supporting a PGO-dream relationship (1). However, an alternative explanation could be that such activity facilitates sleep mentation reporting through an arousal effect (3). The aim of the present study was to investigate sleep mentation from MEMA and nonMEMA Stage 2 sleep. In addition, the amount alpha (8-12Hz) and beta (>13Hz) EEG arousal pre- and post-MEMA was analyzed.

Methods: Subjects: Seven females and nine males aged 21-31 years. Apparatus: Subjects were connected for standard polysomnographic recordings. EMG electrodes were placed at chin muscle (mentalis) and on the right and left sides of the larynx (sternocleidomastoid) muscle, in order to provide a sensitive measure of EMG artifact of MEMA recordings. MEMA was measured using a modified pressure transducer technique. Procedure: Subjects were awakened from Stage 2 sleep in the following order: W1-MEMA, W2-noMEMA, W3-MEMA, W4-noMEMA. In the MEMA condition, subjects were awakened 15 seconds after a MEMA event. In the subsequent noMEMA event, subjects were awakened at the same time into stage 2 sleep as the previous experimental condition, with no MEMA present.

Results: The average incidence of MEMA across the seventeen subjects for each sleep stage is shown in Table 1. REM and Stage 2 clearly showed the highest frequency of MEMA (Friedman Chi-square(4) = 35.12, p<0.001). EEG arousal after MEMA events was significantly longer in duration (M=1.22sec, SD=1.21sec) than the arousal observed before MEMA (M=0.36 sec, SD=0.64sec; t(15)=-4.35, p<0.001). The mentation reports collected were classified by a blind rater as Recall or No-Recall. A Recall report was classified as any report where the subject recalled imagery or thoughts prior to being awakened. The number of Recall reports and average Total Word Count (TWC) across conditions is shown in Table 2. Comparing the first MEMA and second noMEMA condition, no significant differences in the number of recall reports (Sign test, p=0.22) or TWC (Wilcoxon Z=0.56, p=0.58) were observed. Additionally, the third MEMA and second noMEMA condition showed no significant differences in the number of recall reports (Sign test, p=1.0).
or TWC (Wilcoxon Z=0.42, p=0.68).

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>MEMA</th>
<th>NoMEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Stage 2</td>
<td>6.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>REM</td>
<td>6.2</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Recall %</th>
<th>MEMA</th>
<th>NoMEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>W1</td>
<td>70% (n=10)</td>
<td>65% (n=10)</td>
</tr>
<tr>
<td>W2</td>
<td>30% (n=10)</td>
<td>50% (n=10)</td>
</tr>
<tr>
<td>W3</td>
<td>83% (n=10)</td>
<td>63% (n=10)</td>
</tr>
<tr>
<td>W4</td>
<td>7.9</td>
<td>5.5</td>
</tr>
<tr>
<td>TWC</td>
<td>5.8</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Conclusions: These findings are consistent with proposals that PGO-related brainstem events are sometimes found to be related to dream recall through associated cortical arousal rather than signaling pseudo-dorsal PGO dream imagery generation (3).

References:

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299.D

The Possible Relationship between EEG Sleep Spectral Power and Dream Recall

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Introduction: Although, it seems difficult to assign one single function to a given type of oscillatory activity, it has been shown that EEG activity can be correlated with retrieving information from long or short-term memory. In order to better understand the processes of dream recall, we concentrated specifically on the contribution of EEG activity (range 11-45 Hz) to the dream recall. This preliminary experiment, attempted to quantify the correlations during REM sleep, between sigma (11-15 Hz), beta (15-35 Hz) and gamma (35-45 Hz) on one hand and the number of informations in the dream report on the other hand.

Methods: Ten normal female students (age 20-25) were studied for two non-consecutive nights in the sleep laboratory. For each subject, the electroencephalogram (EEG) signal recorded between C4-A1, C3-A2, PZ-O2, was digitized and power spectra were computed by fast fourier transform, for consecutive 4-second epochs over a frequency range 0.5-45 Hz. Subjects were awakened 10 minutes after the onset of the second REM sleep episode. They were asked to write down, with as many details as possible, any thought that they had before awakening. Then, they could continue their night normally. The number of informations in the dream report was scored independently by two different judges, according to a specific scale deviding the informations between different categories.2 Pearson Correlations test was then used between these two parameters (number of informations and EEG frequency bands).

Results: The most evident result so far was the significant correlation between the sigma band and the high number of informations contained in the dream report : r = .68 with C3-A2, r = .67 with C4-A1 and r = .71 with PZ-O2 (p < 0.05). There was no significant correlation between the total number of informations and the beta nor the gamma band.

Conclusions: Although alpha activity has been linked with long-term
memory performance, our results did not show a significant correlation between alpha band and dream recall. However, considering that the sigma band overlaps the upper alpha band, this preliminary experiment partially confirms previous findings showing positive correlation between upper alpha and long-term memory. The time course of all frequency bands between sleep onset to the experimental arousal is still under investigation.

References:

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300.D

Thoughts and Hallucinations in NREM and REM Sleep Across the Night

Fosse R, Stickgold R, Hobson JA
Harvard Medical Shool

Introduction: It is not well understood how higher cognitive, or “executive” functioning fare in the face of the rise in hallucinatory activity during NREM and REM sleep. We have recently found internal deliberations (thoughts) and endogenous percepts (hallucinations) to vary in an opposite, reciprocal way between waking, sleep onset, NREM, and REM (Fosse, Stickgold, & Hobson, 2001). Here we ask whether the reciprocity in thoughts and hallucinations holds equally strongly for each successive NREM – REM cycle of the night.

Methods: The participants were 16 healthy adults (age 18-22, 8 female, 8 male) who were monitored by the Nightcap system (Ajilore et al., 1995) in their home over 14 nights. 229 REM reports and 165 NREM reports were gathered and scored for the occurrence of thoughts and hallucinations. Thoughts were defined as any continued mental effort or occupation, including contemplating, brooding, reflecting, and evaluating as well as attempts to decide, figure out, grasp, and plan. Included in the hallucination category were internally generated (endogenous) sensations in all sensorimotor modalities. Statistical analyses were carried out on average subject scores in NREM and REM for successive NREM-REM cycles. These cycles were defined as follows: cycle 1 (not used), from 40-130 min after sleep onset; cycle 2, 130-225 min; cycle 3, 225-315 min; cycle 4, 315-405 min; and cycle 5, above 405 min.

Results: Hallucinations were more frequent in REM than in NREM for the second (paired t-test, t(10) = 6.9, p < .0001), third (t(13) = 4.5, p = .003), fourth (t(12) = 2.9, p = .007), and fifth cycles (t(11)= 2.3, p = .022; Fig. 1). Thoughts were less prevalent in REM than in NREM in the second (t(10) = 2.2, p = .025) and the third cycles (t(13) = 2.5, p = .013), but did not differ between stages in the fourth or fifth cycle (p > .3). Furthermore, when analyzing changes across the night, for both NREM and REM, hallucinations increased from cycle 2 and cycle 3 to cycle 5 (paired t-tests, p < .05), and the length of reports that contained only hallucinations increased across pairs of successive cycles (p < .02). In contrast, thought prevalence decreased in NREM (p < .05) but remained at a stable, low level in REM across the night (p > .3; Fig. 2).

Conclusions: Thoughts and hallucinations vary differently between NREM and REM in each part of the night as well as within each sleep stage as the night progresses. We attribute the observed differences between NREM and REM mentation to changes in patterns of regional brain activation and chemical neuromodulation (Fosse, Stickgold, & Hobson, 2001). We speculate that as the REM process becomes more intense across the night, the NREM process diminishes and approaches that of REM with respect to its underlying neurophysiological determinants.

References:

REM sleep: A Window into Altered Emotional Functioning

Fosse R
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Introduction: Studies of how emotional behavior, emotional feelings, and brain neurophysiology change together from waking to sleep may increase our understanding of the universal brain-mind correlates of emotions. For this to succeed, precise descriptions are needed of emotional feelings (EF) during sleep. Methodological issues, in particular the frequent use of spontaneous awakenings/diary dreams and third person ratings of EF’s, may have biased our knowledge of EFs in sleep and given rise to the view that REM sleep is a hyperemotional state dominated by feelings of anxiety and fear (Foulkes, 1979; Schredl & Doll, 1998). We hypothesized that use of a controlled methodology would not support this view.

Methods: We studied 9 normal healthy adults, 6 females and 3 males, ages 31-60 years (mean 43.0, SD = 8.7). 88 reports with remembered content (90%) were obtained from 5 to 15 minutes into REM sleep across the night. The study was performed in a home setting using ambulatory polysonmographic techniques and instrumental awakenings over 3 nights. Eight columns along the right hand side of a report form were used to indicate, on a line-by-line basis, any experience of the following EFs; anger, anxiety/fear, sadness, shame, joy/elation, love/eroticism, surprise, and “other” emotions. The intensity of EFs was indicated by using the numbers 1 (low), 2 (medium) and 3 (high). Report forms and reports were written in Norwegian. Analyses were carried out on average subject scores.

Results: 73.9% of the reports contained at least one incidence of EFs, with joy/elation occurring most frequently, followed by surprise, anger, and anxiety/fear (Fig. 1). Anxiety/fear was less intense than joy/elation (post-hoc Fisher PLSD, p = .045), surprise (p = .0004), and anger (p = .0021; Fig. 2). Joy/elation occurred more frequently than anxiety/fear in eight of the nine subjects (Chi square = 9.0, df = 1, p = .0027). The prevalence of positive (PE) and negative (NE) feelings did not differ (paired sample t-test, p > .2). Except for surprise (t(8) = 3.71, p = .0060), no discrete EF or category of EFs (PE, NE) changed from the first part (< 4 hr of sleep) to the second part (> 4 hr) of the night (p > .2).

Figure 1

Prevalence of discrete emotion types in REM reports

Figure 2

Intensity of discrete emotion types in REM reports

Conclusions: When combining instrumental awakenings with first person scoring of EFs on a line-by-line basis, REM sleep appears not to be dominated by intense negative feelings such as anxiety and fear. Joy/elation is indicated to be the most frequently occurring EF, followed by surprise and anger. The finding that no emotion type, except for surprise, increased in prevalence or intensity across the night contrasts to what is found for other mentation features such as bizarreness, mentation report length, and visual vividness, thus indicating that different mechanisms underlie EFs and sensorimotor features in REM (Fosse, 2000).

References:

Incorporation of Episodic Memories in Dreaming

Fosse MJ, Stickgold R, Fosse R, Hobson JA
Harvard Medical School, Boston, USA

Introduction: Studies of memory incorporation in dreaming have focused primarily on the temporal phenomena of day residues and dream-lag effects (Nielsen, 1992). The relevance of different memory types and sources in dreaming have been less thoroughly examined. Episodic memories permit integrated recall across perceptual domains and are characterized by the accurate representation of the location, characters, objects, and actions associated with an event. Based on findings from animal studies that the hippocampal system, which is crucial for the formation and retrieval of episodic memories, produces no cortical output in REM sleep (Buzsaki, 1996), and from human studies showing that the hippocampus is not necessary for hypnagogic dream construction (Stickgold et al., 2000), we hypothesized that episodic memories would not be represented or replayed in dreams.

Methods: 29 adult students in a psychology course kept a log of their daily activities and nocturnal dreams for 14 days and nights. The daily activity log included major activities, personally significant events, and major concerns. The dream records consisted of any sleep mentation that the participants identified any actions, characters, objects, locations, feelings, or themes that seemed like they had been caused by specific waking events or thoughts. The similarity between waking elements and dream details were rated on a scale from 1 (no similarity) to 5 (identical). Participants rated their level
of confidence, ranging from 1 (not confident at all) to 5 (absolutely certain), that the dream element reflected the waking event. To qualify as a possible episodic memory, a dream segment was required to have: location and at least two other aspects scored as strongly similar (4) or identical (5) to the waking memory of the event; domain of similarity identified as percepts and not thoughts; and a confidence level of 3 or better.

Results: Participants provided 299 useful mentation reports (mean = 10.3), containing from 0 to 7 memory entries in each (Fig. 1). Of a total of 364 entries, 297 (82%) were given a confidence level of >= 3. With this confidence level, location was scored as at least "strongly similar" (score >= 4) in only 61 entries (20%), which was less frequent than any other aspect (Fig. 2). In 23 of these 61 entries, two or more additional aspects were scored with a similarity level >= 4. Finally, when requiring that the domain of similarity was percepts, only 12 out of the original 364 entries (3%) remained, thus qualifying as potentially episodic memories.

Conclusions: Episodic memories occur only very infrequently in spontaneously recalled sleep mentation. In contrast, a high proportion of the mentation reports contained elements from waking thoughts and percepts that were less integrated to qualify as episodic memories. These data are consistent with the view that sleep mentation predominantly reflects cortical and not hippocampal/episodic memory processes.

References:

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303.D

Correlations Between Locus of Control and Aspects of Dreaming

Nguyen TT, Picchioni D, Hicks RA
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Introduction: Past research shows evidence to support the correlation between I-E locus of control and the expected outcomes of moods (Henson & Chang, 1998). There is also evidence to support the association between types of dreams, sleep patterns (Hicks & Pellegrini, 1978)2 and levels of anxiety (Hersen, 1971). The present study was conducted in an attempt to bridge a connection between the individual differences regarding their beliefs about their ability to influence life events and its possible effects on dreaming. The purpose of this study was two-fold: (1) to identify the interrelationships between participants’ reports of dreams, in terms of frequency and intensity, and dimensions of personality and (2) if the intercorrelations exist, to examine the differences in dreaming between the “internals” and the “externals.”

Methods: Three hundred and twenty-five undergraduate students completed a battery of questionnaires. The Spadafora and Hunt’s (1990) Dream Frequency Scale, scores ranging from 7 to 35, measures dream frequency. The Belicki’s (1992) Nightmare Distress Scale, scores ranging from 13 to 55, measures nightmare intensity. The Hicks, Ostle, and Pellegrini’s (1980) Unidimensional Short-Form (S-F) of the Taylor Manifest Anxiety Scale, scores ranging from 0 to 20, measures trait anxiety. The Coren’s (1990) Arousal Predisposition Scale, scores ranging from 0 to 60, measures levels of arousability. Glass’s (1977) version of the Jenkins Activity Survey Scale (Type A-B Behavior) with scores ranging from 0 to 20; a higher score indicates type A behavior. The Rotter’s (1966) Internal-External Locus of Control Scale, scores ranging from 0 to 26; a higher score indicates an “internal” view that life outcomes reflect one’s own behaviors and characteristics; a lower score indicates an “external” view that life events happen due to chance. To be conservative, we selected the scale’s median (13) as the cut-off point for the two groups.

Results: Table 1 presents the intercorrelations between personality variables and dreaming variables. The negative correlations indicate that the “internals” scored lower on the Dream Frequency Scale, Nightmare Distress Scale, the S-F Anxiety Scale, the Arousal Predisposition Scale, but higher on the Type A-B Behavior Scale than did the “externals.” Table 2 shows the means, standard deviations, and one-way ANOVA results between “internals” and “externals” on all other variables.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>DFS</th>
<th>NDS</th>
<th>APS</th>
<th>Type A-B</th>
<th>S-F AS</th>
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<td>.15**</td>
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<td>-.10</td>
<td>-.10</td>
<td>-.40**</td>
<td>-.12*</td>
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<td>-.31**</td>
<td>.17**</td>
<td>.51**</td>
<td>-.19**</td>
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<tr>
<td>Type A-B</td>
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<td>-.10</td>
<td>.17**</td>
<td>.20**</td>
<td>-.19**</td>
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<tr>
<td>S-F AS</td>
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<td>.40**</td>
<td>.51**</td>
<td>.20**</td>
<td>-.19**</td>
</tr>
<tr>
<td>I-E</td>
<td>.18**</td>
<td>-.12*</td>
<td>-.19**</td>
<td>.15**</td>
<td>-.19**</td>
</tr>
</tbody>
</table>

N = 325; *p < .05, **p < .01

SLEEP, Vol. 24, Abstract Supplement 2001
Results

Subjects were then awakened 90 seconds after each signal verified tone until EM signal verification was observed and sleep was maintained. Stage 2 and REM sleep. Tones were presented at increasing volume, instructed before sleep to produce an EM signal whenever they heard a tone.

References


304.D

Poor Recall of Eye-movement Signals from NREM Compared to REM Sleep: Implications for Models of Dreaming.

Conduit R, Crewther S, Coleman G

Introduction: An implicit and untested assumption of dream research is that mental activity recalled on awakening from sleep is a direct reflection of sleeping cognition (1). It is assumed that since dreams are more often reported from REM, they must be occurring more often during this sleep stage. An alternative hypothesis to this widely held assumption is that dreaming exists through verbal report on awakening. However, dreaming exists through verbal report on awakening. Howev-

Methods: 18 Subjects were connected for standard PSG recording and instructed before sleep to produce an EM signal whenever they heard a tone presented during the night. Tones were presented to subjects during Stage 2 and REM sleep. Tones were presented at increasing volume, until EM signal verification was observed and sleep was maintained. Subjects were then awakened 90 seconds after each signal verified tone (SVT) presentation and asked if they could remember hearing the tone and doing the EM signal.

Results: Only one subject from Stage 2 sleep and nine subjects from REM were able to produce a successful signal verification without arousal according to Rechtschaffen and Kales (1968) criteria. When the criteria for arousal was relaxed to at least 30 seconds of alpha within the 90 sec interval between the SVT and awakening, ten subjects were then able to provide data from both sleep stages. Consistent with a differential-recall model of sleep mentation, it was found that SVT presentations were recalled significantly less often from Stage 2 sleep (65%) than REM (100%; t(9) = 2.65, p = 0.027). Furthermore, SVT recall rates were significantly correlated with subject estimates of dream recall frequency at home (r = 0.76, p < 0.02), suggesting the same processes involved in recalling SVTs may also be involved in dream recall.

Conclusions: These results indicate that these dimensions of personality are intercorrelated with one another. Compared with the “externals,” the “internals” show an association with lower levels of arousability and anxiety, and have a tendency to be categorized as Type A individuals. Among aspects of dreaming, all four dimensions of personality are correlated with dream frequency and nightmare distress. Only Type A-B Behavior is not correlated with nightmare distress. The differences between the “internals” and the “externals” are not statistically significa-

References:


305.D

Differential Associations of Psychopathology with Nightmare Frequency and Nightmare Suffering

Blagrove MT, Farmer LH, Williams ME

University of Wales Swansea

Introduction: There have been conflicting results on whether nightmare frequency correlates with psychopathology. Chivers & Blagrove(1) sug-

Table 2: The Means, Standard Deviations, and One-way ANOVAs Between Internals and Externals for the Personality and Dreaming Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Internal</th>
<th>External</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>13.33</td>
<td>14.23</td>
<td>3.54</td>
<td>.06</td>
</tr>
</tbody>
</table>
| NDS      | 19.38    | 19.85    | .46 | n.s.
| APS      | 31.79    | 33.41    | 4.42| .035|
| S-FAS    | 7.40     | 8.82     | 3.32| .050|
| Type A-B | 7.64     | 7.02     | 3.15| .08 |

Internal n = 103; External n = 222

*p < .05; **p < .01
gested that the failure to find such correlations is partly due to using retrospective questionnaires, rather than daily diaries, to assess nightmare frequency. They found that nightmare frequency, assessed by 2-week diaries, was significantly related to stress/psychopathology. However, Levin(2) showed that the global psychopathology - nightmare frequency correlation becomes insignificant when nightmare suffering is partialled out, and that nightmare suffering is significantly correlated with global psychopathology even when frequency is partialled out. Our aim was to replicate Levin’s method of controlling for nightmare suffering when assessing the relationship between waking psychopathology and nightmare variables, and also to assess emotional tone (or suffering) during nightmares and dreams.

Methods: Participants (89 females, 16 males, mean age = 22.6 years (SD=9.2), range 17-67) were recruited from members and associates of the university population. They were given Zadra’s definition of a nightmare as ‘a very disturbing dream in which the unpleasant visual imagery and/or emotions wake the person up.’ The distinction with night terrors was made clear. They completed a retrospective questionnaire on their frequency of having dreams and also nightmares; to be included in the study they had to report remembering at least one dream or nightmare per week. They were assessed for stress/psychopathology by the General Health Questionnaire-16, Neuroticism by the Eysenck Personality Questionnaire-RS, Anxiety and Depression by the bipolar POMS, and, if they had nightmares, they answered Belicki’s (1992) nightmare questionnaire. They then 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 7 point scale of very pleasant (1) to very unpleasant (7). Mean emotional tone was calculated for dreams and nightmares combined.

Results: On the retrospective questionnaire participants reported having a mean of 1.9 nightmares per month (SD=2.3, range = 0-10). Over the 2 weeks of the diary nightmares were recalled on a mean of 0.9 nights (SD=1.5, range = 0 - 9), there was no significant sex difference on this, nor on the psychopathology measures. Mean emotional tone of dreams and nightmares was 4.0 (SD=0.8, range = 2.4 - 6.0). Table 1 shows generally low correlations between psychopathology measures and nightmare frequency, these being even lower if only individuals who have nightmares are studied. Nightmare suffering has much higher correlations with psychopathology. Table 2 shows the partial correlations.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Q.maire nightmare frequency</th>
<th>2 week diary nightmare frequency</th>
<th>Emotional tone of dreams and nightmares</th>
<th>Q.maire nightmare suffering</th>
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<tr>
<td>All subjects</td>
<td>n=105</td>
<td>n=105</td>
<td>n=105</td>
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<tr>
<td>Anxiety</td>
<td>.16*</td>
<td>.10*</td>
<td>.20*</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.20*</td>
<td>.11*</td>
<td>.23*</td>
<td></td>
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<tr>
<td>Neuroticism</td>
<td>.18*</td>
<td>.17*</td>
<td>.17*</td>
<td></td>
</tr>
<tr>
<td>GHQ-Stress</td>
<td>.18*</td>
<td>.20*</td>
<td>.16*</td>
<td></td>
</tr>
<tr>
<td>Nightmare subjects only</td>
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<td>n=83</td>
<td>n=83</td>
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<tr>
<td>Anxiety</td>
<td>.11*</td>
<td>.05*</td>
<td>.18*</td>
<td>.38***</td>
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<tr>
<td>Depression</td>
<td>.16*</td>
<td>.07*</td>
<td>.18*</td>
<td>.38***</td>
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<tr>
<td>Neuroticism</td>
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<td>.13*</td>
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<td>GHQ-Stress</td>
<td>.19*</td>
<td>.21*</td>
<td>.17*</td>
<td>.38***</td>
</tr>
</tbody>
</table>

*p<.05
** p<.01
*** p<.001

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Q.maire nightmare frequency</th>
<th>2 week diary nightmare frequency</th>
<th>Emotional tone of dreams and nightmares</th>
<th>Q.maire nightmare suffering</th>
</tr>
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<tbody>
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<td>Anxiety</td>
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<td>.08*</td>
<td>.13*</td>
<td>.27**</td>
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<tr>
<td>Depression</td>
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<td>.06*</td>
<td>.13*</td>
<td>.38***</td>
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<tr>
<td>Neuroticism</td>
<td>.00*</td>
<td>.06*</td>
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<td>GHQ-Stress</td>
<td>.02*</td>
<td>.09*</td>
<td>.11*</td>
<td>.38***</td>
</tr>
</tbody>
</table>

* p<.05
** p<.01
*** p<.001

Conclusions: Nightmare suffering remained significantly correlated with psychopathology when nightmare frequency was partialled out, and nightmare frequency had little relationship with psychopathology when only people with nightmares were studied, and no relationship once nightmare suffering was partialled out. We have thus replicated Levin’s findings, and extended them by finding a similar pattern between psychopathology and emotional tone during dreams and nightmares.

References:

306.D

Psychophysiological Comparison of Dream Property Scale Ratings of Sleep Onset Mentation and Laterality Index of EEG Alpha Wave Power

Massicotte CJ, Ogilvie RD, Takeuchi T
Brock University

Introduction: Sleep onset (SO), or the process of falling asleep, is generally defined as the transition from waking EEG to sleeping EEG (Wake to Stage 2), based on physiological, behavioural and psychological changes. This process, however, is not well understood, and the present study was aimed at describing microscale changes within this period. Specifically, Dream Property Scale (DPS)(1) measures of hypnagogic imagery (HI) and FFT changes during the sleep onset period (SOP) were examined. The methods for scoring sleep into discrete stages have remained largely unaltered since Rechtschaffen and Kales (1968) methods became ubiquitous, but since more frequent changes in SOP EEG can be examined using the 9-stage system developed by Hori(2). It was hypothesized 1) that DPS Bizarreness ratings of HI would increase as Hor sleep Onset stages II, III & V were entered and 2) that right hemisphere EEG would show greater alpha power than the left when subjected to FFT analysis.

Methods: Right-handed students, (2 males, 9 females, aged 18 to 30 years (M = 21.09, SD=3.62)), who were free of sleep disorders, spent 2 nights in the laboratory. They were awakened three times during sleep onset, at Hor sleep stages II, III and V, to assess SO mentation, using the Dream Properties Scale. FFT analysis was performed on Fp1, Fp2, F7, F8, FZ, C3, C4, CZ, T5, T6, 01, 02 to examine laterality shifts in alpha power.
Conclusions: The current study explored brain wave and cognitive differences during the Sleep Onset Period. The study further validates the use of the DPS for HI studies, and the use of Horii stages for scoring SO. DPS findings indicate that the Bizarreness subscale of the DPS may be sensitive to the disappearance of alpha during SOP as predicted, making it particularly useful for analyzing subsequent dream-like imagery. Alpha frequency EEG appears to parallel processes that regulate thought such that when alpha disappears, bizarre imagery tends to occur. The DPS provides a valid tool for examining SO imagery, which removes variability encountered when examining mental imagery at SO by providing participant-rated assessments of HI. Further studies might expand the DPS, specifically tailoring it for visual imagery by increasing the number of items sensitive to visual hypnagogic imagery.

References:

307.D
The Effects of Daytime Sleepiness and Sleep Onset REMS Period (SORP) on Reported Dream Recall
Myers P, Pagel JF

Introduction: Few variables are known to consistently alter dream recall. Sleep stage before awakening from sleep is the primary variable altering reported recall of sleep associated mentation (dreams). Personality, age, gender and RDI have been shown to have inconsistent effects (1,2). It has been proposed that waking is not one state, but a series of states with at least as much variability as the various stages of sleep (3). One of the few assessments routinely made of the waking state is the study of daytime sleepiness done by use of the Multiple Sleep Latency Testing (MSLT). The MSLT is utilized clinically in this sleep laboratory as a clinical test for Narcolepsy, and to access an individual’s level of daytime sleepiness. Individuals with Narcolepsy generally show severe daytime sleepiness and at least two SORP’s in the four or five 20 minute naps which comprise the MSLT. Daytime sleepiness is generally rated: (< 5 min. = severe, 5-10 min. = moderate, 10- 15 min. = mild).

Methods: The authors hypothesize that both these variables (SORP and daytime sleepiness) will alter reported dream recall. Individuals with SORP are likely to have increased dream recall. A non-absolute correlation exists between REMS and dreaming, and alterations in dreaming are frequently reported in narcoleptic patients (hypnagogic hallucinations and sleep paralysis). Daytime sleepiness is postulated to have a negative effect on the integration of dreaming into waking thought as accessed by reported dream recall.

Results: Reported dream recall was obtained by questionnaire as part of the routine intake of 56 individuals undergoing polysomnography (PSG) and MSLT in this sleep laboratory. RDI was obtained from the PSG (no significant variability in RDI exists between groupings). Results are analyzed based on six clinical groupings based on degree of daytime sleepiness and the presence of absence of SORP: Table 1

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Mean Sleep Latency (min)</th>
<th>Mean RDI</th>
<th>Dream Recall</th>
<th>Significance</th>
</tr>
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<tr>
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<td>7.8</td>
<td>3.7</td>
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<td>11.1</td>
<td>8.1</td>
<td>2.6</td>
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<td>Idio-RD</td>
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<td>11.1</td>
<td>8.1</td>
<td>2.6</td>
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</tbody>
</table>

Conclusions: Significant variability was present between the groupings large enough to permit reasonable statistical analysis. These results support the author’s hypotheses. Severe sleepiness can be shown to suppress reported dream recall in individuals without SORP. In individuals with the REMS pressure associated with SORP’s, dream recall is higher despite the presence of severe daytime sleepiness. Reported dream recall could be used to differentiate sleepy individuals with SORP’s from those without SORP’s. Decreased dream recall may be a marker for daytime sleepiness.

References:

308.D
Physiological Correlates of REM Sleep in Idiopathic and Posttraumatic Nightmare Patients.
Saucier S,1 Germain A,1,2 Nielsen TA,1,3 Barbier S1
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Introduction: Some studies report increased physiological activity in REM sleep, such as increased REM density, increased muscular events, and increased phasic leg activity in REM sleep (see Mellman, 1997). However, previous reports do not specify whether PTSD patients had frequent nightmares. The recurrent experience of frequent nightmares and/or elevated rates of co-morbidity, rather than PTSD per se, may explain increased physiological activity in REM sleep.

Methods: Nine PTSD-NM sufferers and 11 idiopathic nightmare sufferers (Idio-NM) reporting > 1 NM/week, using no medications, drugs, or alcohol, and who had no other major psychiatric, sleep or neurological disorders were studied. Nine healthy participants constituted the control group (CTL). All slept in the laboratory for 2 consecutive nights. They were fitted with electrodes for recording sleep stages (EEG, EOG, chin EMG), as well as a 19-channel EEG montage, digitized at 128 Hz. Eye movement density was computed as the absolute number of REMs. Submental phasic muscular events were determined as movements lasting between 0.5-4 sec. Heart rate (HR) was calculated from R-R intervals. All variables were computed from the last five minutes of the first four REM sleep episodes, and averaged.

Results: There were no differences among groups for REM density and phasic submental muscular events. A significant effect was found for HR (F2, 26 = 3.96, p = 0.04). Post hoc comparisons showed that Idio-NM exhibited an overall lower HR than PTSD-NM (p = 0.03) and CTL (p =
Dream Content Analysis in Asperger’s Syndrome

**Introduction:** Asperger’s Syndrome (AS) is a Pervasive Developmental Disorder related to autism. A recent pilot study suggest that patients with AS present a poor quality of dream reports. Furthermore, autistic children tend to talk about their dreams later than normal children and are more likely to misunderstand the dream concept. To better address the dreaming features of this disorder, we analyzed the dream content of Idio-NM patients.

**Methods:** Five adult patients with AS (5M, 1F, 20.6 ± 3.8 years) were diagnosed according to DSM IV criteria and using the Autism Diagnostic Interview. Inclusion criteria were a score above the cut-off point in the areas of social communication and restricted interest as well as an absence of delay for language. They were compared to five age- and gender-matched participants (5M, 1F, 20.6 ± 2.9 years) screened for psychiatric, neurologic and clinical sleep disorders. All participants were recorded for two consecutive nights in the sleep laboratory. On both nights patients were awakened during REM sleep and interviewed for dream content after the following criteria were met: at least 420 minutes had elapsed since sleep onset, and the REM sleep period was at least 15 minutes long at the moment of awakening. The spontaneous mental activity reports and the semi-structured interview that immediately followed were tape-recorded. Patients were allowed to go back to sleep after a REM sleep awakening; a second dream interview was performed if sufficient REM sleep occurred again. Two independent judges analyzed one dream report from each participant using the coding system of Hall and Van de Castle. Number of words in dream reports, number of verbal interventions by the experimenter and dream content elements from both groups of participants were compared using Mann-Whitney U-tests for independent samples.

**Results:** Compared to controls, dream reports of patients with AS had fewer words despite an equal number of verbal interventions by the experimenter and included significantly less total number of objects (15.0±1.6 vs 5.4±2.8) and descriptive elements (10.0±2.8 vs 3.2±2.1) in their reports. Mention of Social Interactions (2.0±0.4 vs 2.4±1.3) and Face Elements (1.2±0.6 vs 0.2±0.2) were equally frequent. When the number of words in dream reports were controlled for, patients with AS used less words than control participants to express most of scored dream elements.

**Conclusions:** The findings are consistent with recent studies confirming an overall lack of REM sleep disturbances in PTSD patients compared to healthy subjects (Engdahl et al., 2000, Hurwitz et al., 1998). Lower HR in REM sleep may be a physiological marker of disturbed dreaming in Idio-NM patients.

**References:**


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310.D

Eye Movement During EEG-defined Hypnagogic Sleep Onset

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Introduction: Although Rechtschaffen and Kales (1) considered slow eye movement “a most important indication of Stage 1,” Tanaka, Hayashi, and Hori (2) do not use eye movement to score any of their nine stages of hypnagogic sleep onset. Because Tanaka et al.’s stages overlap with Rechtschaffen & Kales’s Stage 1, we investigated Tanaka et al.’s stages 1 – 9 in respect to eye movement and EEG frequency bandwidth.

Methods: Five subjects (one male and four females), aged 20 to 21 years, free of medical or psychiatric illness or medication, slept in the laboratory for two nights. Alcohol, caffeine, and naps were forbidden within 24 hours of sleep recording. EEG (C3 or C4), EOG (DC), and EMG were recorded using BIOPAC (Santa Barbara, CA) hardware. Data from the second night were analyzed. Sleep onset stages were assessed using Tanaka et al.’s criteria. In addition, EEG was characterized in each stage as the magnitude ratio of theta to alpha bandwidths (determined by Fast Fourier Transform in AcqKnowledge™). To compare theta-alpha ratio to eye movement, EEG data were analyzed in epochs of 8192 samples (16.38 seconds). Eye movement velocities were determined using a simplified differentiation algorithm.

Results: Eye movement velocity. Unsurprisingly, sleep onset eye movement velocities were much lower than Stage REM velocities. Nonetheless, within the velocity range of sleep onset eye motion the data displayed a clear “main sequence” of amplitude x velocity (R = 0.652, R² = 0.425, F (1, 174) = 128.46, p = 0.00). Eye movement frequency. Eye movement frequency varied according to Tanaka et al.’s sleep onset stages, peaking notably in Stage 5 (Figure 1). Theta:Alpha Magnitude Ratio. The ratio of theta magnitude to alpha magnitude was linearly related to sleep onset stage. Linearity was strongest in stages 2 through 7 (Figure 2, R = 0.8162, R² = 0.6662, p = 0.00). Consistent with Tanaka et al.’s shift to EEG “ripples,” theta magnitude first exceeded alpha magnitude in Stage 5. The further increase of theta magnitude in Stages 6 and 7 coincides with the appearance of high amplitude vertex sharp waves (VSW), typical of late sleep onset (Rechtschaffen & Kales’s late Stage 1; Tanaka et al.’s Stages 6-8).

Figure 1

Figure 2

Conclusions: Among Tanaka et al.’s hypnagogic sleep onset stages, Stage 5 uniquely joins a singular peak of eye movement to the ascendency of theta EEG rhythms prior to VSW onset. This conjunction suggests physiologic similarity to Stage REM. Differences between Stage 5 of sleep onset and Stage REM require explanation. The results suggest, however, that Stage 5 should be exempted from the label “NREM” that is traditionally accorded Rechtschaffen & Kales’s Stage 1, and should be treated by investigators as unique among Tanaka et al.’s stages of sleep onset.

References:

311.D

Needs and Dreaming Processes: Observations on Dreams of Abstinent Heroin Addicts

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Introduction: The effect of needs on dreaming processes rarely has been investigated in dream research. This situation could be attributed, in part, to the difficulty to measure the variables implicated in needs and motivations (e.g. ethical problem in biological needs frustration) and to recognize their influence on dream content. In this paper, I wish to draw attention to some clinical observations on dreams of abstinent heroin addicts. These patients characteristically shown an abnormal strong wish to use heroin, namely, “drug craving”, therefore the study of their dreams seems to give a methodological opportunity to examine the role of needs in the formation process of dream.

Methods: The subjects were 7 patients who attended a pharmacological substitution drug treatment in a Service for Drug Addictions. They reported the dreams during the supportive psychotherapy sessions.

Results: They recalled gratifying dreams in which they used heroin in the same period in which they stopped or drastically reduced the use of it (awake state). In a typical dream report the patient goes to buy the drug, he prepares it and uses it. More rarely (two subjects) the patient before using heroin had an anxious awakening. In most patients (six subjects) the neurophysiological deficit of heroin abstinence (i.e. withdrawal syndrome) was blocked because they assumed the methadone (chemical substitute of heroin). In this view it’s more parsimonious affirm that these dreams were influenced primarily by cognitive-psychological dependence rather than physical dependence.
Conclusions: All these dreams (gratifying and non-gratifying) show that a vital need significantly influence dream content. These observations are coherent with previously case reports (1). Furthermore similar dreams of drug use are present also in other types of addictions. Particularly, drinking-dreams are frequent in abstinent alcoholics, smoke-dreams are frequent in abstinent smoker and drug-dreams are frequent in abstinent polydrug users (2). Probably the study of dream in addiction (heroin or other) may represent a paradigm of investigation on the role of needs in the formation process of dream because in these situations, compared to normality, there is clearly present an abnormal quantitative need and/or wish. While in most dreams we do not have the opportunity to observe or control the variable “need”, in these patients the measure of the period of abstinence (e.g. sum of the days of abstinence) and the measure of drug craving may permit a control of the variable “need”.

A similar experimental situation is represented by studies on effect of biological vital needs frustration (e.g. thirst) on dream content where needs are experimentally intensified in presleep period. The gratifying dreams found in addiction seem to dissuade the exclusion of the needs and motivational factors in the study of dream processes. Indeed Solms’ neuropsychological studies have shown the involvement in dreaming of brain areas implicated in motivations (3).

References:

312.E

Effects of Sustained-Release Melatonin on Daytime Sleep and Subsequent Alertness during a Simulated Night Shift

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Introduction: Disturbed sleep and on-the-job sleepiness are widespread problems among night shift workers. Exogenous administration of the pineal hormone melatonin may be a promising treatment for improving night workers’ daytime sleep and therefore may also improve their nighttime alertness. Exogenous melatonin improves subjective ratings of daytime sleep and has also been shown to improve polysomnographically-recorded (PSG) daytime sleep. No previous investigation has studied melatonin’s effects on daytime sleep after a full night of wakefulness as occurs in night shift work, or assessed night-time alertness after daytime melatonin administration. Our study used a placebo-controlled, doubleblind, cross-over design to investigate whether melatonin can improve PSG sleep and nighttime alertness compared to placebo in subjects who stayed awake for simulated night shifts and then slept during the day.

Methods: Twenty-one healthy young adults (9 women, 12 men; ages 18-37 years) participated. Subjects completed two 6-day sleep laboratory sessions consisting of 3 nights of adaptation and baseline PSG, 2 night shifts each followed by a daytime PSG recording, and 1 recovery PSG. All scheduled sleep episodes were 8 hrs long, and subjects were required to stay in bed for the entire 8 hrs. The average ± SD baseline bedtime was 23:27 ± 00:55. The night shifts occurred at the same clock time as scheduled baseline sleep, and there was 1 hr between the end of the night shifts and day sleep bedtime. Subjects took 1.8 mg sustained-release melatonin 1/2 hr before both daytime sleep episodes in one session, and placebo 1/2 hr before the daytime sleep episodes in the other session.

Four Multiple Sleep Latency Test (MSLT) naps were given at 2 hr intervals during the night shifts. Sleep was scored in 30-second epochs using Rechtschaffen/Kales standard criteria. Sleep latency was defined as the first 30-second epoch with > 15 seconds of sleep. Data were analyzed using repeated-measures ANOVA and planned contrasts.

Results: Melatonin increased sleep duration on day sleep 1, mainly by increasing sleep time during the second half of the sleep episode (F(1,11)=4.99, p<.05; see Fig. 1). Subjects had an average of 24 ± 42 minutes more sleep after melatonin compared to placebo. Melatonin did not affect sleep during day sleep 2. The increase in sleep time during day sleep 1 did not improve alertness during the subsequent night shift; melatonin administration had no effect on the MSLT during the second night shift (see Fig. 2).

Figure 1

Conclusions: These findings suggest that although melatonin can help night workers obtain more sleep during the day, they are still likely to face difficulties working at night because of sleepiness due to circadian rhythm misalignment. The apparent tolerance to melatonin, i.e., the fact that melatonin increased sleep on the first day but not the second, needs further investigation.

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313.E

Underlying Sleep Pathology May Cause Severe Fatigue and Decrement of Performance in a Group of Shift Workers at an Underground Mine

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Introduction: About 20-25% of the population in primary health care settings complains of chronic fatigue but it has been under-emphasized compared to sleepiness in clinical practice. Shift workers are particularly vulnerable due to various fatigue-related personal and public morbidity and mortality. Fatigue can be caused by sleep restriction or sleep dis-
ruction, either or both can be caused by a broad range of sleep disorders. The goal of this clinical investigation was to establish if fatigue severity could be used as a predictive tool to identify any underlying sleep pathology along with performance decrement.

Methods: 23 most fatigued and 23 least fatigued miners were selected based on the scores on Fatigue Severity Scale (FSS) which was administered to 193 subjects in an underground mine in Timmins, a Northern Ontario town. The subjects were almost exclusively male (95.7%), 41.9±7.0 years mean age, married (84.2%), working at the mine for 17.6±5.7 years. The FSS is a 9 item self-report questionnaire providing a subjective measurement of daytime fatigue that is independent of daytime sleepiness1. Mean FSS score for the most fatigued subjects was 5.1 and the least fatigued was 2.1 (p < 0.0001). The subjects from each group had undergone objective evaluation of sleep (polysomnography) to identify certain sleep disorders and performance testing (Mackworth Clock Test)2 for assessing decrement in vigilance and reaction on two consecutive occasions. The purpose of two consecutive sleep studies was to minimize the “first night effect”, which is physiological response in healthy individuals characterized by alteration of the sleep architecture due to natural stressors, such as sleeping at an unfamiliar surroundings.3

Results: 14 out of 23 (61%) of the most fatigued subjects have displayed sleep related breathing abnormalities, periodic limb movements, oxygen desaturation and significant alteration of sleep architecture due to repeated arousals and awakenings. Any or all of the above sleep pathology may cause sleep fragmentation and/or non-restorative sleep, ultimately producing fatigue in the shift workers. Compared to that, only 6 out of 23 (26%) of the least fatigued subjects have findings suggesting underlying sleep pathology. Although detailed analysis is pending, subjective evaluation revealed significant decrement of performance in most fatigued individuals.

Conclusions: We conclude that, fatigue severity can predict underlying sleep pathology and can be an useful screening tool to identify which high risk individuals are likely to need sleep evaluation and subsequent medical treatment to improve sleep and performance.

References:
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314.E

The Effects of a Rapidly Rotating Shift Pattern on the Sleep of Air Traffic Controllers

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Introduction: Counter-clockwise, rapidly rotating schedules are often employed to compress the work week, minimize the number of night shifts worked and maximize days off (Cruz, et al. 2000). In air traffic control such a work pattern involves a very short daytime break before the night shift, which is the last shift of the working week. This paper focuses on the progressive changes in sleep across the roster cycle and the sleep consequences in relation to the night shift.

Methods: Twenty-eight operational air traffic controllers completed logbooks and wore actiwatches throughout 4 complete roster cycles. A typical roster cycle pattern was: afternoon, day, morning, night shift (commencing at either 2230 hours or 2330 hours). Individual baseline sleep values were calculated from sleep on days off and compared to sleep obtained across the working week to produce the amount of sleep lost (or gained) in successive 24-h periods from midday to midday. Consecutive periods of sleep loss (gain) were summed to calculate the level of cumulative sleep loss. Mixed model ANOVAs were utilized in the analysis of data, to allow modeling for individual variance and covariance amongst repeated sleep measures.

Results: The length of main sleep periods changed significantly across the week (F(6, 573) = 35.40, p < .001; Table 1), with the shortest main sleep occurring prior to the morning shift. Due to the reduction in sleep the mean cumulative sleep debt by midday prior to the night shift was 2.9 hours (SD = 1.46, n = 104) with all individuals experiencing some debt although values ranged widely (0.12 – 6.80 hours) see Figure 1. Individuals slept on 89% of occasions between midday and commencing the night shift, obtaining a mean of 2.3 hours sleep (SD = 0.99, range = 0.28 – 5.03 hours, n = 95). During the night shift individuals had the opportunity to nap for 40 minutes on 2 of the 4 night shifts they worked. This nap opportunity did not alter the length, quality or timing of post night shift sleep, although the earlier starting night shift resulted in longer post shift sleep because of the earlier finishing time (F(1, 39.3) = 7.36, p = .01). In the subsequent 24-h period, recovery sleep exceeding baseline values was evident, lessening the mean sleep debt. However, as expected the mean cumulative debt does not return to zero, as sleep is not recovered hour for hour.

Table 1

<table>
<thead>
<tr>
<th>Main Sleep Length Across the Study Period</th>
<th>Mean length</th>
<th>SD</th>
<th>Range</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>Pre-cycle day 1</td>
<td>8.23</td>
<td>1.49</td>
<td>3.97 – 12.10</td>
<td>99</td>
</tr>
<tr>
<td>Pre-cycle day 2</td>
<td>8.33</td>
<td>1.43</td>
<td>5.17 – 12.38</td>
<td>106</td>
</tr>
<tr>
<td>Workday 1</td>
<td>7.53</td>
<td>1.23</td>
<td>5.05 – 10.13</td>
<td>104</td>
</tr>
<tr>
<td>Workday 2</td>
<td>6.61</td>
<td>0.96</td>
<td>4.58 – 8.95</td>
<td>106</td>
</tr>
<tr>
<td>Workday 3 (no main sleep due to night shift)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workday 4</td>
<td>8.58</td>
<td>1.40</td>
<td>3.78 – 12.28</td>
<td>105</td>
</tr>
<tr>
<td>Post-cycle day</td>
<td>8.28</td>
<td>1.31</td>
<td>3.15 – 12.38</td>
<td>106</td>
</tr>
<tr>
<td>Post-cycle day 2</td>
<td>8.46</td>
<td>1.73</td>
<td>0.43 – 12.38</td>
<td>70</td>
</tr>
</tbody>
</table>

Figure 1

Cumulative Sleep Debt Across the Study Period

Conclusions: The counter-clockwise, rapidly rotating shift cycle with a
short turn around prior to the night shift results in air traffic controllers commencing the night shift with varying levels of sleep debt. The efficacy of a nap during the night shift for the neurophysiological alertness and performance of air traffic controllers is currently being investigated. The findings of the present study have implications for any workforce where progressively early shift start times or short turn-arounds between shifts are required and/or where night work is scheduled.

References:

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315.E

Diurnal Variations of Retinal Function in Morning-Type and Evening-Type Individuals

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Introduction: Retinal melatonin secretion is controlled by an endogenous circadian oscillator located in the retina. This oscillator has the same period and the same phase-response to light as the hypothalamic oscillator controlling pineal melatonin (1). It is therefore possible that, in entrained individuals, secretory episodes of both pineal and retinal melatonin show the same circadian phase. The exact role of retinal melatonin is not known, but it has been suggested that it could be the neurohormonal signal by which the retinal circadian clock controls rhythms of various retinal functions (2). In the present study, diurnal variations in retinal functions were compared between entrained individuals with an early or a late endogenous rhythm of melatonin secretion.

Methods: Subjects (17W, 7M; 19-25 yrs) were selected according to their score on a morningness-eveningness questionnaire: 12 morning types (ME scores > 59) and 12 evening types (ME scores < 39). Subjects were admitted to the Visual Electrophysiology Laboratory from 19:30 in the evening to 09:30 on the next day. Scotopic electroretinograms (ERGs) were recorded at 22:30 and at 08:00 with 11 blue flashes of increasing intensities. Photopic ERGs were recorded 30 minutes later with 15 white flashes of increasing intensities. Subjects were kept in dim light (< 10 lux), except during the photopic ERG recordings (background light of 16 cd/m2). Salivary melatonin was sampled every half-hour from 20:30 to 24:00, and from 06:30 to 09:30.

Results: As expected, evening types had low melatonin concentrations at 22:30 compared to morning types, but higher melatonin levels at 08:00 (Group-by-Time interaction: p < 0.001). For both scotopic and photopic ERGs, two measures were calculated: the amplitude of maximal response (Vmax, in mV) and the sensitivity (light intensity necessary to elicit half of the Vmax response). For the scotopic ERG (Fig.1), both groups showed a lower Vmax (p < 0.01) and a lower sensitivity (p < 0.05) at 08:00 compared to 22:30. The photopic ERG (Fig.2) revealed a Group-by-Time interaction for the Vmax measure (p < 0.01). Photopic Vmax amplitude was low when salivary melatonin concentration was high.

Conclusions: A diurnal variation was found in both scotopic and photopic retinal responses, although with a different pattern. The variation in scotopic response was the same in both groups of subjects and could be related to a direct effect of light/dark exposure. On the other hand, the negative relationship between the photopic responses and melatonin concentration suggests a circadian control of photopic retinal sensitivity. As suggested before (3), an endogenous circadian variation in retinal function can have a significant impact on the entrainment of the hypothalamic circadian pacemaker and contribute to maintain an early or late circadian phase even in the absence of large variations in light/dark exposure.

References:

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316.E

The Interaction of Food, Time of Day and Sleep Loss on Metabolism, Sleepiness, Hunger and Performance During 24h of Continuous Activity

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Introduction: There is very little knowledge available on how food intake is related to the development of sleepiness and performance, particularly at night. Our objective was to study the effects of a high-carbohydrate (HC) meal vs. a high-lipid (HL) vs meal on alertness, hunger and performance during the day and night, and relate these to metabolic/endocrine responses.

Methods: A six-day high-carbohydrate meal (HC; 65 E% carbohydrates, 20 E% fat and 15 E% protein) and a six-day high-lipid meal (HL; 40 E% carbohydrates, 45 E% fat and 15 E% protein) was given to 6 healthy subjects in a crossover design. On the last day subjects were kept awake for 24-hours in a metabolic laboratory while substrate utilisation and energy expenditure were measured by indirect (respiratory) calorimetry. The subjects were given isocaloric meals every four hours. Blood samples were taken and mood ratings were given every hour and the EEG was measured continuously. Within the 1st and 4th hour after food intake, the KDT-Karolinska Drowsiness Test (1) was performed during which the subjects kept their eyes open and focussed for five minutes followed by a 5-min eye closure. Performance was measured 0.5h and 3.5h after food intake, using a serial reaction time test and a simple arithmetic test. 3-way ANOVAs were calculated using the factors meal (CHO/lipid), time of day (six blocks in 24h) and session (measurements within each 4h block). In a second study the same procedure was followed, but no food was given at 2400h and 0400h.

Results: The subjects altered the macronutrient utilisation according to meal. Thus the HC meal increased carbohydrate oxidation (F=27.6, p<0.01) and HL increased the fat oxidation (F=99, p<0.001). Energy expenditure was significantly higher with the HL meal (HL=11200±1600 kJ/24h, HC=10300±1100kJ/24h, p<0.05). Among hormones and other substances related to metabolism, both cortisol, glucose, glycerol, FFA (fatty acids), triacylglycerols and TSH showed a significant (p<0.05) time of day pattern but only cortisol, fatty acids and tri-
acyl glycerols showed a significant effect of meal (p<.05). Insulin showed a significant effect only for session (p<.01) - no circadian effect. Hunger showed a highly significant effect of time since meal (p<.01), but also a significant effect of time of day (p<.05), with a decrease during the night hours. All subjective symptoms of sleepiness and performance measures showed a significant time of day pattern (p<.01) with pronounced early morning peaks. Several symptoms (irresistible sleepiness, heavy eyelids and sleepiness) also showed higher levels for the HC meal (p<.05). Performance did not differ between meal conditions, but a significant interaction between meal and performance within each 4-hour block showed that the reaction time performance fell (RT increased) after each HL meal (F=8.2 p<.01) whereas it remained constant after HC meals. Arithmetic performance also fell with time after meal (p<.01), but without any difference between meal types. After a spectral analysis of the EEG KDT measures for eyes closed showed a significant time of day effect (F=9, p<.0001) for the Theta/Alpha ratio but showed no effect of meal. It should be emphasised that the HC meal had 30% more weight (and volume) than the HL meal due to its lower energy content. This may have affected the results. The study with night meals excluded resulted in the expected metabolic changes (falling glucose, insulin and rising glucagon, etc), and a pronounced increase in hunger. The nighttime fall in alertness and performance was partly counteracted by the extended lack of food. The latter results are presently being analysed.

Conclusions: Hunger, alertness and performance are reduced at night and carbohydrates marginally raise sleepiness, whereas food deprivation initially lowers sleepiness and performance.

317.E

Relationship Between Plasma Homocysteine Levels and Sleep Parameters in Shiftwork Bus Drivers

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Introduction: Many work settings require individuals to displace sleep from the normal nighttime hours, leading to disturbed sleep, which may affect performance and safety (1). Disruption of the biological process that programs daytime wakefulness and nighttime sleep can result in reduced opportunities to sleep and poor sleep quality, affecting the shift worker’s health. Previous studies have indicated an association between shiftwork and coronary heart disease with a 40% increase in cardiovascular disease risk (2), probably due to factors like circadian rhythm disturbances. Recent studies with humans and animals have shown that hyperhomocysteinemia is associated with increased risk of cardiovascular disease (3). Abundant epidemiological evidence shows a parallelism between hyperhomocysteinemia and cardiovascular risk factor that is independent of other conventional risk factors. There are factors like nutritional deficiency of vitamins (folic acid and B12) that participate in homocysteine metabolism, which can lead to metabolic disruption and potentially to hyperhomocysteinemia. The present study investigated the possibility of a relationship between plasma homocysteine levels and sleep parameters in professional bus drivers.

Methods: Thirty drivers were submitted to polysomnography after an initial night of adaptation to the sleep laboratory. Sleep was recorded for 8 hours by Medilog Recorders (Oxford Instruments Ltd.). The blood fasting samples for biochemical analysis were collected at 8 a.m. on the day of sleep recording. Homocysteine analysis was determined in plasma by high performance liquid chromatography, with fluorescence detection. Plasma folic acid and vitamin B12 were determined by enzyme immunoassay.

Results: Plasma homocysteine levels of bus drivers were higher than those observed in the health population (mean ± SEM) (18.57 ± 1.74mM; normal range 5-15mM); however, no alterations were observed in folic acid (5.08 ± 0.41hg/mL; normal range 1.1-20 hg/mL) and vitamin B12 (367.76 ± 20.86 pg/mL; normal range 211-911 pg/mL) levels. The bus drivers showed sleep alterations including: sleep efficiency was 84.2 ± 2.15 %, arousal per hour were 35.89 ± 3.69 and apnea/hypopnea index was 6.1 ± 2.14. There was weak correlation between homocysteine and sleep onset latency (rs=. 058), sleep efficiency (rs=. 039) and number of apnea/hour (rs=. 043).

Conclusions: These results indicated that neither correlations between sleep parameters and homocysteine levels nor vitamin status can explain the elevated plasma homocysteine levels above those observed in the general population. Probably, hyperhomocysteinemia is due to other factors associated to shift work, such as circadian rhythm disturbances. However, hyperhomocysteinemia may be an explanation for the elevated indices of cardiovascular disease in shift workers, since it is a recognized independent risk factor for these diseases.

References:

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318.E

The Relationship Among Circadian Rhythms in Mood, Cortisol, and Melatonin

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Introduction: The circadian rhythms of core body temperature, cortisol, and melatonin are well established, as are the rhythms of performance and mood. It has been shown that core body temperature, cortisol, and melatonin correlate well with performance; however, mood does not necessarily correlate highly with performance (Monk et al., 1997). It has yet to be determined if mood correlates with circadian markers. The present study collected data from 10 subjects over a 3-day period and correlated subjective mood with cortisol and melatonin to determine what relationship existed among these variables.

Methods: Saliva samples were collected and mood questionnaires were given every 2 hours beginning at 0705 and ending at 2305 for 3 days from 10 subjects (9 males and 1 female). Cortisol and melatonin levels were determined by Enzyme-linked Immunosorbent Assay (ELISA), while mood was assessed by the Visual Analogue Scale (VAS) and Profile of Mood States (POMS). A repeated measures analysis of variance (ANOVA) was used to determine time of day effects, and correlations were calculated to determine the relationship between subjective mood and cortisol and melatonin levels.

Results: The ANOVA indicated significant time-of-day effects for the sleepiness and alertness scales from the VAS (F(8,72)=9.35, p<.0001; F(8,72)=10.48, p<.0001). Sleepiness showed significant linear and quadratic trends, while alertness showed significant quadratic and cubic trends. The Mood Disturbance Score (MDS) from the POMS indicated a time-of-day effect as well (F(8,72)=13.76, p<.0001), with significant linear, quadratic, and cubic trends. Cortisol had a significant time-of-day effect (F(8,72)=5.83, p<.0001), with a significant linear trend. Melatonin
showed no time-of-day effects (p > 0.05). Correlations among the variables indicated small relationships, but no consistent pattern emerged. Visual inspection of the curves indicated troughs in the variables at 1300 for MDS, 2000 for cortisol, 1100 for melatonin, 1000 for sleepiness, and 0700 for alertness. Peaks occurred at 2300 for MDS, 1300 for cortisol, 1900 for melatonin, 2300 for sleepiness, and 0900 for alertness.

Conclusions: While mood, cortisol, and melatonin all show circadian fluctuations during the 24-hour day, there is little evidence to indicate that a close relationship exists among these variables. It appears that the timing of the troughs and peaks of the curves are different for each, and one cannot assume that subjective mood follows the same pattern as physiological indices.

References:

319.E

Failure to Alleviate Jet Lag with Timed Light/Dark Exposure

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Introduction: Flights across multiple time zones result in a mismatch between the endogenous biological clock and external time cues. This condition - termed "jet lag" - is characterized by sleep disturbances, daytime sleepiness, as well as, impaired mood and performance. Timed exposure to bright light can reset the biological clock and therefore may accelerate adaptation to the new time zone, thus ameliorating jet lag symptoms. The aim of this pilot field study was to examine the effectiveness of a portable light-box (Apollo Light Systems), used in a light exposure/avoidance paradigm, in alleviating jet lag.

Methods: Nine subjects (5f, 4m; aged 26-33 yrs, mean 29.4) flying across 6 time zones from New York to Zürich were studied. On the day of departure and on the two days after arrival subjects were exposed for 1.5 hrs to either bright light (2500 lux, active treatment, n=5) or dim red light (< 20 lux, control treatment, n=4). The light treatment was scheduled to occur after an individual’s temperature minimum (determined in a pre-flight baseline lab assessment) in order to achieve a phase advance. The active group also wore dark sunglasses at pre-defined times when changes in sensitivity of the circadian timing system to light may occur after an individual’s temperature minimum (determined in a pre-flight baseline lab assessment) in order to achieve a phase advance. To assess the degree of phase shift, the melatonin onset (DLMO) was assessed at baseline and two days after the flight, upon treatment completion. Wrist activity was continuously recorded beginning one week prior to departure until five days after the flight. Subjects also completed daily questionnaires to assess sleep quality, vigor and mood. At the end of the study, overall level of jet lag and efficacy of the light treatment were rated. Data assessed before and after the flight were averaged and referred to as baseline and post-flight values. Repeated measures ANOVA and t-tests were used to evaluate group differences.

Results: Based on actigraphy data, subjects in both conditions immediately adapted their bedtimes and waketimes to Zürich local time and no impairment of sleep quality was found. The active group exhibited a sleep efficiency (sleep onset until sleep end) of 94% both before and after the flight, while the control group showed a slight increase from 93 to 95% (n.s.). In the bright light group, sleep latency was unchanged from baseline to post-flight conditions (20 min) whereas the time to fall asleep was three times longer after the flight in the control group (34 min vs. 11 min, n.s.). Post-flight sleep quality assessed by the Göertelmeyer Sleep Questionnaire was improved over baseline, twice as much in the active group compared with the control group (13% vs. 7%, n.s.). Adaptation to the new time zone was not supported by the DLMO data: upon study completion, in six subjects (3 actives, 3 controls) no DLMO was detected before bedtime (0030h) suggesting that regardless of treatment, there was no phase advance. Three subjects (2 actives, 1 control) showed minor phase advances of 1.29, 3.05, and 3.97 hrs, respectively. Bright light but not dim red light positively affected vigor as assessed by Monk’s standardized global vigor and affect questionnaire. In the active group, vigor was improved after the flight by 8% compared to baseline whereas in controls it was decreased by 4% (n.s.). An increase in mood was observed in both groups: 13% in actives vs. 15% in controls (n.s.). The overall jet lag rating did not differ between treatment groups. However, when subjects rated the treatment efficacy, bright light treatment was reported to be significantly more effective (63%) than the control condition (p < 0.05).

Conclusions: Although bright light treatment was perceived as effective in alleviating jet lag, our hypothesis that timed light exposure/avoidance would accelerate the adaptation process to the new time zone could not be confirmed in this field setting. Interestingly, none of the subjects suffered from the typical jet lag symptoms. The reason may lie in our choice of subjects who belong to an age group known to be “phase-tolerant”, i.e. less affected by phase shifts. In addition, motivation may have influenced perception of jet lag, as our subjects consisted of young Swiss professionals living in NY and traveling for pleasure to visit family and friends. More meaningful results might be obtained in future studies targeting subject samples who are more vulnerable to jet lag.

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320.E

Melatonin Sensitivity to Light in Adolescents: Preliminary Results

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Introduction: Sleep during adolescence tends to delay. We hypothesize that changes in sensitivity of the circadian timing system to light may influence this tendency. Thus, maturing adolescents may become more sensitive to light during the phase delaying portion of the phase response curve, i.e., the evening hours; or they may become less sensitive to light during late-night/early-morning phase advancing portion of the phase response curve (1).

Methods: Healthy children with relatively regular sleep patterns, screened for medical and psychological problems, received brief physical examinations and Tanner staging. Twenty pre/early pubertal participants (Tanner2) pubic hair stages 1 or 2, ages 9 to 12.4 years (5 girls) completed the study. Children had an initial 10-night entrainment at home sleeping from 2100 to 0700 wearing eye shades. Compliance was confirmed by actigraphy, diary, and telephone call-in. Condition assignment (evening vs. morning light) was based upon participant availability. Four light levels were tested for 1 hr in each participant on consecutive nights: ~0.1 lux, 15 lux, 150 lux, and 500 lux, respectively. Saliva was collected at 30-minute intervals, frozen, and melatonin assayed subsequently. Room lights were off (0 lux) or dim (~0.1 lux) from 2100 to 0730 during in-lab nights, with sleep scheduled as shown in Figure 1. Light administration for the evening group occurred from 2300 to midnight and for the morning group from 0300 to 0400.
Results: Melatonin data were converted to percentages based upon the mean of each subjects’ two samples immediately before light exposure. Bonferroni-adjusted planned comparisons were performed between light conditions for samples occurring at 30 and 60 min of light exposure. Figure 2 illustrates the results. For 30- and 60-min samples during evening light administration, no differences occurred between 15 lux or between 150 and 500 lux; all other comparisons showed statistically significant (p<.001) differences. The pattern of responses to morning light exposure differed principally in showing a significant suppression of melatonin to 15 lux (p = .003) in the 30-min sample, but not the 60-min sample. All other comparisons (except 150 vs. 500 lux, no difference) were statistically significant (p≤.003).

Conclusions: This preliminary analysis indicates that pre/early pubertal participants suppressed melatonin to 15 lux given late in the subjective night; evening light did not suppress melatonin at 15 lux. Too few pubertal adolescents (n = 7 to date) have completed the study to determine whether developmental differences exist; however, preliminary trends do not show suppression to 15 lux evening or morning. If suppression of melatonin is a marker for phase-shifting effects of light, an adolescent decline in early morning light sensitivity may explain why early rising times due to early school starting times do not seem to mitigate adolescent adolescents’ tendencies to phase delay(3).

References:

Research supported by NIMH MH52415 and NIMH MH01358

Figure 1
Sleep and Light Schedules

Figure 2
Melatonin Response to Light

Results: The time course of performances during the 36-hr protocol did not significantly differ between morning and evening type subjects. Neither sleep latency or total number of sleep onsets differed between the 2 groups. Nevertheless we observed a group effect in the subjective sleepiness scores (F=4.9, p=0.04). Evening type subjects rated themselves more sleepy than morning type subjects especially during day 3 morning time of (8:30-14:30) and day 4 morning time (8:30-11:30).

Conclusions: In unmasking condition, evening type subjects do not perform significantly better than morning type subjects especially during nocturnal period. Compared to morning type subjects, evening type subjects overestimate their subjective sleepiness during morning time.

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321.E
Performance, Somnolence and Morningness/Eveningness During Extended Wakefulness
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Introduction: Morningness/eveningness may be related to differences in phase relationship between sleep/wake schedules and circadian pacemaker. Previous study have shown that, in masking condition, evening type subjects are more sleepy during the morning than morning type subjects. In addition evening type subjects are less sensible to sleep deprivation. We tested this hypothesis in an unmasking condition.

Methods: 18 active healthy male subjects (9 morning type and 9 evening type subjects, 21.4±1.9 years) were included in this study. They were instructed to keep regular activity and sleep-wake schedule during the 2 weeks before experiment. They spent 2 baseline nights in the laboratory with a fixed sleep-wake schedule (bedtime : 23:30, wake time : 7:30). On the third morning, they began an unmasking 36-hour constant routine protocol. Simple reaction time test (mean reaction time, 10% slowest reaction time and lapses > 500ms) and self-rated sleepiness (Visual analogic scale, 100 mm) were assessed every hours. Repeated test of sustained wakefulness were performed at 9:00, 11:00, 13:00, 15:00, 17:00 and 19:00 of day 3 and day 4. Two-way analysis of variance for repeated measures (time*group) were performed for each variable separately.

Results: The time course of performances during the 36-hr protocol did not significantly differ between morning and evening type subjects. Neither sleep latency or total number of sleep onsets differed between the 2 groups. Nevertheless we observed a group effect in the subjective sleepiness scores (F=4.9, p=0.04). Evening type subjects rated themselves more sleepy than morning type subjects especially during day 3 morning time of (8:30-14:30) and day 4 morning time (8:30-11:30).

Conclusions: In unmasking condition, evening type subjects do not perform significantly better than morning type subjects especially during nocturnal period. Compared to morning type subjects, evening type subjects overestimate their subjective sleepiness during morning time.

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322.E
Evidence for a Specific Circadian Rhythm of Temperature Drops Associated with Recumbency and Sleep
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Introduction: Within a short time of going to bed (i.e. good night time (GNT)), a temperature drop (TD) occurs. It is not known whether these TDs follow a circadian rhythm independent of the underlying core body temperature rhythm, or whether TDs are only affected by factors such as age, current body temperature, time spent asleep (TSA), or cumulative sleep loss. We used a 90-minute day paradigm to investigate these questions.

Methods: Subjects (10 Old, 18 Young) underwent a 90-minute-day protocol of 40 sequential 60-minute enforced awake periods each followed by a 30-minute enforced recumbent period of permitted sleep. Core body temperatures and polysomnographic parameters were collected throughout. Sleep onset was defined as Stage 2 onset. Individuals’ times of tem-
perature minimum (Tmin) were estimated using cosinor analysis of each individuals’ complete temperature data. GNTs were rescaled to Tmin, and coded into 90-minute bins. TD was defined as temperature at GNT (GNTTEMP) minus the temperature at “night’s” end. As a first step, we fitted a linear mixed model to remove the influence of individually-variable effects of GNTTEMP, AGEGROUP and TSA on TD (Model 1) and plotted its residuals to inspect for any circadian rhythm. We then fitted an expanded, second linear mixed effects model (Model 2) to test for presence of a TD circadian rhythm, and to estimate its phase and amplitude. Model 2 used sine and cosine functions of time bins relative to Tmin to estimate its phase and amplitude.

Results: Figure 1 displays means and standard deviations of phase bins of GNTTEMPs, confirming a robust core body temperature rhythm. Figure 2 displays means and standard deviations of Model 1 temperature residuals, clearly suggesting a circadian rhythm of TD’s. The cosine and sine terms in Model 2 were significant (p < 0.05), indicating the presence of a TD circadian rhythm corrected for the variables included in Model 1. TD rhythm amplitude was estimated to be 0.08°C, with a 9-hour phase delay in relation to Tmin.

Figure 1

![Figure 1](image1.png)

Figure 2

![Figure 2](image2.png)

Conclusions: TD demonstrated a significant circadian rhythm in this 90-min day protocol, even after statistically correcting for GNTTEMP and other linear effects. This TD rhythm is not simply a reflection of the core temperature rhythm, since they are out of phase (compare Figure 1 with Figure 2). Correcting for GNTTEMP made this conclusion possible. Time in study did not affect TD appreciably, suggesting that mild cumulative sleep loss incurred during the protocol does not affect TD. TSA and AGEGROUP appeared to be minor and interacting linear effects. Age-dependent differences in TD amplitude and/or phase position are still a possibility, and might correlate with age-related differences in sleep propensity and timing. Parameter estimates for core body temperature rhythms are not only affected by changes in posture and sleep-wake state, but possibly also by the circadian times when those changes occur. Conceivably the upright/waking temperature rhythm may have a different phase than the supine/sleeping temperature rhythm.

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323.E

Effect Of Exercise And Aging On Locomotor Activity And Melatonin Rhythms In The Siberian Hamster (Phodopus sungorus)

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Introduction: Aging is associated with changes in circadian rhythms in humans and in rodents. Among the changes are an increase in fragmentation of the activity rhythm and, although reports are variable, a reduction in the amplitude of nocturnal melatonin secretion. Enhanced activity is capable of entraining circadian rhythms and may ameliorate some of the effects of aging on the circadian system. This study tested the hypothesis that exercise, provided by access to a running wheel, improves the expression of activity rhythms and melatonin rhythms in hamsters of various ages.

Methods: Male Siberian hamsters were raised on a 16:8 h light-dark cycle (LD 16:8) and placed in individual cages at 3, 10, or 17 months of age. Half the animals of each age group had a running wheel in their cage to stimulate running activity; the remainder were placed in a cage without a wheel. Running wheel activity was recorded for hamsters housed with a wheel. Total locomotor activity was recorded for all hamsters using infrared motion detectors. Activity was recorded for two weeks under LD 16:8. The period of melatonin secretion of Siberian hamsters is proportional to the length of the night. To verify that the melatonin rhythm of aged males expands with an increase in night length, the photoperiod was changed to LD 6:18. Ten weeks later hamsters were implanted with an atrial catheter and blood samples were drawn throughout the night under dim red light. Serum was analyzed for melatonin using radioimmunoassay. Activity data were analyzed using ClockLab Software (Actimetrics, Inc.).

Results: Preliminary analysis indicates that the presence of a running wheel ameliorates the age-dependent decline in nocturnal melatonin amplitude (Repeated measures ANOVA: Age p <.001, Age x Wheel x Time p = <0.001). In aged males in which an increase in melatonin was detected, the duration was appropriate for the length of the night. Aging was associated with a significant decline in the strength of the activity rhythm (power of FFT) as measured during the last two weeks of the experiment (ANOVA: Age, p = 0.02). There was a significant interaction between aging and the presence of a running wheel (p = 0.03). Contrary to expectations, aged males exposed to a running wheel had poorer activity rhythms than aged males without a running wheel.

Conclusions: Exercise may enhance melatonin secretion in aged hamsters. The melatonin rhythm may be a better measure of rhythm integrity in this study because of a conflict between the presence of the running wheel and the monitoring of locomotor activity using infrared motion detectors. Additional analysis of both running wheel activity and infrared activity and from other periods during the experiment will be employed to resolve this question.

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324.E

In Mouse Restraint Stress at Light Onset Produces an Increase in REM Sleep Whereas Restraint at Dark Onset Does Not

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Introduction: Restraint stress induces a specific increase in REM sleep
in rodents. However, whereas most physiological, endocrine and behavioral consequences of restraint are strongly dependent on the time of day at which it takes place (1,2), no study has directly addressed the question whether the REM sleep promoting effect of restraint stress is also time dependent.

**Methods:** Adult male C57BL/6J mice were implanted with permanent electrodes to record EEG and EMG. After at least 2 weeks of recovery, sleep-wakefulness patterns were recorded for 2 days. The first day was a baseline recording and on the second day the mice were subjected to 1 h of restraint stress starting at either the onset of the light phase (n=8) or at the onset of the dark phase (n=8).

**Results:** Restraint stress at light onset resulted in a significant increase in REM sleep, especially in the subsequent dark phase. This increase in REM sleep was much larger than the amount of REM sleep that was lost during restraint and therefore could not be attributed to a rebound from sleep deprivation. In contrast, restraint stress at dark onset did not induce a significant increase in REM sleep, neither in the remainder of the dark phase nor in the subsequent light phase.

**Conclusions:** These results support earlier findings that restraint stress can induce an increase in REM sleep in mice. At the same time, however, the data show that this REM sleep inducing effect is strongly dependent on the time of day at which the restraint takes place.

**References:**


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325.E

**The Effect of Circadian Phase on Sleep Efficiency in Blind People with Free-running Rhythms**

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**Introduction:** Sleep disturbances are common among totally blind people with free-running circadian rhythms (1), but the dependency of sleep quality on circadian phase has been documented in only a few studies (2,3). We investigated whether the sleep quality of such individuals depends on the circadian phase of the endogenous melatonin rhythm.

**Methods:** Seven blind subjects wore wrist activity monitors for 1-2 months. Melatonin concentrations were measured from 24-hour blood samples obtained at 2-3 week intervals. The slope of the regression line fitted through the timing of the onset of endogenous melatonin secretion (> 10 pg/ml) was used to calculate circadian period. The circadian period of each subject was then used to predict the daily melatonin onsets (MO) and corresponding circadian phases (circadian phase 0 degrees = MO at 21:00h).

**Results:** The figure below shows sleep efficiency (averaged in 15-deg bins) double-plotted in relation to the circadian phase of melatonin rhythm. Lowest values (i.e. < 60%) were more frequently observed when the onset of the endogenous melatonin secretion occurred between 05:00 to 07:00 h (120 -150 degrees).

**Conclusions:** These data confirm that the quality of sleep depends on the circadian phase of the endogenous biological clock. Our results also show that the daytime rise in melatonin concentration will not always be associated with poor sleep in blind subjects, but only when the melatonin secretion begins within a critical window, i.e. in the early morning hours.

**References:**


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326.E

**Individual Differences in Cognitive Performance Relating to Circadian Typology and Subjective Sleep Quality in the Presence of a Stressor**

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**Introduction:** A meta-analysis of sleep deprivation studies (Pilcher and Huffcutt, 1996) suggested that total sleep deprivation impairs human performance and that partial sleep deprivation (<5 hours in a 24-hour period) has a greater effect on functioning than either long-term or short-term total sleep deprivation. This finding has implications for individuals who are partially sleep deprived. Such factors as circadian type (morningness/eveningness) and acute stress may be associated with partial sleep deprivation in the absence of pathology and subjective sleep quality may be a marker of partial sleep deprivation. This study tests the hypotheses that cognitive performance is worse in individuals reporting poor sleep quality when confronted with a stressor and that performance
is also worse for testing sessions that occur out of sync with circadian type.

Methods: Participants: A total of 121 undergraduate students (ages 18 to 50, mean = 24.1, sd = 7.4) participated in this study; however, four participants were excluded from the final analysis due to diagnoses of attention deficit disorder and drug use. 90 participants were women and 23 were men. None reported a diagnosed sleep disorder. Procedure: Participants were randomly assigned to either a “stressor present” or a “stressor not present” condition. A six-minute mental arithmetic task (MAT) was used as an acute situational stressor. Participants completed a demographics fact sheet. Horne and Ostberg’s Morningsness-Eveningsness Questionnaire (MEQ) (1976), and the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, & Monk, 1989). Those assigned to the stressor present condition then completed the MAT. All participants then completed a battery of cognitive tasks, including an attentional vigilance task, mental rotation task, and wordlist and digit span subtests of the Wechsler Memory Scale-III (WMS-III). Tasks were counterbalanced across participants. The wordlist subtest of the WMS-III was presented before the other tasks, and the second presentation occurred after completion of the other tasks.

Results: A 2 x 2 ANOVA of stressor present / stressor not present by sleep quality (median split: good/poor) revealed a significant main effect of stressor on mental rotation errors (F(1,109) = 5.662, p < .05), reflecting more mental rotation errors in those exposed to the acute stressor. We found a main effect of sleep quality on digit span (F(1,109) = 8.357, p < .01): poorer sleep quality was associated with poorer performance. No significant interaction effects were found for this analysis. A 2 x 2 ANOVA of stressor condition by synchrony of testing time with circadian phase preference (synchrony/asynchrony) revealed a main effect of synchrony on wordlist retention (F(1,48) = 4.853, p < .05), such that asynchrony was associated with diminished wordlist retention. No significant interactions were found.

Conclusions: No significant interactions emerged from the data to implicate an influence of acute stress on the effects of sleep quality or circadian phase preference on cognitive performance. Nonetheless, the findings provide evidence to support the hypotheses that subjective sleep quality and circadian phase preference influence certain aspects of cognitive performance as a function of testing time.

References:

327.E

Effect of a 75/150 minute Sleep-Wake Schedule on the Accumulation of Slow-Wave Sleep and Wakefulness after Lights off

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Introduction: There is a large body of evidence that slow-wave sleep (SWS) is primarily regulated by the sleep homeostat (for a review see 1). We investigated dynamics of SWS and wake accumulation across a 75/150-min sleep-wake paradigm and its repercussions on the buildup rate of these two variables during the subsequent recovery night.

Methods: Following two days in the laboratory (16h scheduled wakefulness and 8h of sleep) in which subjects slept at their habitual bedtimes, six male and two female subjects (age: 21-32y) underwent a 40-h nap protocol under constant posture conditions. In the course of this protocol, subjects completed 10 alternating cycles of 150 min of scheduled wakefulness (~8 lux) and 75 min of scheduled sleep (~0.03 lux). An 8-h recovery night starting at habitual bedtime followed the nap protocol. The EEG was recorded continuously from a 12-ferential EEG lead, and sleep stages were visually scored according to established criteria.

Results: During the ten 75-min naps, subjects slept a total of 434.3 min ± 31.5, which did not differ significantly from total sleep time in the 8-h baseline night (431.4 min ± 10.5). However, accumulated SWS during the nap protocol was significantly higher than during baseline sleep (83.5 min ± 8.6 vs. 69.6 min ± 8.3; figure, upper panel). During recovery sleep, SWS accumulation was significantly reduced when compared with corresponding values during the baseline night (interval 2 to 4, p <0.05, Wilcoxon matched pairs test). Furthermore, accumulated wakefulness after lights off in the scheduled nap episodes reached 305.7 min ± 29.1 at the end of the nap protocol and was significantly enhanced at the beginning of the recovery night (interval 1 and 2, p <0.05, figure, bottom panel).

Figure 1

Conclusions: Living under a 75/150 min sleep-wake schedule resulted in the same amount of total sleep (~7.2h) and wakefulness (~32.8h) as under a 16:8h sleep-wake schedule for the duration of 40 hours. However, SWS was enhanced, mostly at the cost of stage 2 and REM sleep. As a consequence, sleep pressure at the end of the nap protocol was low. Evidence for that comes from the reduction of SWS below baseline together with an increase in wakefulness after lights off in the subsequent recovery night. Thus, by distributing short sleep episodes over the entire circadian cycle, it was possible to produce enough SWS in order to maintain sleep pressure at a lower level than under entrained conditions (16:8h). Our data give evidence for a sleep stage specific modulation of the homeostatic sleep pressure.

References:

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Evening and Morning Gender Differences in Waking Delta EEG Activity in Young Adults

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Introduction: Studies have reported that women tend to have more EEG delta power in non-REM sleep than men, while others have not.1-3 Authors have proposed several hypotheses to explain these gender differences, including possible differences in sleep regulatory mechanisms.1 In the present study, we analyzed waking EEG activity in young men and women prior to and following a night of sleep, using different recording conditions.

Methods: 13 healthy women (age: 21.5 ± 1.8 years) and 13 healthy men (age: 22.9 ± 3.9 years) spent two consecutive nights in a sleep laboratory. Night 1 served as an adaptation night and screening of sleep disorders. On night 2, waking EEG recordings with eyes closed were performed for five minutes at three different moments: 1- in the evening before going to bed (lights off, between 22h00 and 23h00); 2- after going to bed (lights out), between “Good night” and sleep onset; 3- on the following morning (lights on, between 07h00 and 08h00). A 12-electrode montage referred to linked ears was used: C3, C4, Fp1, Fp2, F7, F8, T3, T4, P3, P4, O1, O2. EEG amplitude power (µV/Hz, 0.75Hz to 19.75Hz) was determined with spectral analysis performed on 10 to 15 four-second artefact-free epochs. Frequency bands were created but the present report will be restricted to Delta (0.75-3.75 Hz). Statistical comparisons were made separately for each hemisphere. For lights on conditions, Gender x Moment Anovas and LSD post-hoc tests were used. For the for the lights out condition, t-tests were used.

Results: The Anova showed a significant Gender effect on the evening and morning conditions; Moment and interaction were not significant. Post hoc comparisons showed significantly higher Delta values in women for Central and Parietal leads while Temporal and Frontal leads were not different; results for occipital leads were equivocal. EEG recordings between “Good night” and sleep onset did not yield different results in men and women.

Conclusions: This study had two objectives. First we wanted to determine whether gender differences in waking Delta EEG activity vary according to the moment of recording (i.e., a.m. vs p.m.). In young adults. Second, we wanted to verify how results collected according to the sampling protocol used by Ehlers et al.3 compared to that. The fact that women had higher delta power spectral values both in the evening and in the morning suggest that time, whether it is spent sleeping during the night or awakened during the day, does not interfere with this gender difference, and that gender differences previously shown for delta activity during NREM sleep1,3 are also present at various moments of the waking state. On the other hand we did not find differences between the delta range waking EEG of men and women after lights out (i.e., between “Good night” and sleep onset). This suggests that the process of trying to fall asleep minimizes EEG gender differences while maintenance of wakefulness undiscloses them. The topographic distribution of the observed differences further substantiate the need for a better understanding of the underlying neural networks involved in EEG gender differences.

References:

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Effect of Day Length on Sleep Quantity in Irregular Work Schedules

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Introduction: Because of the 24-hour-a-day operations maintained by the railroad industry, locomotive engineers are frequently required to work under irregular work schedules. Although few would deny that irregular work schedules should have some impact on sleep, little information is available on the effect of irregular work schedules on sleep. One previous study (Pitcher & Coplen, 2000) examined the effects of shorter-than 24 hour work/rest schedules (where engineers were required to report to back to work before 24 hours had elapsed) on sleep. This study reported that engineers on a shorter-than 24-hour schedule reported less sleep and poorer sleep quality than engineers on a longer-than 24-hour schedule. Instead of defining day length by work times, the current study defined a circadian day based on wake-up times from major sleep episodes. The purpose of the current study is to examine the effect of different length circadian days (defined as short, normal, and long) on self-report sleep quantity in locomotive engineers.

Methods: The current data were gathered as part of the Federal Railroad Administration’s fatigue program by the Volpe National Transportation Systems Center (Pollard, 1996). The original data set consisted of 14 days of work-rest activity in 198 locomotive engineers (mean age: 44±6.7) working a variety of work shifts in the railroad industry. Each day was defined from midnight to midnight, often resulting in one sleep episode being artificially split between two different days. To develop a better estimate of sleep times, the days in the original data set were redefined as circadian days, with each day defined from wake-up time to the next wake-up time following major sleep episodes. Major sleep episodes were typically classified as a sleep period of at least 4 hours. In some cases, decisions had to be made when there were either two or more similar length sleep episodes occurring or when no sleep episode of at least 4 hours in length occurred for 36 hours or more. In those cases, major sleep episodes were usually defined as a sleep episode that occurred at night. Not all subjects provided consistent enough data indicating sleep times to be included in the modified data set. The redefined data set con-
sisted of 179 locomotive engineers (mean age: 43.5±6.4). To examine the effect of day length on sleep quantity, we calculated the length of each circadian day and then divided the day lengths into 3 categories: a short category (< 22 hours), a normal category (between 22 and 26 hours, inclusive), and a long category (> 26 hours). After removing all days with incomplete sleep time data, a two-way MANOVA on 2006 days was completed using the day length category and subject number as factors. A Tukey’s Studentized range statistic, which accounted for different numbers of participants in each factor grouping, was used for the post hoc analysis to identify the source of significant main effects.

Results: Of the 2006 useable days in the data set, 512 days (25.5%) were classified as short days (mean length: 18.43±2.8 hrs), 952 days (47.4%) were classified as normal days (mean length: 24.0±1.0 hrs) and 542 days (27.0%) were classified as long days (mean length: 31.9±5.9 hrs). The MANOVA indicated that total sleep duration (F2,2003=175.83, p<.0001), total napping duration (F2,2003=239.51, p<.0001), and total number of naps reported (F2,2003=3.48, p<.05) differed significantly across the three day length categories. A post-hoc analysis indicated that total sleep duration differed significantly between each of the three day length categories with the most sleep being reported in long days (9.19±2.7 hrs), about 8 hours of sleep reported on normal days (8.09±1.6 hrs), and the least sleep being reported in the short days (6.78±2.1 hrs). An additional post-hoc analysis indicated that total napping time was significantly greater in long days (1.70±0.7 hrs) than in either normal (0.68±0.7 hrs) or short (0.18±0.2 hrs) days. Last, a post-hoc analysis indicated that the number of naps reported on long days (1.10±13.5) was significantly greater than the number reported on short days (0.07±0.25).

Conclusions: The current data indicate that over half of the days reported in the activity logs were either longer or shorter than the typical 24-hour day, with circadian day lengths ranging from 8.75 to 56 hours long. Furthermore, the varying length of circadian days had a differential impact on sleep habits. Long circadian days resulted in significantly more total sleep time as well as napping time than either normal or short days. In addition, short circadian days resulted in less total reported sleep than either long or normal days. Furthermore, long days resulted in more napping periods than short days. These data indicate that different day lengths caused by irregular work/rest cycles significantly impact sleep habits.

References:
(1) Pilcher JJ, Coplen MK. Work/rest cycles in railroad operations: effects of shorter than 24-h shift work schedules and on-call schedules on sleep. Ergonomics, 2000, 43, 573-588.

Note: The views of the authors do not purport to reflect the position of the Federal Railroad Administration or the Department of Transportation.

330.E

Midafternoon Increase in Spectral Power Measures of Drowsiness Phase-Shifts With Morning and Evening Bright Light

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Introduction: It has been hypothesized that the afternoon nap zone represents the effects of accumulated wakefulness (process-S) being terminated by a light sensitive (SCN-dependent) circadian arousal process (Broughton 1994). To test this hypothesis we phase advanced and phase delayed the circadian clock using light stimulation.

Methods: 8 normal male subjects, mean age (24.78 ± SD 2.5) years, were monitored on two separate occasions under low ambient light (150 lux). Night sleep hours were maintained at 2300-0600h. PSG monitoring included EEG (C3-A2, O2-A1), right EOG-M1, left EOG-M2, submental EMG and core body temperatures recorded continuously throughout the trial by combined Oxford Medilog 9000 8-channel ambulatory recorders and Minilogger systems. Following a baseline 24-hour day bright light stimulation (10,000 lux) was given on two consecutive days either in the evening (20:00-22:00) or morning (06:00-08:00) in counter balanced fashion with 30 day washout periods between. Other than during light stimulation, the level of daytime alertness was assessed every 60 min by quantified EEG followed by a simple reaction time test (reported elsewhere). For each test session, 3 min. of eyes open and eyes closed EEG was fed in parallel from the Medilog recorders to a data collection computer which permitted online data visualization. EEG was divided into frequency bands: delta1 (1.0-1.5Hz), delta2 (2.0-3.5), theta1 (4.0-5.5), theta2 (6.0-7.5), alpha1 (8.0-9.5), alpha2 (10.0-11.5) and sigma (12.0-15.5). These were analyzed by spectral analysis following FFT on artifact-free segments. A three way ANOVA with repeated measures was applied to 2 conditions across 11 times and 7 bands.

Results: For evening light stimulation (phase delay), the baseline and post stimulation temperature minima were respectively at 03:40h ± SD 32.0 min; and 05:26± SD 47.0 min; and following morning light stimulation (phase advance) they were 03:48± 45.0 and 02:55 ± 38.0. In the baseline condition a transitory period of decreased arousal (indexed by increased EEG total spectral power (1.0-15.5 Hz combined) was regularly present in the mid-afternoon. Evening light stimulation phase delayed and increased maximum spectral power, whereas morning light phase advanced it (see Fig. 1 & 2 for eyes closed, 02). All changes from baseline in timing of temperature minima and in maxima QEEG power were significant at p<.01 or better. All individual EEG bands other than sigma showed similar patterns.

Figure 1

Figure 2
morning light supports both the hypothesis and existence of a SCN-dependent circadian arousal system in humans similar to that described by Edgar et al. (1993) in sub-human primates.

References:

331.E
Salivary Melatonin as a Phase Marker in Older Subjects
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Introduction: Plasma melatonin concentrations have been demonstrated to be a robust phase marker of the circadian pacemaker in humans. Recent investigations using salivary melatonin have shown this to be as accurate as the more costly, invasive, and labor-intensive process of plasma collection. With few exceptions, those studies used data from only young adults. Here we compared estimates of circadian phase and amplitude using salivary and plasma melatonin levels in young and older subjects.

Methods: 12 young (mean + SD = 22.4 + 2.9 years) and 10 older (67.8 + 3.7 yrs) subjects participated in studies between 1994 and 2000. All were healthy, medication free, and on regular sleep/wake schedules prior to study. Following three baseline days, subjects began a constant routine, during which, hourly blood and saliva samples were collected. Samples were frozen and then plasma was assayed within 3 months of collection and saliva within 3 years, using an I-RIA kit (inter-assay cv = 13%, intra-assay cv = 8%; DiagnosTech International, Osceola, WI). A 3 harmonic waveform was fit to the data and its maximum was used as an estimate of circadian phase. The concentration ratio was estimated from the amplitude of the fitted waveforms.

Results: The average difference between saliva and plasma phase was greater in the older subjects [1.10 + 0.95 hours (absolute value)] than in the young subjects (0.40 + 0.35 hours), approaching statistical significance (paired T-test, p = 0.051). Older subjects had significantly greater variability between saliva and plasma phase (F-test, p < 0.01; Figure 1: dashed line represents line of unity). The amplitude of salivary melatonin concentration was 22.04 + 8.8% that of the plasma melatonin concentration in the young and 25.24 + 15.2% in the older subjects (T-test, p = 0.94). Older subjects had significantly greater variability in the salivary to plasma melatonin ratio (F-test, p < 0.02), though this was due to data from a single subject (with subject omitted, p = 0.74).

Conclusions: We found a larger difference and significantly greater variability between the salivary and plasma melatonin phases of older subjects. The relative melatonin concentrations in saliva and plasma are comparable to previous reports. The older subject who contributed to the increased variability in the relative concentration ratio had the lowest plasma melatonin levels of all subjects. Given our finding of a decrease in the concordance between the calculated phases from salivary and plasma melatonin in these individuals, we caution investigators planning to use salivary melatonin as the primary measure of circadian phase and amplitude in older subjects to balance the benefits of a less costly and invasive collection process with the potential for greater variability when using this measure.

References:

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332.E
Sleep Hygiene, Daytime Sleepiness, and Chronotypology in Young Adults
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Introduction: Chronotypology refers to individual differences in peak performance times mediated by circadian rhythm. Chronotype is categorized as morning (M-type), intermediate (I-type), or evening (E-type). (1) The purpose of this study was to examine the relationship between sleep hygiene, daytime sleepiness, and chronotype. Previous research has suggested that E-types engage in less adaptive sleep hygiene relative to M-types and I-types. (2) It was hypothesized that E-types would engage in less adaptive sleep hygiene without elevations in daytime sleepiness. It was further hypothesized that there would be a significant negative relationship between adaptive sleep hygiene and daytime sleepiness for M-types and I-types, whereas no significant relationship would exist for E-types.

Methods: Data were collected from 150 subjects between the ages of 18

Figure 1
Relationship between the Phases of Plasma and Salivary Melatonin

and 40 (mean age = 21.75 years, SD = 4.4 years). Subjects were excluded if a chronic medical or psychiatric disorder was indicated. Subjects completed a survey packet that included the Epworth Sleepiness Scale (ESS), Horne – Ostberg Morningness/Eveningness Questionnaire (HOMEQ), and the Sleep Hygiene Scale (SHS). Subjects were divided into morning (n = 26), intermediate (n = 77), and evening (n = 47) groups based on the HOMEQ score.

Results: One-way ANOVA revealed significant differences among the chronotype groups on the SHS (F3, 147 = 9.017, p < .001) and ESS (F3, 147 = 4.3, p < .05). Post hoc comparisons, made with Tukey’s HSD, indicated significantly less adaptive sleep hygiene (p < .05) in E-types (M = 111.49, SD = 11.8) compared with I-types (M = 117.57, SD = 9.8) and M-types (M = 123.04, SD = 14.9). ESS scores indicated significantly less daytime sleepiness (p < .05) for M-types (M = 7.72, SD = 3.06) compared with I-types (M = 9.49, SD = 2.94) and E-types (M = 9.57, SD = 3.99). Significant negative correlations were observed between the SHS and ESS for M-types (Pearson r = -0.581, p < .001), and I-types (Pearson r = -0.226, p < .05), whereas this relationship was not significant for E-types (Pearson r = -0.042, ns).

Conclusions: As predicted, E-types demonstrated less adaptive sleep hygiene while no elevations in daytime sleepiness were noted. Further, no correlation between sleep hygiene and daytime sleepiness was found for this group. Although E-types demonstrate relatively poor sleep hygiene, these individuals may be more resistant to the negative impact of these behaviors. M-types reported significantly less daytime sleepiness than did E-types and I-types with sleep hygiene scores comparable to I-types. It may be that M-types are especially sensitive to the effects of sleep hygiene. Future research examining sleep hygiene and daytime sleepiness in young adults is warranted and should consider chronotype as an important factor.

References:

333.E

Single, Moderate-Intensity, Short Duration Light Pulses Can Shift Circadian Rhythms

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(2) Faculté de Médecine, Université Libre de Bruxelles

Introduction: Light is an important entraining agent for the biological clock. It was once believed that only light of high-intensity and long duration was capable of shifting the biological clock of humans, but this has been contradicted by recent studies. Low-intensity light (180 lux) for 5 hours in the early morning for 3 days advances the profile of the melatonin rhythm by +1.2 hours when measured under a constant routine sleep wake cycle. Unpublished data indicate that a phase shift of similar magnitude was obtained following a single exposure to moderate-intensity light (3 – 4000 lux) for 3 hours at night in subjects who were allowed to sleep at their usual bedtime. In order to further investigate the response of the biological clock to light of varying duration, we conducted a study on the response of the melatonin rhythm to a single, 1-hour pulse of moderate-intensity light on subjects maintained on a dim light/dark cycle.

Methods: Eight healthy young subjects (4 male and 4 female, 29.5 ± 4.1 years) were admitted for two stays in the Clinical Research Center, each lasting 4 nights/3 days. Subjects were maintained under a modified constant routine during waking hours (room light < 20 lux, semi-recumbent wakefulness in bed, snacks of 200-250 kcal every two hours) and slept for 8 hours in the dark at their usual bedtime. Following a habituation and baseline night, subjects were exposed to 1 hour of light centered at 2½ hours before the baseline core body temperature nadir (estimated by cosine analysis with demasking). Subjects were exposed to either dim (20 lux) or moderate-intensity light (3 – 4000 lux) in a crossover design. Blood samples collected from 4pm to 10am on the nights before and after light exposure were analyzed by radioimmunoassay for melatonin. The rising and declining phases in the profile of the melatonin rhythm were defined as: onset=20% of peak, synoff=75% of peak, offset=20% of peak. Phase shifts were assessed as the difference in the baseline and post-treatment melatonin profiles.

Results: At baseline, the timing of core body temperature minimum was 4.83 ± 1.62 h (n=7) in the moderate-intensity light condition and 4.27 ± 1.82 h (n=2) in the dim-light condition. Melatonin levels have been analyzed for the first 4 subjects in the moderate-intensity light condition. Exposure to 1 hour of light at 3 – 4000 lux prior to core body temperature minimum delayed the onset (-0.50 ± 0.43 h), synoff (-0.13 ± 1.44 h), and offset (-0.25 ± 0.50 h) of the melatonin profile. These results will be compared to the phase shifts seen in the dim-light condition upon completion of the assays.

Figure 1

Conclusions: These preliminary results indicate that 1 hour of light exposure prior to core body temperature minimum leads to modest delays of up to 30 minutes in the circadian phase of young adults maintained under a dim light/dark cycle with sleep at the usual bedtime. This research may provide valuable information for the development of practical interventions in the treatment of disorders of sleep and circadian rhythms.

References:

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334.E

Bright Light Treatment for Correction of Shift Work Fatigue

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Introduction: This study was designed to see if bright light at the beginning of shift work would improve total sleep and improve work per-
performance. There are a number of high intensity light treatments commercially available. There has been little clinical evaluation to determine if bright light treatments are an effective tool in clinical settings. We felt that if this is an effective tool to reduce work related fatigue and improve performance, work related errors would be significantly reduced.

Methods: The subjects were ICU nurses in medical resident training hospitals. We have evaluated a total of 7 subjects to date 6 female 1 male. Average age of the subjects was 45 years. Each subject was randomized to receive 10,000 Lux bright light at the start of shift work for a minimum of one hour or to the control group. The subjects received the bright light with “photon glasses” each night at the beginning of the shift (two to six nights). During the control shifts no light treatments were given. Each subject was then crossed over to the opposite treatment during the next series of night shifts (always the same number of nights on each arm of the study). The subjects were given a ActiTrac motion detector during the evaluation period, filled out an Epworth Sleepiness Scale and Stanford Sleepiness Scale questionnaire at the completion of their series of night shifts, and underwent a psychomotor vigilance task (PVT) at baseline and at the completion of their series of night shifts. All data was kept in confidence and no subject was informed or influenced on performance at any time. The data analysis was with base line, to control to light treatments. Means and Standard deviations were computed across the series.

Results: Epworth sleepiness scale Average & (STD) for the control score was 1.6(1.57), Light treatment score was 1.3 (2.3). Stanford sleepiness score for the control 3.3 (0.5) and for the light treatment group 2.3(0.5). PVT results for the rested subject was a percent change in slope of –1.65 (2.6), in the light treatment group percent change in slope was –11.8 (6.1), for the control a percent change in slope of -22.1 (5.8). Total sleep average for the control group at 5.75 hours and for the Light treatment group 6.25 hours.

Conclusions: The above series of subjects is showing an interesting trend in improved work performance and an improvement in feeling of rest. Although not currently statically significant the data suggest that further study in this area is needed. If work performance as measured by the psychomotor vigilance tests is a reflection of improve concentration and therefore a reduction in work related errors, this could have a significant impact on improved out comes in sensitive areas where high intensity work is constantly required.

335.E

Circadian Firing Pattern of 95 Patients with Automatic Implantable Cardioverter Defibrillators (AICDs)

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Introduction: Automatic interventricular defibrillators (AICDs) have been documented as effective life-extending devices for patients with a history of malignant arrhythmia or awaiting cardiac transplant. A circadian pattern of sudden death and arrhythmia has long been reported in the literature; however no conclusive etiology has been found.

Methods: Retrospective chart review of patients with AICDs firing patterns documented at the Stanford University Hospital Center from 1993 through January of 2000. Of 227 patients with AICDs, 103 received shocks; 75 were alive, and 28 were deceased. (See Table 1). Data were available from 74 men and 21 women. 18 of the men and 6 of the women died during the course of the study. Due to the disparity in numbers, data analysis was confined to the men. Repeated shocks were grouped into minimum 1-hour intervals. Each cardiac event requiring defibrillator firing was allocated to a two-hour time period. A mixed model analysis of variance was conducted on the data for male subjects. Time was a repeated factor (12 x two-hour periods) and state at the end of the study (alive or deceased) was a between-subjects factor. Cross correlation analysis was also conducted comparing the two time series.

Results: The analysis indicated no difference in the firing pattern for the deceased and alive group. There was no evidence for a circadian pattern for the firing of AICDs in the study population. Further evaluation of the female subgroups will help determine if the firing pattern for the deceased is different from the alive group.

Table 1

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<th>Alive</th>
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<tr>
<td>Females</td>
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<td>50(21)</td>
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<td>60-69</td>
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<td>70-79</td>
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<td>31.8(6.8)</td>
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</table>

Figure 1

Conclusions: There appears to be no significant pattern for the firing of AICDs in the study population. Further evaluation of the female subgroups will help determine if the firing pattern for the deceased is different from the alive group.
Modafinil Improves Alertness and Performance During Simulated Night Work

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Introduction: It has been well documented that night shift workers experience excessive sleepiness and associated impairment in performance. The novel wake-promoting therapeutic, modafinil has previously been demonstrated to safely and effectively promote wakefulness in patients with sleep disorders and in healthy volunteers tested in acute sleep deprivation.1,2 We report here the first investigation of modafinil’s ability to promote wakefulness and improve performance in healthy subjects tested in a simulated night shift work protocol.

Methods: Subjects were tested in a multi-center, repeated-measures, placebo-controlled, double-blind, randomized design. Sixteen healthy subjects, (7F, 9M) completed the investigation (mean age 26.9 SD 4.7). Subjects were free from any acute or chronic medical or psychiatric conditions. Additionally, subjects were free from all medications beginning at least two weeks before the start of the investigation. Sleep wake times were fixed at 2300 to 0700 for one week immediately prior to the laboratory phase of the investigation. Compliance with sleep-wake times was verified by Actiwatch-L wrist activity/light monitors and with sleep diaries. Following this ambulatory recording week, subjects participated in seven days of intensive physiological laboratory monitoring, conducted at either the BWH/HMS or UPENN laboratories. Following two nights and two days of baseline nighttime sleep and daytime waking performance assessment, subjects were tested in four nights of simulated night shift work with sleep episodes displaced exactly 12 hours. Neurobehavioal alertness and performance were assessed every two waking hours throughout the laboratory admission. Performance was assessed by the Neurobehavioral Assessment Battery, including a twenty minute long Psychomotor Vigilance Test (PVT). Subjective sleepiness was assessed hourly using the visual analog scale (VAS) and the Karolinska Sleepiness Scale (KSS). Modafinil (200 mg) or identical looking placebo was administered at 0300, 30 minutes prior to the beginning of the 12.5 h simulated night shift. The effects of nighttime modafinil administration on PSG-recorded sleep were assessed throughout the daytime sleep opportunities from 0700-1900 h.

Results: In the placebo condition, subjective self-estimates of sleepiness and PVT lapses in performance increased throughout the night (see Figures 1 and 2). Modafinil, however, significantly attenuated this nocturnal decline in alertness and performance. Modafinil significantly improved KSS subjective alertness, as evidenced by a significant main effect for treatment condition (p<0.05). Modafinil also reduced the number of PVT lapses as evidenced by a significant treatment by time of night interaction (p<0.05). Modafinil was associated with increased intensity of both headaches and nausea, although both were still mild to moderate in severity and resolved on their own. Modafinil treatment did not significantly affect total sleep duration or sleep architecture in subsequent 8-hour fixed daytime sleep opportunities.

Conclusions: Compared to placebo, modafinil (200 mg) significantly improved nighttime waking alertness. Modafinil also significantly improved neurobehavioral performance across four consecutive nights of simulated night shift work. Modafinil was well tolerated and did not significantly alter daytime recovery sleep. These results suggest that modafinil may be a safe and effective treatment for performance-impairing sleepiness associated with night shift work.

References:

The Temperature Rhythms Delay of Intensive Care Patients After Surgery

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Introduction: Many contributory factors may disturb the continuity and quality of sleep of intensive care patients i.e.: external conditions (noise, light, temperature), factors related to the medical staff activity and discomfort due to the equipment and also factors due to the disease itself including pain and medications. However we found no study about the circadian effects of intensive care units nursing. The preceding factors may interfere with the circadian rhythms of the patients and may have therefore consequences on their rehabilitation from surgery.
Methods: We surveyed 16 patients hospitalised in an intensive care unit (ICU) following a coronary bypass heart surgery. All patients were men volunteers for the study (average age 66 years old) and had signed an informed consent to participate. The patients had to complete a Pittsburgh Sleep quality Index (PSQI) and a Leeds questionnaire. They had also to evaluate the quality of their sleep on a visual analogic scale VAS before surgery and after the first 24 hours passed in the ICU. Circadian aspects were assessed by the Horne and Otsberg questionnaire and by the continuous measurement of the skin temperature during the 36 hours following the admission. Lightness and external temperature in the room of patients were also notified six times a day.

Results: Patients complained of great difficulties to sleep during the first 24 hours in the ICU. The most disturbing factors reported were: noise for 14 of them, light for 7 patients, heat for 3, pain for 3, and treatments for 3 of them. The skin temperature curve in the total group was greatly delayed in comparison with the usual temperature profile. The temperature minimum was at 3 p.m. and the maximum at midnight.

Conclusions: The phase delay of the temperature of our patients hospitalised in an ICU following a coronary bypass surgery may be attributed to several causes. Surgery by itself may have modified the temperature rhythm, the external factors such as light, medical activity and heat may also had a role. However the light inside the room was not very different in the ICU and in ordinary life. The treatment administrated after surgery: cortisone, analgesics may also play a role. This observed modification of temperature may contribute partially to the sleep difficulties assessed by patients.

338.E
One Week of Night Shift: Cardiac Autonomic Activity During Daytime Sleep

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Introduction: Shiftworkers are 40% more likely to suffer from cardiovascular disease compared to non-shiftworkers (Boggild and Knutsson, 1999). This statistic can be partially explained by the high prevalence of well known cardiovascular risk factors such as smoking, hypertension and obesity among the shiftworking population. However, it is possible that the reversal of the sleep/wake cycle may have a specific negative impact on cardiovascular health. Therefore the aim of the current study was to assess the impact of continuous nightshift on the cardiovascular system by investigating cardiac autonomic activity during daytime sleep.

Methods: 10 (5M; 5F) young subjects aged between 18 and 25 attended an adaptation and baseline night before commencing one week of continuous night shift within a laboratory setting. During night shift subjects performed psychomotor performance tests and were not allowed to nap. Salivary melatonin data also was collected during this time and light levels ranged from 35 to 300 lux. In order to simulate the light exposure that occurs when driving home after a nightshift, between 0700 and 0800 subjects went outside for 20 minutes. Subjects then slept in dark, quiet, individual bedrooms maintained at 21°C until they naturally awoke. Prior to sleep they were fitted with a polysomnographic montage of electrodes and rectal, chest, forehead, foot and respiratory thermistors. Impedance cardiography allowed the measurement of heart rate, respiratory sinus arrhythmia (RSA; a measurement of parasympathetic activity) and pre-ejection period (PEP; inversely proportional to sympathetic activity).

Results: NA

Conclusions: Preliminary analyses indicate that total sleep time, amount of slow wave sleep and amount of REM sleep obtained during each sleep period did not vary across the study. However, less light NREM sleep was obtained during the day and the timing of REM sleep altered over the week. During typical night sleep cardiac parasympathetic activity is known to progressively increase with deepening NREM sleep while sympathetic activity has been reported to show the opposite changes (Van de Borne et al., 1994). Further analyses will investigate the generalisability of this relationship to daytime sleep. In addition to exploring the relationship between sleep parameters and cardiac autonomic activity, the influence of circadian factors on cardiac activity during daytime sleep will be assessed.

References:
Sleep-Wake Behavior Patterns and Eye Closure States in Juvenile Greater Rheas (Rhea americana)

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Introduction: Sleep necessarily occurs at the expense of wakefulness. Consequently, animals face a situation in which sleep and wakefulness are inevitably in conflict. Some animals have essentially side-stepped this problem by simultaneously engaging in both wakefulness and sleep; one cerebral hemisphere sleeps while the other remains awake, a unique state known as unihemispheric slow-wave sleep (USWS)\(^1\).\(^2\). The study of sleep in birds has revealed important information about the function of sleep, especially as it relates to unilateral eye closure behavior and USWS\(^1\).\(^2\). Unilateral eye closure has been reported in 29 species and 13 orders of birds, but not in ritches\(^3\). This raises a question about the breadth of this behavior in birds and suggested that USWS evolved only in relatively modern birds. In our present study, we observed the sleep-wake patterns of juvenile Greater Rheas (Rhea americana), large flightless birds that are related to ostriches. In evolutionary terms, these ritches represent an ancient line of birds. Clearly, studies of sleep behavior in ritches will shed light on the evolution of avian sleep.

Methods: Three juvenile rheas (3-6 weeks post hatch) were purchased from a local exotic animal farm. We developed a rhea husbandry protocol using a 12/12 LD (lights on 6:00, lights off 18:00 h) simulated sunlight and simulated moonlight (4 W). Water was provided ad libitum. Feeding was once per day with commercial rattle food and probiotic supplements. The rhea room (4 x 6 m) was maintained between 74-78 F. Duck decoys and rubber matting were placed in the room to enhance the environment. Behavior was videotaped 24 h / day, for 13 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 patterns (bilateral and unilateral) were evaluated frame by frame using focal animal sampling when both eyes could be observed. Rhea behavior was determined from a single instantaneous sample of each bird’s behavior / hour. Behavior categories included sleep postures (sitting with head-on-floor, head-on-back, or head-up) and awake behavior (walking, preening, feeding, or other). Results are reported as average hours ± SE of each behavior / 24 h throughout the 13-week period, and n is the number of hours sampled.

Results: Rheas concentrate their sleep during the night with very few daytime sleep bouts. Individuals sleep between 8 to 14 h per 24 h (average sleep duration is 10.3 ± 0.28 h, n=323). In the first hour after lights out (18:00-19:00) and prior to lights on (5:00-6:00 h), rheas would quietly sit in the “preferred” roost corner of the room, sometimes preening or stretching just before sleeping or after awakening. Within the first hour of darkness, they would assume a sleep posture by resting the head on the back (65.4%, n=212), resting part of the neck on the floor while keeping most of the head and neck upright (28.3%, n=91), or resting their head on the floor mat (6.3%, n=20). In the head-on-back sleep posture, the eyes were often obscured by slightly raised scapular feathers. When both eyes could be observed, the eyelids would bilaterally close and open. Only two events of unilateral eye closure were coded using instantaneous sampling. Focal animal sampling was more effective at detecting bilateral and unilateral eye closure events. After rheas sustained sleep in a head-up posture, the head and neck would slowly descend to the floor. Occasionally, the head would rapidly drop to the floor then slowly roll to one side. The rhea would then jerk its head upright, awaken, and repeat this sleep-wake cycle several times during the night.

Conclusions: The rhea average sleep duration was similar to most modern bird species. Short-term head drooping events suggest that nuchal atonia may be an indicator of a REM like sleep state in birds, which has a duration of less than one minute\(^2\). Unilateral eye closure was observed, but was much less prevalent than other bird laboratory studies by our research group\(^1\).\(^3\). However, the observation of unilateral eye closure indicates a potential for USWS in ritches as well as suggesting a potentially long evolutionary age for this behavior. This further suggests the possibility that dinosaurs had unilateral eye closure, as they are believed to be ancestors to birds. Our next step will be recording bilateral hemispherical EEG’s during unilateral eye closure and subsequent analysis of possible USWS epochs.

References:

Charles Amlaner was supported by an Indiana State University sabbatical leave during 2000.

340.F

Fos Expression in the Pigeon (Columba livia) During Wakefulness and Sleep

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Introduction: Despite being distantly related, birds and mammals are the only animals known to display unequivocal slow-wave sleep (SWS) and rapid eye-movement (REM) sleep. Given the remarkable similarity between avian and mammalian sleep, birds provide a unique and largely unexplored opportunity to investigate the functional basis of sleep. Aspects of sleep restricted to either birds or mammals are likely to reflect peculiarities specific to sleep in either group, whereas features shared between birds and mammals are likely to reflect more fundamental aspects of sleep. Recently, several studies have shown that changes in Fos, the protein product of the immediate early gene, c-fos, are associated with changes in behavioral state in mammals. In general, Fos increased during waking and decreased during sleep (Cirelli and Tononi, 2000). Herein we report preliminary findings of the first study to investigate behavioral state-related changes in Fos expression in birds.

Methods: Sleep-wake behavior was recorded in adult pigeons (2 male, 2 female) maintained under a 12:12 LD photoperiod. Eye-state was used to measure behavioral state (Rattenborg et al. 2000). Each bird was assigned to either an AWAKE group (N=2) or an ASLEEP group (N=2). AWAKE birds were sacrificed one hour after the dark-light transition, following a 1-hour period dominated by spontaneous active wakefulness. ASLEEP birds were sacrificed 1-hour before the dark-light transition, following at least a 3 - hour period dominated by behavioral sleep. Immunocytochemistry was performed using an antibody for avian Fos (c-Fos K-25, Santa Cruz Biotechnology, #sc-253).

Results: Preliminary inspection of forebrain regions revealed little difference in Fos staining between the AWAKE and ASLEEP groups. In both groups, staining was diffuse and relatively low in the ectostriatum, neostriatum, paleostriatum and hyperstriatum ventrale. Conversely, in both groups, a relatively high level of Fos staining was observed in the
area encompassing the hippocampus, parahippocampus and possibly the adjacent hyperstriatum accessorium. In contrast to the forebrain, the tectum showed higher Fos staining in the AWAKE group in comparison to the ASLEEP group.

Conclusions: Preliminary analysis of Fos expression in the pigeon revealed little difference between the AWAKE and ASLEEP groups in most forebrain structures. With the exception of the hippocampus, parahippocampus and adjacent areas, possibly including the hyperstriatum accessorium, Fos expression was relatively low throughout the forebrain in both groups. Based on prior studies in mammals, the distribution of Fos and the apparent similarity between AWAKE and ASLEEP birds in the forebrain were unexpected. In contrast to the forebrain, Fos was higher in the tectum of AWAKE when compared to ASLEEP birds, which may be related to wakefulness, light and/or visual input. Ongoing studies will clarify whether these preliminary results reflect a fundamental difference between birds and mammals, and may influence our understanding of the functional basis of sleep-wake changes in gene expression in mammals.

References:

341.G

Arousal To Acoustic Stimuli In Children With The Obstructive Sleep Apnea Syndrome (OSAS)

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Introduction: Unlike adults, children do not usually arouse in response to obstructive apneas. This suggests either a primary or secondary defect in arousal mechanisms. However, the effect of sleep stage on arousal has not been evaluated in this population. Normal children have lower arousal thresholds to acoustic stimulation during REM sleep than NREM sleep. Previously, we showed that normal children also had lower arousal thresholds to respiratory stimuli (hypercapnia [1] and inspiratory resistance loading [2]) during REM than NREM. In contrast, children with OSAS had blunted arousal thresholds to these respiratory stimuli, and their arousal thresholds were higher during REM than NREM. Therefore, we hypothesized that children with OSAS would have higher arousal thresholds to non-respiratory stimuli during REM than NREM sleep.

Methods: We evaluated the arousal threshold to non-respiratory (acoustic) stimuli during different stages of sleep in children with OSAS compared to healthy controls. During polysomnography, an incremental acoustic stimulus (30-100 dB) was delivered via an ear piece during different sleep stages.

Results: We studied 9 children with OSAS (age 5 ± 1 [mean ± SD] yr.; apnea hypopnea index ([AHI] 40 ± 22/hr; SaO2 nadir 84 ± 6%; peak end-tidal PCO2 55 ± 3 mm Hg) compared to 4 controls (age 5 ± 2 yr.; AHI 0 ± 0/hr; SaO2 nadir 94 ± 1%; peak end-tidal PCO2 48 ± 4 mm Hg). We found that most children in both groups did not arouse during NREM sleep even when the maximal stimulus (100 dB for 5 minutes) was applied. 50% of controls and 22% of OSAS aroused during slow wave sleep, and 25% and 22% respectively during stage 2 sleep (NS). In contrast, most children in both groups aroused during REM sleep: 100% of controls aroused, at a mean sound level of 64 ± 26 dB, and 89% of OSAS aroused, at a mean of 59 ± 24 dB (NS).

Conclusions: We conclude that children with OSAS have normal arousal responses to acoustic stimuli during REM sleep. Both normal children and children with OSAS have very high arousal thresholds to acoustic stimuli during NREM sleep. We speculate that the impaired arousal responses to respiratory stimuli in children with OSAS is a result of habituation to chronic respiratory abnormalities (such as hypercapnia) during REM sleep, when childhood OSAS is at its worst (3).

References:

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342.G

Pediatric Sleep Questionnaire (PSQ): Prediction of Periodic Leg Movements During Sleep in Children.

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Introduction: Periodic leg movements during sleep (PLMS) can occur in children and may be associated with insomnia, sleepiness, or behavioral problems that improve with treatment designed to reduce PLMS (Picchetti et al., 1998, Walters et al., 2000). Therefore, identification of PLMS in children may be important, but few children with behavioral problems undergo polysomnography. The extent to which PLMS can be detected by a clinical history is unknown. We sought to clarify this question and assess the utility of a questionnaire-based scale in the identification of children with PLMS.

Methods: Subjects were patients between the ages of 2 and 18 years who underwent polysomnography because sleep disordered breathing (SDB) was suspected. Parents completed a Pediatric Sleep Questionnaire (PSQ) that contains several potential components of a PLMS scale (see Appendix). The PSQ includes 70 closed-ended questions about children’s sleep; a parent, with help from the child, must answer yes (scored as 1), no (scored as 0), or don’t know (scored as missing data) to each item. On polysomnography, PLMS were scored when they met criteria for duration (0.5 to 5 seconds), periodicity (5 to 120 seconds between each movement), and number (at least 3 in a row). Rates of PLMS above 5 per hour of sleep were considered to be potentially significant.

Results: Subjects (n=113) had a mean age of 9.8 ± 4.0 years and 73 (65%) were male. Significant SDB (more than 5 apneas or hypopneas per hour of sleep, or esophageal pressures more negative than -20 cm of water) was found in 59 (52%) of the subjects, and 29 (26%) had 5 or more PLMS per hour of sleep (PLMI = 5). Severity of SDB was not different among those with and without PLMI = 5. Responses to several question-items — about restless legs, growing pains, leaving the bed at night, waking more than twice per night, waking feeling unrefreshed, and morning headaches — showed some association with PLMI = 5 and were averaged to obtain a composite PLMS score, artificially weighted toward the first two items by counting them twice. The PLMS score averaged 0.40 ± 0.31 and ranged from 0.0 to 1.0; a one s.d. increase was associated with PLMI = 5 (O.R. = 1.87, 95% C.I. [1.15, 3.13], p= 0.014) after adjustment for age, sex, and SDB severity (rates of apneas and
hypopneas, and minimum oxygen saturation). Sensitivity of a PLMS score > 0.33 for PLMI = 5 was 0.79, specificity was 0.56, positive predictive value was 0.38 and negative predictive value was 0.89 (Figure 1). Internal consistency was reasonable (Cronbach’s alpha = 0.71) as was test-retest reliability (rho = 0.62, p=0.0026, n=21 separate subjects).

**Figure 1**
Receiver-operator curve (ROC) for PLMS score as a test for PLMI ≥ 5. Position on the curve for the criterion score of 0.33 is shown.

![ROC Curve](image_url)

**Figure 2**
Appendix
Pediatric Sleep Questionnaire items tested and retained (bold) in the PLMS subscale, and percent of sample for whom each item was positive.

<table>
<thead>
<tr>
<th>Item</th>
<th>Percent Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>A12</td>
<td>Does your child have restless sleep? (82%)</td>
</tr>
<tr>
<td>A13</td>
<td>Does your child describe restlessness of the legs when in bed? (38%)</td>
</tr>
<tr>
<td>A13a</td>
<td>Does your child have “growing pains” (unexplained leg pains)? (46%)</td>
</tr>
<tr>
<td>A13b</td>
<td>Does your child have “growing pains” that are worst in bed? (25%)</td>
</tr>
<tr>
<td>A14</td>
<td>While your child sleeps, have you seen brief kicks of one leg or both legs? (64%)</td>
</tr>
<tr>
<td>A14a</td>
<td>While your child sleeps, have you seen repeated kicks or jerks of the legs at regular intervals (i.e., about every 20 to 40 seconds)? (20%)</td>
</tr>
<tr>
<td>A16</td>
<td>At night, does your child usually get out of bed (for any reason)? (57%)</td>
</tr>
<tr>
<td>A40</td>
<td>Does your child have difficulty falling asleep at night? (44%)</td>
</tr>
<tr>
<td>A44</td>
<td>Does your child wake up more than twice a night on average? (30%)</td>
</tr>
<tr>
<td>B1</td>
<td>Does your child wake up feeling unrefreshed in the morning? (69%)</td>
</tr>
<tr>
<td>B2</td>
<td>Does your child have a problem with sleepiness during the day? (50%)</td>
</tr>
<tr>
<td>B4</td>
<td>Has a teacher or other supervisor commented that your child appears sleepy during the day? (44%)</td>
</tr>
<tr>
<td>B6</td>
<td>Is it hard to wake your child up in the morning? (69%)</td>
</tr>
<tr>
<td>B7</td>
<td>Does your child wake up with headaches in the morning? (24%)</td>
</tr>
<tr>
<td>C8</td>
<td>This child often is easily distracted by extraneous stimuli (42%)</td>
</tr>
<tr>
<td>C14</td>
<td>This child often is “on the go” or often acts as if “driven by a motor” (41%)</td>
</tr>
</tbody>
</table>

**Conclusions:** The PSQ items that assessed restless legs, growing pains, sleep-maintenance insomnia, unrefreshing sleep, and morning headaches showed a statistically significant but decidedly moderate association with recorded PLMS. The results suggest that the PSQ-based PLMS score may provide some utility in research settings but not reliable identification of PLMS in pediatric practices.

**References:**

**343.G**
**Hyperactivity and Polysomnographic Findings in Children Evaluated for Sleep-Disordered Breathing**

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**Introduction:** Reported clinical series suggest that children with sleep-disordered breathing (SDB) or periodic leg movements during sleep (PLMS) often have hyperactive behavior that improves when the sleep disorder is treated (1,2). However, previous investigators have not compared referred patients who have sleep disorders to those with normal polysomnograms, and few have used validated quantitative measures to assess behavior. To determine what polysomnographic features of SDB might be associated with hyperactive behavior, we studied behavior, SDB, and PLMS in a series of patients.

**Methods:** Subjects were children (n = 113) aged 2 to 18 years who were referred for suspected SDB to a University-based sleep disorders laboratory. Parents completed the well-validated and commonly used Connors’ Parental Rating Scale; results for the hyperactivity index were converted to age-adjusted T-scores, which range from 0 to 100, average 50, and show a standard deviation of 10. Children underwent laboratory-based polysomnography, with esophageal pressure monitoring when requested (n = 19) by referring physicians. In this study, SDB was considered present when the rate of apneas and hypopneas was 5 or more per hour of sleep (n = 49), or when esophageal pressures reached -20 cm of water or more negative values (n = 10).

**Results:** Children with SDB (n = 59) showed high hyperactivity scores (mean 59.5 ± 18.3 s.d, 95% C.I. [54.7, 64.2]) but these scores were no higher than those of children without SDB (59.0 ± 15.1, [54.8, 63.1]). Abnormal hyperactivity scores (> 2 s.d.’s above normal) were present in 15 (25%) of subjects with SDB and in 12 (22%) of subjects without SDB. Hyperactivity showed no significant associations with the rate of apneas and hypopneas, minimum oxygen saturation, or most negative esophageal pressure (p > 0.10), but did show an association with the presence of 5 or more PLMS per hour (p = 0.02). The number of PLMS per hour of sleep (PLMI) showed a linear association with hyperactivity among those subjects with SDB (p = 0.002, Figure 1; HIT = hyperactivity index T-score), but no association among those subjects without SDB (p = 0.64, Figure 2 [two subjects with PLMI > 35 not visible]).
Parental Work Status and Sleep Habits of School-Aged Children

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Introduction: Relatively little research has investigated the sleep of elementary school children or the factors that affect sleep habits and sleep problems. Specifically, no research has considered the effects of parental work status on the sleep habits of school-aged children.

Methods: Parents of 213 students (108 girls, 101 boys, 4 unspecified) between 6 years and 12 years and 7 months (M = 111.42 months; SD = 20.65) participated in this study. All participants were recruited from grades 1 through 6 from two Catholic elementary schools. Parents of the children completed a demographic questionnaire, which included information on parental work status (e.g., full-time, part-time, not working) and other items concerning working (e.g., hours worked per week, shifts worked). Parents also completed the Sleep Habits Questionnaire (SHQ; Acebo et al., 1994), which assesses sleep patterns (e.g., usual bedtime, total sleep time) and specific behaviors associated with sleep (e.g., child resists going to bed, child wakes more than once per night). Five sub-scales are derived from this scale: bedtime problems, sleep problems, night waking, morning problems, and daytime sleepiness.

Results: After excluding for medication use and single parent homes, 187 students were included in the analyses. Children were grouped into one of three categories based on parental work status: 2 parents working full-time, 1 full time working parent/1 part time working parent, 1 full time working parent/1 parent at home. Overall, few differences were found across the children in the three groups, although (1) children with two parents working full time had earlier wake times than those with a parent at home full-time; (2) children with two full time working parents had shorter night awakenings than children in the other two groups; and (3) children with one parent working part time had more problems with sleep behavior and night wakings than the children with one parent at home full-time.

Conclusions: These findings suggest that hyperactive behavior is common among children referred for suspected SDB, regardless of the presence or severity of SDB. Current observations cannot prove causality, but they are consistent with the hypothesis that PLMS may contribute to hyperactivity and SDB may act as an effect modifier.

References:

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344.G

Sleep, Well-being and Health-related Behaviour in Early Adolescence: Preliminary Data on an Italian Sample

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Introduction: A problematic sleep has been frequently described in adolescence and difficulty in initiating sleep is one of the most common features in this life span. There is evidence that such problem can persist relatively unchanged over many years. However, few studies have investigated the relationship between sleep and other health-related behaviours in an adolescent, non-clinical population. Certain health-related lifestyles may start in adolescent years and may have major implication for later morbidity. Thus, health-related behaviour, as well as family, school, peer settings and peer relationships need to be explored to better understand the patterns of health in adolescents and to design health promotion programs for this population.
Methods: The Health Behaviour in School-Aged Children (HBSC) is an international, cross-sectional research study coordinated by the WHO Regional Office for Europe, aiming to increase the understanding of health behaviour, lifestyles and the environmental context in this age group and to promote health education programs. The Italian survey reported here is part of a pilot study aimed at testing the questionnaire designed by the HBSC group, which investigates a wide range of health behaviours, health indicators and the social environment. For this purpose the questionnaires were administered, in a classroom setting, to 373 students of 11, 13 and 15 year of age, coming from the urban areas of Turin and Rome. The final, cleaned sample consisted of 303 students (155 males and 148 females), equally distributed across age groups.

Results: Difficulty in initiating sleep, defined as inability to fall asleep for at least twice a week in the last six months, were reported by 30% of the students (17% males and 13% females); no significant differences were found regarding sex, or across different age groups. Using the variables describing the main health-related areas investigated in the HBSC questionnaire, seven scales were constructed: Well-being (three items; Cronbach’s alpha: 40), Self-esteem (three items; Cronbach’s alpha: .55), Somatic complaints (four items; Cronbach’s alpha: .52), Mood (three items; Cronbach’s alpha: .74), Substance use (eleven items; Cronbach’s alpha: .46), Peer relationships (five items; Cronbach’s alpha: .53) and Family relationships (four items; Cronbach’s alpha: .53). For each item the responses, rated in a Likert-type format, were combined into two categories, on the basis of the frequency of the investigated behaviour. The final scale was created summing-up the scores of the different items. In order to better understand the influence of these factors on sleep difficulties we performed a multiple logistic regression. We initially included in the model a dichotomised variable, representing sleep difficulties, as dependent variable and all the above-mentioned scales as independent variables, plus sex and age as potentially confounding variables. Subsequently, we excluded the variables not significantly related to sleep difficulties. The final model (Chi2 23.65; p<.001) showed that general health and well-being (OR= 0.56; IC 95%: 0.38-0.83) and a good relationship with friends (OR= 0.78; IC 95%: 0.62-0.98) act as protective factors, decreasing the risk of sleep onset insomnia. Surprisingly, having a younger age increased the probability of the onset of difficulty in falling asleep (OR= 0.70; IC 95%: 0.51-0.97).

Conclusions: The results of this preliminary study, although based on self-reported data, confirm the high prevalence of sleep onset problems also in younger teens and suggest that sleep is closely related to health, well-being and social environment. Although further studies are needed to better clarify the interplay between sleep and other measures of health, these data provide additional support for the importance of better understanding sleep and its relationship to daily life in a young and healthy non-clinical population. This consideration is particularly important because sleep onset insomnia may be a life long problem. Since sleep seems to be consistently related to positive health, it may be considered as an early indicator of potential concern for health and well-being.

References:

346.G

Factors Associated With the Establishment of a Consolidated Sleep-Wake Cycle in Infants: An Epidemiological Study
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Introduction: Sleep disorders in children are a major concern for parents and one of the most common problems seen in clinical pediatrics. A significant continuity was observed for frequent nocturnal awakenings from 6 months of age until school years (1). The effects of poor sleep are many and impact on all aspects of child development. The aim of this study was to identify the factors likely to impede or foster the process of developing a consolidated sleep-wake cycle.

Methods: This survey of 2115 five-month-old infants had a stratified, three-stage sampling design and data were weighted in order to infer the sample data to the entire population of the province of Quebec. Data were collected by questionnaire and home interviews. Chi squared and t-tests were used to compare infants who were not sleeping through the night with those who did on different variables. A logistical regression was used to identify the most determinant variables of sleep consolidation.

Results: As reported by their mother, 78.6% of Quebec infants were sleeping through the night at five months. The regression analysis identified 5 variables that correctly classified 71% of the infants who were sleeping through the night and 76% of those not doing so. In order of importance, these are: 1) parental behaviors surrounding sleep periods; 2) infant’s temperament; 3) co-sleeping or not with parent; 4) breast or bottle feeding and 5) sex of the infant. Babies who did not sleep through the night at 5 months were put to bed already asleep (for the night or for naps) in a greater proportion than those who did (60% vs. 48%). The former were also fed (76%) in response to awakenings more often than the latter (28%) who were comforted in their own bed more often (28% vs. 9.5%). The former scored higher on the difficult temperament scale than the latter (13.8 vs. 10.5). The babies who did not sleep through the night slept in a greater proportion in the parental bed than those who did (56% vs. 33%). Twice as many babies who were not sleeping through the night were being breast fed at 6 months compared to those who slept through the night (56% vs. 28%). More baby boys than girls were not sleeping through the night (57% vs. 43%). Other significant factors included: use of a transitional object, birth order and parent overprotectiveness. Neither the baby’s chronological age, premature status, birth and current weight and health status nor the socioeconomic status and type of family (intact, step or single-parent) seemed to be associated with sleep consolidation at five months.

Conclusions: Parental behaviors around sleep periods were found to be the most influential variable in their infant’s developing sleep patterns. Infants must learn to fall asleep on their own to be able to go back to sleep without signaling their awakenings (crying) (2). Also, it was shown that the timing between feeding and sleep (shorter delay with breast feeding) rather than the feeding method makes the difference (3).

References:
Changes in Autonomic Controls and Arousability: Implications in Sudden Infant Death Syndrome (SIDS)

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Introduction: Both impairment in arousability and in autonomic controls have been implicated in the development of SIDS (1,2).

Methods: 1. Future SIDS infantsTo evaluate autonomic reactivity in response to obstructive events in future victims of SIDS, polysomnographic sleep recording of 18 future victims of SIDS and those of 36 matched control infants were studied. An autoregressive spectral analysis of heart rate was performed preceding and following the obstructive apneas. High-frequency component (HF) reflected parasympathetic tonus. The low frequency to high frequency power ratio (LF/HF) was computed to evaluate sympathovagal balance. 2. Environmental factors: The incidence of SIDS has been linked to environmental factors. Prone body position, high ambient temperature, head covering and maternal smoking are reported to increase the risk of SIDS. Otherwise, pacifier use may contribute to protect the sleeping infant. The effects of these 5 factors were evaluated on autonomic nervous tonus and polygraphic auditory arousal thresholds in 302 healthy neonates and infants.

Results: Future SIDS victims were characterized by increased sympathovagal balance and decreased autonomic responses to obstructive events during sleep. Environmental conditions favoring increased risks for sudden death such as prone body position, high ambient temperature, head covering and maternal smoking both decreased auditory arousability and increased sympathovagal balance. In addition, infants pacifier users had a lower auditory arousal threshold and a decreased cardiac sympathovagal balance compared to control infants.

Conclusions: The description of the mechanisms responsible for SIDS is still far from complete, but appears to involve both arousal response and cardiac autonomic controls during sleep/wake processes. The changes in autonomic controls could be associated with a resetting of the infant’s baroreflexes (3). The decreased baroreflexes responses could hinder increases in blood pressure in response to various stimuli. As a rise in blood pressure is associated with an arousal response, reduced or lack of increase in blood pressure response could contribute to reduce arousal from sleep.

References:

The Effects of Blood Glucose Levels on the Quality of Sleep in Children with Type I Diabetes Mellitus

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Introduction: Children sleep between 8-14 hours of sleep per day, and sleep disturbances can result in excessive daytime sleepiness, cognitive impairment (including impaired achievements in school), behavior problems, and even growth and/or developmental delay. Type I Diabetes Mellitus is a quite prevalent disease among children. Since normal glucose balance on a minute-by-minute basis is only rarely achieved, children with diabetes may be exposed to nocturnal hypo and hyperglycemia.

Methods: In the present study, we sought to determine whether diabetes results in sleep disturbances. Theoretically, both hypo and hyperglycemia may result in sleep disruption. Hypoglycemic events can result in catecholamine surges, which may cause sleep fragmentation, while hyperglycemia can produce nocturia, and again awakenings from sleep. Furthermore, blood glucose levels may have a direct effect on sleep centers in the brain, and alter sleep architecture. We hypothesized that diabetic children will sleep better when their blood glucose levels are better controlled.

Results: All children went to sleep with well-controlled glucose levels (100-200mg%). Two children demonstrated profound hypoglycemia during the night (below 40mg%). One additional child demonstrated an initial increase in glucose levels to 400mg%, followed by a decline to 150mg%. The rest of the children had stable glucose levels throughout the night. The rate of the decrement in blood glucose levels, but not the absolute glucose levels, was associated with awakenings from sleep and sleep disruption. A fall of more than 2 mg% glucose per minute was associated with an arousal response. Paradoxically, when hypoglycemia was stable (at 40mg% or less), the percentage of slow wave sleep increased dramatically, and the EEG recordings at that time demonstrated high amplitude hypersynchronized delta activity. Diabetic children with well-controlled glucose levels had a similar sleep pattern to normal, age-matched control children.

Conclusions: Sharp changes in glucose levels may disrupt sleep and this should be taken into consideration when treating diabetic children. Stable hypoglycemia, even if profound, may not result in an arousal response and thus may pose a risk for medical complications (e.g. convulsions). Thus, measuring frequent glucose levels during the night adds important data for treatment of these children.
that measurement of upper airway dynamics following topical anesthesia of the pharynx during wakefulness would assist in the diagnostic accuracy of the clinical evaluation of snoring children.

**Methods:** Upper airway measurements were performed using acoustic pharyngometry in otherwise normal children referred for evaluation of suspected OSA. At least 4 separate measurements were performed each time and were considered acceptable if they deviated < 10% from each other. Baseline measurements were conducted (PRE), and were followed by application of Cetacaine 1% spray to the pharyngeal introitus under visual inspection (POST). The volume of a 1 cm segment corresponding to the smallest segment in the pharyngeal airway was analyzed, and upper airway collapsibility (UAQ) was determined as the % change from PRE to POST. Overnight polysomnographic studies were conducted in all patients, and scored by one of the investigators who was unaware of the results of the pharyngometry measurements. The apnea index (AI), apnea-hypopnea index (AHI), and %TST with Sa02 < 90% were tabulated. Linear regression analysis, 2-tailed student t tests, and receiver operator curves were calculated from the data. A P value <0.05 was considered as statistically significant.

**Results:** Mean age of the 31 children studied thus far was 10 ±3 years [SD], and I I were female. In 17 children with abnormal sleep studies (AHI>5), the mean AHI was 26.7±21.7/hr TST, desaturation index was 8.4±10.4 %TST, and UAC was 42.4±12.8%. In contrast, in the 14 children with normal sleep studies, mean AHI was 2.3±1.4/hr TST, desaturation index was 0. 1±0.2 %TST, and UAC was 8.8±19.8% (P<0.000 1). A UAC> 20% accurately identified all children with AHI>5.

**Conclusions:** Children with OSA have a more collapsible pharynx while awake than children with primary snoring. Assessment of upper airway dynamics during wakefulness in response to a topical airway anesthetic may provide a useful clinical adjunct to the evaluation of snoring children and more accurate identification of those children with OSA. It remains unclear whether this technique may differentiate among children with upper airway resistance syndrome.

**References:**

Research supported by National Institutes of Health HL-65270, HL-63912 and HL-66358 the American Heart Association AHA-0050442N.

350.G

The Alerting Effects of Caffeine on a 12 Year Old Child

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(1) Lower Moreland High School, (2) Holy Redeemer Hospital

**Introduction:** Caffeine causes improved attention in adults at doses of 1 mg./kg. We propose that similar alerting effects on attention will occur in a child. We are unaware of published data on the effects of this low dose on normal children in the classroom. The first author performed a double blind study on himself.

**Methods:** Two liter bottles of caffeinated and non-caffeinated cola were purchased. Identical bottles were randomly filled with 12 oz. of caffeinated or non-caffeinated soda. The type of soda could not be distinguished by color or taste. The numbered bottles were then selected randomly to be consumed at lunch on that day. The 12 oz. of soda were consumed at lunch at 1:00 p.m. Alertness was self rated using a 10 point scale (with 5 being a normal feeling) at 1:00 p.m., 1:20 p.m., 1:45 p.m., and 2:10 p.m. The bottle code was not broken until all of the data had been accumulated. The procedure was performed over 20 school days. The data was analyzed by using a “t-test” for the comparison of sample means.

**Results:** At the times 1:20 p.m., 1:45 p.m., and 2:10 p.m. caffeinated soda had a statistically significant alerting effect on the child with p<.05. These times correspond to 20, 45, and 70 minutes after the dose of caffeinated soda.

**Figure 1**

**Conclusions:** We found that soda with 1 mg. per kg. of caffeine had a small, but statistically significant alerting effect on a 12 year old child. Children commonly consume this dose. More tests are needed to fully understand caffeine’s effect on children.

**References:**

351.G

Parasomnias Due To Cluster Headaches

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**Introduction:** Nocturnal spells of agitated arousal in otherwise healthy young children are often related to NREM parasomnia (night terrors). However, in patients with acute onset or increased frequency of parasomnias, organic causes of discomfort must be excluded. We report four cases of young children whose parasomnias were caused by nocturnal cluster headaches.

**Methods:** Four children aged 2-10 years were evaluated for recurrent nocturnal arousals associated with agitation. Incoosolable crying and change in facial appearance was reported in 3 out of 4 patients, and head banging was noted in 2 out of 4 patients. Patients were asymptomatic between episodes, which also occurred during the day. 3 out of 4 patients had a normal neurological exam and 1 patient had a previous diagnosis of Tuberous Sclerosis (TS). Brain MRI was normal in 3 patients and con-
sistent with TS in 1 patient. All patients were started on Indomethacin based on a clinical diagnosis of cluster headaches.

**Results:** Indomethacin 25-75/day produced rapid and sustained relief in all patients, with marked reduction in frequency and severity of nocturnal arousals, as well as daytime episodes.

**Conclusions:** Cluster headache is a rare, but treatable headache disorder in early childhood. Since cluster headache may present as a periodic paroxysmal disorder, patients may often present with nocturnal episodes of cluster headache, which lead to agitated arousals. If cluster headaches are suspected by clinical presentation, a short diagnostic trial of Indomethacin is warranted.

352.G

**Associations of Home Atmosphere, School Perceptions, Sleep Disorders, and Selected Health Behaviors with Perceived Alertness in 15-year-olds**

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**Introduction:** Good home atmosphere including good relationships with parents is important for adolescents' sleep quality and perceived alertness. School is another important environment in adolescents' everyday lives and it may be either a resource or a risk for their subjective health and well-being. Previous studies have indicated that adolescents' irregular sleep patterns, inadequate sleep and frequent use of psychoactive substances, such as alcohol, are significantly related to poor alertness. Problems with sleep affect also alertness, daytime functioning in general and even school performance. The present study examines how perceived home atmosphere, school perceptions, sleep disorders, sleep patterns, leisure time physical activity and use of psychoactive substances are associated with perceived alertness among 15-year-olds.

**Methods:** The sample consisted of 15-year-old Finnish pupils (n=1545). The study used the data from a larger, WHO-coordinated cross-national survey of school children's health and life-style (the HBSC Study). Nationally representative data were collected in spring 1998 using a standardized questionnaire. Pupils were asked about their home atmosphere, sleep patterns, school perceptions, leisure time physical activity and use of psychoactive substances. The analyses were done separately for boys and girls and they included simultaneously both the confirmatory factor analysis and structural equation modeling.

**Results:** Structural equation models indicated that school perceptions form the most important factor in associations with perceived alertness in girls and together with sleep disorders also in boys. Perceived home atmosphere, as a natural 'background' factor, had a significant association with sleep disorders, school perceptions, and most health behaviors studied. Among boys the model explained 46% and among girls 34% of the variance of perceived alertness. In both models associations proved to be very complex.

**Conclusions:** The results of this study emphasize the role of school perceptions, especially among girls, in associations with adolescents' perceived alertness. School is children's workplace and much more attention should be paid, for example, to general working conditions, human relations and safety of school environment in school health promotion activities. This would help pupils to be more alert and improve their experiences of school.

**References:**


Research supported by the Academy of Finland (project 48764)

353.G

**Sleep Problems in Children with Epilepsy-Results of Overnight Polysomnography**

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**Introduction:** Questionnaire studies of children with epilepsy have shown higher rates of sleep disorders, particularly poor quality sleep and anxieties about sleep. One third of adults with medically refractory epilepsy without a history of sleep related breathing disturbance (SRBD) have recently been reported following polysomnography to have evidence of obstructive sleep apnea (OSA) (2). This study is a retrospective review to determine if overnight polysomnography in children with epilepsy will provide objective evidence of sleep disturbance.

**Methods:** All children with epilepsy referred to a single pediatric neurologist for evaluation of sleep disturbance/daytime fatigue between January 1999 and July 2000 were reviewed. Children were seen in consultation and only referred for polysomnography if the symptoms were not attributed to poor sleep hygiene. Overnight polysomnography with an expanded frontal-temporal montage and video recording was analyzed for evidence of ictal or interictal activity, respiratory or other sleep disturbance, and sleep efficiency.

**Results:** Seven children were studied ranging in age from 4-17 years. The number of antiepileptic drugs the children were on was one (n=3), two (n=2), three (n=1) and none (n=1). One child was seizure-free having had recent epilepsy surgery. All children were referred for disrupted sleep or daytime fatigue. One child was referred for questionable recent apnea. In this group of children sleep efficiency ranged from 83-95.3% (mean=89.6%). One study included a MSLT documenting moderate daytime sleepiness. Only one child had normal sleep architecture. The other 6 children had a variety of abnormalities including abbreviated onset to REM (n=2), decreased REM (n=1), delayed REM (n=1), and/or frequent stage changes with arousals (n=5) and periodic leg movements (n=1). Three children had interictal epileptiform activity. One child had a slow wave sleep arousal but no child had a seizure recorded. No child, including the one referred for apnea had evidence of SRBD.

**Conclusions:** This small series of children with epilepsy confirms earlier questionnaire studies that there is a high rate of poor quality sleep with decreased sleep efficiency and abnormal sleep architecture in this population. Only one child had periodic leg movements with no other unsus-
pected sleep disorder including SRBD being diagnosed. The children were on a variety of AED’s making it difficult to evaluate the impact of an individual drug. Intercital epileptiform activity and the effect of drugs likely leads to sleep disruption and daytime fatigue in this population. Further research is needed in order to understand the impact of epilepsy on sleep in children and provide effective treatments.

References:

354.G

Sleep Disorders in Children with Mucopolysaccharidosis

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Introduction: Mucopolysaccharidosis (MPS) is a lysosomal storage disorder characterized by multiple skeletal, ocular, visceral, cardiovascular, respiratory and nervous system abnormalities. Enzyme deficit leads to accumulation of glycosaminoglycan in the upper airway producing progressive narrowing of pharynx and nasal cavity. Central nervous system abnormalities lead to agitation during both wakefulness and sleep in most of the 7 different clinical syndromes reported. The aim of this study is to report the prevalence of sleep-disordered breathing and behavioral-sleep disorders in children with mucopolysaccharidosis.

Methods: Clinical evaluation was performed in all children referred from the Genetics outpatient clinic with the diagnosis of mucopolysaccharidosis. The initial evaluation included a clinical questionnaire for sleep disorders and physical examination. Children who had symptoms of upper airway obstruction during sleep were submitted to standard polysomnography.

Results: Twenty six children underwent clinical evaluation, 10 were females. Hunter and Maroteaux-Lamy were the most frequent syndromes. Six children with Sanfilippo syndrome had difficult falling asleep that required medication or parent co-sleep. The polysomnographic electroencephalogram of three children with Sanfilippo syndrome showed diffuse 12-15 Hz activity alternated with high voltage slow activity, no spindles, and absent vertex sharp waves. Twelve of the 22 children who had sleep studies showed obstructive sleep apnea hypopnea syndrome (OSAHS), with mean (±sd) apnea-hypopnea index of 36.6 ± 25.2 events/hour.

<table>
<thead>
<tr>
<th>MPS</th>
<th>Syndrome</th>
<th>N</th>
<th>Polysomnography</th>
<th>OSAHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I7</td>
<td>Hurler</td>
<td>1</td>
<td>Primary snoring</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>10</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>Sanfilippo</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>Morquio</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>VI</td>
<td>Maroteaux-Lamy</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Total 26 10 12

Conclusions: In this cohort of patients with mucopolysaccharidosis we found that 54% of the children had OSAHS. Most of these children had severe OSAHS. Sleep-disordered breathing was more frequent in Hurler, Hunter and Maroteaux-Lamy syndromes, while behavioral problems to sleep was present in Sanfilippo syndrome.

References:

Funded by Associacao Fundo de Incentivo a Psicofarmacologia (AFIP)

355.G

Analysis of Sleep Microstructure Through Cyclic Alternating Pattern in School Age Children

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Introduction: Recent studies analyzed the normative values of cyclic alternating pattern (CAP) in different age groups (Parrino et al., 1998). CAP rate showed a U-shaped trend with high values in adolescence (43.4%), a decrease in young adulthood (31.9%) and in the middle-aged (37.5%), and then an increase in the elderly (55.3%). Since no studies have analyzed the sleep microstructure in school age children, aim of this study was to evaluate the CAP parameters in this age range.

Methods: Ten normal healthy subjects were asked to perform a two-night polysomnographic study in our sleep lab. Mothers were asked to answer a structured interview on sleep habits, pattern and concurrent sleep disorders, and to fill-out a sleep diary for at least two weeks before the PSG study. All subjects underwent a PSG recording after one adaptation night, according to the normal sleep-wake schedule of each child. Sleep data were stored on the computer using a polysomnography digitai system (Embla, Flaga, Iceland). Sleep recordings were scored following R&K criteria (1968) for macrostructural analysis and Terzano and Parrino criteria (2000) for microstructural analysis. The analysis software (Somnologica 2.0) allowed us to select the desired EEG pattern with the mouse and then assign the events A1, A2 or A3. A text file with all the events related to macro and microstructural scoring was exported and read by a specific software of automatic analysis of CAP parameters created by one of us (FR). Recordings were analyzed by two raters (DMG and FB), that concurrently established phases A classification.

Results: Table 1 showed the mean CAP parameters of the 10 subjects (6M,4F; mean age 6,6 yrs, range 5-10). No age or gender differences have been found in macro- and microstructural variables. Comparing our data with normative data of older people we confirmed the U-shaped trend of CAP rate with higher values in childhood and elderly (Parrino et al., 1998). CAP time and number of cycles were similar to those of older ages; age distribution of phases A showed that A1 was more frequent in childhood while A2 and A3 were less represented.
Table 1
Sleep microstructure: CAP parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP rate (%)</td>
<td>46.48</td>
<td>7.65</td>
<td>39-60</td>
</tr>
<tr>
<td>CAP rate in S1</td>
<td>36.43</td>
<td>14.66</td>
<td>20-60</td>
</tr>
<tr>
<td>CAP rate in S2</td>
<td>34.71</td>
<td>8.34</td>
<td>25-49</td>
</tr>
<tr>
<td>CAP rate in SWS</td>
<td>60.31</td>
<td>10.36</td>
<td>42-75</td>
</tr>
<tr>
<td>CAP time (min)</td>
<td>139.61</td>
<td>32.65</td>
<td>101-217</td>
</tr>
<tr>
<td>CAP cycles number</td>
<td>316.80</td>
<td>85.15</td>
<td>223-494</td>
</tr>
<tr>
<td>CAP cycle mean duration (sec)</td>
<td>28.72</td>
<td>3.05</td>
<td>23-33</td>
</tr>
<tr>
<td>Phase A1 %</td>
<td>85.82</td>
<td>5.85</td>
<td>74-93</td>
</tr>
<tr>
<td>Phase A2 %</td>
<td>5.99</td>
<td>2.87</td>
<td>2-11</td>
</tr>
<tr>
<td>Phase A3 %</td>
<td>8.17</td>
<td>5.46</td>
<td>1-19</td>
</tr>
<tr>
<td>Phase A mean duration (sec)</td>
<td>11.26</td>
<td>1.68</td>
<td>9-14</td>
</tr>
<tr>
<td>Phase B mean duration (sec)</td>
<td>22.11</td>
<td>2.79</td>
<td>17-27</td>
</tr>
</tbody>
</table>

Conclusions: This study represents the first analysis of normal sleep microstructure in school-age children. The arousal fluctuations reflected by CAP, analyzed through computerized techniques, could lead to the development of different microstructural indexes that could reflect the sleep quality and the restorative function of sleep; in this direction we developed a parameter named A ratio [derived from the following formulas: if A1>(A2+A3) then A ratio=A1/A total*(A2+A3) per minute; if A1<(A2+A3) then A ratio=(A2+A3)/A total*A1 per minute; if A1=(A2+A3) then A ratio=0]. This parameter and others that could be developed have to be evaluated also in pathologic conditions in order to assess their validity and specificity.

References:
(2) Terzano MG and Parrino L. Origin and Significance of the Cyclic Alternating Pattern (CAP). Sleep Medicine Reviews, 2000; 4:101-123

356.G

Pulse Arterial Tonometry Identifies REM Sleep in Children: A Preliminary Report

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Introduction: REM sleep is associated with increased sympathetic activity compared to non-REM sleep. In adults, a new finger plethysmographic technique developed for measurement of pulse arterial tonometry (PAT) revealed that the enhancements in sympathetic nervous system tone can be reliably identified with PAT technology (1). We hypothesized that REM-associated changes in autonomic nervous system tone would be detected using PAT in children.

Methods: Normal children ages 6-7 years of age were studied in the sleep laboratory using a standard polysomnographic montage. PAT was recorded throughout the night and analyzed separately from the sleep record by independent scorers. Periods corresponding to REM were identified using Rechtschaffen and Kales criteria (2) and by a sustained (>60sec) period of >50% attenuation in PAT signal (1). RR intervals were also measured for periods corresponding to NREM and REM sleep stages and Poincare plots (R-Rn vs. R-Rn+1) were constructed for assessment of moment-to-moment heart rate variability (HRV).

Results: Seven children have been studied thus far. Their polygraphic recordings were interpreted as normal, and a total of 23 REM periods were identified. PAT correctly identified all of the 23 periods (see Figure). However, PAT erroneously identified 2 additional periods corresponding to quiet wakefulness. In addition, PAT-derived REM onset preceded polygraphic REM onset by 17±4 sec. Poincare plots showed significant differences in HRV between REM and non-REM, confirming increased sympathetic tone during REM sleep.

Figure 1

357.G

Evaluation of Apnea and Hypopnea Index in Obese Adolescents

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Introduction: Obesity is one of the factors that may contribute to the increase of sleep apnea (SAOS) and others respiratories disturbs. The objective of this study was to evaluate SAOS index in obese males adolescents.

Methods: After the adaptation night at the laboratory using the equipment, twenty four subjects were evaluated using polysomnography (PSG) (Oxford/Medilog, 16 channels).

Results: The results are: weight (kg): 105.04 (±12.77); height (cm): 170.33 (±18.79); age: 16.96 (±1.51); total fat (g): 37268.67 (±7296.76); total lean mass (g): 60910.75 (±6297.08); sleep latency (min): 9.62 (±9.35); sleep onset latency to REM (min): 138.40 (±55.10); total sleep time (min): 409.25 (±46.31); sleep efficiency (%): 88.54 (±6.81); % stage 01: 4.24 (±2.29); % stage 02: 47.33 (±10.38); % stage 3/4: 31.10 (±10); % REM sleep: 17.34 (±4.17); PLM-RLS/h: 5.61 (±4.99); apnea/hypopnea index: 2.78 (±3.19); arousal (total): 37.11 (±16.8);

Conclusions: REM sleep is associated with decreased HRV (increased sympathetic activity) and can be identified by PAT technology in children. PAT amplitude alone however can not differentiate between quiet waking and REM sleep.

References:
Conclusions: Respiratory disorders in obese adults are frequently reported by the literature. Our results showed that obese adolescents did not present pathologic index of apnea and hipopnea. This may be due to the fact that adults may present a larger complacency and resistance of the upper airways. We also found a reduced sleep efficiency, probably by the great percent of stage 2, arousal and total awake time during the PSG showed by the subjects. Thus, we propose a longitudinal following of this population, using PSG to access at which age the respiratory disorders will be present more frequently.

Supported by: CEPID/FAPESP; Associacao Fundo de Incentivo a Psicofarmacol. (AFIP)

358.G

Ataxic Respiration and Increased Upper Airway Resistance during Sleep in a Child Following Treatment for Posterior Fossa Medulloblastoma

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University of Michigan

Introduction: Ataxia, defined as an inability to smoothly coordinate muscle movement, usually results from neurologic disorders affecting the cerebellum or posterior columns of the spinal cord. Although it most prominently affects gait, truncal stability, and dexterity of the limbs, involvement of speech and respiration may occasionally occur. We describe the unusual findings of ataxic respiration and excessively increased upper airway resistance without obstructive apneas during the sleep of a child previously treated for posterior fossa medulloblastoma.

Methods: The patient is a 7-year-old girl who presented one year previously with several weeks of headache, vomiting, and increasing gait ataxia. Imaging revealed a large tumor obliterating the fourth ventricle, which was identified as medulloblastoma at the time of surgical resection. Additional therapy has included radiotherapy as well as chemotherapy using cisplatin, CCNU, and vincristine. The patient remains radiographically free of recurrence at present, but postoperative neurologic problems have included transient cerebellar mutism, moderately ataxic speech and gait, and mild dysmetria of the upper extremities. Polysomnography was requested for evaluation of snoring and witnessed respiratory pauses during sleep. Technician-attended polysomnography was performed, with digital recording of central and occipital EEG, EOG, submentalis and anterior tibialis EMG, ECG, airflow, thoracoabdominal motion, and esophageal pressure (Pes). The tracing was scored manually in 30-second epochs.

Figure 1

Results: The split-night polysomnogram recorded 344.5 minutes of sleep during the 541.6 minute study, yielding a reduced sleep efficiency of 63.6%. The baseline portion of the study was characterized by significant irregularity of respiratory rate and effort consistent with ataxic respiration [Figure 1]. This was seen throughout stage I, stage II, and REM sleep with partial normalization during slow wave sleep. Discrete respiratory events were seen 16.0 times per hour of sleep at baseline, consisting exclusively of hypopneas (44 events) and central apneas (23) without any obstructive apneas. In addition, frequent periods of stridor, paradoxical respiratory effort, and elevated esophageal pressure fluctuations (Pes d) as high as 50 cm water were seen in the absence of scoreable respiratory events consistent with partial airway obstruction [Figure 2]. Treatment with CPAP at pressures of 5 cm and 7 cm water produced no significant improvement of these respiratory disturbances.

Conclusions: This case illustrates the potential for ataxia resulting from structural lesions of the cerebellum and posterior fossa to affect respiratory drive during sleep in addition to its more typical motor manifestations during wakefulness. Furthermore, these lesions may also produce complex upper airway obstruction characterized by stridor, paradoxical respiratory effort, and excessive fluctuations of esophageal pressure independent of scoreable respiratory events.

359.G

Adenotonsillectomy in Children: Indications, Practices, and Outcomes Reported by Otolaryngologists

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Introduction: Despite more conservative practices in recent decades, adenotonsillectomy (AT) remains among the most frequent childhood surgical procedures. In the past, recurrent tonsillar infection was the predominant indication, but recent studies suggest that obstructed breathing is now an important indication in an equal number of patients. Many patients with obstructed breathing are suspected to have obstructive sleep apnea (OSA) and associated behavioral problems. Otolaryngological literature, however, often places less emphasis on preoperative polysomnographic or behavioral testing than does literature from sleep and psychiatric specialties. The purpose of this study was to better define otolaryngologists’ attitudes and opinions about diagnosis and outcomes among children who undergo adenotonsillectomy.

Methods: A survey was mailed to 603 members of two national otolaryngology societies. The survey requested recipients to report on their 5.0 to 12.9 year-old patients who had undergone AT within the past year. Recipients were asked to estimate frequencies of several surgical indi-
Caretakers were recruited from local shopping malls, day-care centers, and community activities and asked to complete a short form requesting their name, telephone number, preferred interview times, and the age(s) and sex of their children. Using this information, caretakers were contacted via telephone and administered the CSWS. Data were collected on 161 children (82 male, 79 female), ages 2 to 5 years (mean = 3.5, SD = 1.1). Response rate was 89%. Subscales were assessed for internal consistency with Cronbach’s a-coefficient. Item analysis was conducted using correct item-total correlations and item means. Phase III / Factor Analytic Study: This study employed the recruitment procedure outlined above, as well as a “snowball” sampling strategy (caretakers refer other potential participants). Data were collected by telephone interview on 485 children (236 males, 249 females), ages 2 to 8 years (mean = 4.9, SD = 2.0). Response rate was 88%. Subscales were reassessed for internal consistency. A confirmatory factor analysis (CFA) using LISREL was conducted to determine (a) whether the 5-factor model fit the data better than other available models, including a 4-factor model (GTB+FA, AA, RS, RTW), a 3-factor model (GTB+FA, AA+RS, RTW), a 2-factor model (GTB+FA+AA+RS, RTW), and a 1-factor model (GTB+FA+AA+RS+RTW) and (b) whether the 5-factor model of sleep provided a good absolute fit to the data.

Results: Of the original 77 items, 38 were deleted based upon item analysis. The internal consistency of the entire CSWS was 0.89. Alpha coefficients for the subscales are presented in Table 1. The fit indices for all the models are shown in Table 2.

Table 1

<table>
<thead>
<tr>
<th>Subscale</th>
<th># items</th>
<th>mean</th>
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<th>α</th>
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<td>Going to Bed</td>
<td>10</td>
<td>22.66</td>
<td>4.57</td>
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<tr>
<td>Falling Asleep</td>
<td>7</td>
<td>17.43</td>
<td>3.08</td>
<td>0.71</td>
</tr>
<tr>
<td>Arousing/Awakening</td>
<td>8</td>
<td>19.49</td>
<td>3.34</td>
<td>0.73</td>
</tr>
<tr>
<td>Reinitiating Sleep</td>
<td>6</td>
<td>20.84</td>
<td>3.09</td>
<td>0.78</td>
</tr>
<tr>
<td>Returning to Wakefulness</td>
<td>8</td>
<td>17.99</td>
<td>5.00</td>
<td>0.89</td>
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</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Fit Indices for the Models</th>
<th>1 factor model</th>
<th>2 factor model</th>
<th>3 factor model</th>
<th>4 factor model</th>
<th>5 factor model</th>
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<tr>
<td>χ²</td>
<td>4864.5*</td>
<td>3182.7*</td>
<td>2590.6*</td>
<td>2148.9*</td>
<td>2096.4*</td>
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<tr>
<td>df</td>
<td>.702</td>
<td>.701</td>
<td>.699</td>
<td>.696</td>
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<td>GFI</td>
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<tr>
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<td>RMSEA</td>
<td>.086**</td>
<td>.086**</td>
<td>.075**</td>
<td>.067**</td>
<td>.064**</td>
</tr>
<tr>
<td>NFI</td>
<td>.37</td>
<td>.58</td>
<td>.66</td>
<td>.72</td>
<td>.73</td>
</tr>
<tr>
<td>CFI</td>
<td>.40</td>
<td>.64</td>
<td>.73</td>
<td>.79</td>
<td>.80</td>
</tr>
</tbody>
</table>

*p<.001 **RMSEA<.05

GFI = Goodness of Fit Index; AGFI = Adjusted Goodness of Fit Index; RMSEA = Root Mean Square Error of Approximation; NFI = Normed Fit Index; CFI = Comparative Fit Index

Conclusions: Based on the criterion of .70 for research instruments, the internal consistency coefficients for each subscale are above acceptable
standards. As shown, the fit indices all converge in suggesting the superiority of a 5-factor model. The CSWS provides a reliable and convenient method for the study of sleep patterns of children.

Research supported by Aubrey K. and Ella Ginn Lucas Endowment for Faculty Excellence

361. G

Facial Pattern of Sleep Breathing Disordered Children Using Ricketts’ Method.

Kikuchi M, Higurashi N, Miyazaki S, Itasaka Y, Chiba S, Nezu H
(1) Cosmos Orthodontic Office, Narita, Japan, (2) Department of Otorhinolaryngology, Akita University School of Medicine, Akita, Japan, (3) Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, Japan, (4) Nezu Orthodontic Office, Kawasaki, Japan

Introduction: We reported the facial pattern of adult’s obstructive sleep apnea patients was dolico facial pattern at APSS meeting (1999). We took the cephalograms to analyze the facial pattern of obstructive sleep apnea children.

Methods: We chose 29 children under 15 years old who had tonsil and/or adenoid, and had a problem of sleep disorder (Patients group, the mean age was 6.6 ± 3.1 years old). We digitized the lateral-cephalograms of them using Ricketts analysis and examined facial pattern. Then we compared the results with the mean of control 9-years old Japanese children (Control group, n=41).

Results: 5 (17.2%) of Patients group had tonsil, 7 (24.1%) had adenoid, and 17 (58.6%) had both tonsil and adenoid. There were significant differences (p<0.005) between Patients group and Control group on Facial Axis (Patients 81.8±3.1, Control 86.0±3.0), Lower Facial Height (Patients 54.6±5.3, Control 49.0±4.0), Mandibular Arc (Patients 21.2±4.8, Control 25.0±4.0), Total Facial Height (Patients 68.4±4.5, Control 64.0±3.0), and MacNamara-Pogionion (Patients -9.1mm±5.4, Control -6.0mm±2.0). According to Ricketts analysis, there are 3 facial pattern classifications among the orthodontic patients: 1) brachycephal facial pattern (short face), 2) mesio facial pattern (medium face: this is the Control -6.0mm, Control 64.0, Patients 54.6), and 3) dolico facial pattern (long face). The facial pattern of Patients group was dolico facial pattern. The facial pattern of adult’s obstructive sleep apnea patients was dolico facial pattern, and that of children were also dolico facial pattern, however the data of children was weaker tendency in SD 4th grade children where there will be a probably interaction because the abstract development needs more energy to association.

Conclusions: The facial pattern of obstructive sleep apnea children was dolico facial pattern (long face).

References:

SLEEP, Vol. 24, Abstract Supplement 2001

362. G

Cognitive Dysfunction in 7 to 10 Years Old Sleep Disorders Children

Carvalho LC, Atallah NA, Silva AB, Prado GF, Prado LF, Silva L, Silva TA, Almeida MM, Teruel MR, Dal Oca VV
Sector of Sleep Disorder of Neurology-Neurosurgery and Internal Medicine Department, UNIFESP-EPM, Sao Paulo, Brazil

Introduction: Context: the sleep disorders (SD) may determine many clinical repercussions, like behavioral alteration in children, excessive somnolence, cognitive disorders (CD) among others. In previous study, Natale (1998) identified the follow sleep disorders: bruxism (11.67%), sleep talking (24.56%), sleep breathing disorders (15.28%), bed-wetting (5.51%), nocturnal terror with sleepwalking (9.63%) and rhythmic movement disorders (24.36%). Objective: children with sleep disorders may have cognitive disorders that may affect the school performance.

Methods: Method: 85 children, 39 female and 46 male, 7 to 10 years old in the elementary school, from 1st to 4th grade, of 2 State Schools of central district of Sao Paulo, Brazil. The children were submitted to Sleep Disorder Questionnaire (Bruni ET AI, 1996) and randomized in case group (positive sleep disorder - SD) 41 children and control group (negative sleep disorder - NSD) 44 children. The randomized children were submitted to Cognitive Evaluation by Bender Test.Independent variables: SD, bruxism, sleep talking, sleepwalking, nocturnal terror, sleep-breathing disorders, bed-wetting, rhythmic movement disorders. Dependent variables: CD, memory, discrimination, sequence, maturity, orientation, attention, concentration.

Results: Results: The association between SD and CD was not significant: 27% of the SD and 31% of the NSD children had CD (n=85, p=0.95, X2 = 0.035); 26% of the SD female children and 38% of the NSD had CD (n = 41, p=0.78, X2=0.71); 28% of the SD male children and 24% of the NDS had CD (n=44, p=0.98, X2=0.0011). It was not significant for age: 44% of DS 7 years old children and 25% NSD had CD (n=16), 23% of DS 8 years old children and 32% NSD had CD (n=22), 38% of DS 9 years old children and 46% NSD had CD (n= 24), 39% of DS 10 years old children and 48% NSD had CD (n= 24). For grades either: 40% of SD 1st grade children and 14% NSD had CD (n=22), 21% of SD 2nd grade children and 21% NSD had CD (n=24), 28% of SD 3rd grade children and 57% NSD had CD (n=21), and 50% of SD 4th grade children and 33% NSD had CD (n=18). These results showed no relation between sleep disorders and cognitive disorders. There was a tendency to SD 7 years old children had CD, these children were neurological and cognitive developing yet. There were be these tendency in SD 4th grade children where there will be a probably interaction because the abstract development needs more energy to associations.

Conclusions: Conclusion: in these data there were no relation between sleep disorders and cognitive disorders.

References:
Effects of Vesperal Methylphenidate (MPH) Administration on Diurnal and Nocturnal Activity in ADHD Children: An Actigraphic Study

Konofal E, Lecendreux M, Bouvard MP, Mouren-Siméoni MC
Department of Child and Adolescent Psychiatry

Introduction: Previous sleep studies using polysomnography, MSLT, video-analysis or actigraphy, have shown abnormalities such as high levels of nocturnal activity, increased daytime somnolence, alteration of sleep architecture in ADHD children. MPH is effective in reducing daytime symptoms of ADHD but nocturnal abnormalities are rarely addressed. Recently, late-afternoon administration of MPH has been proposed to reduce evening symptoms and showed no adverse effects on sleep.

Methods: Objectives: The aim of the present study is to evaluate the effects of vesperal MPH Objective: The aim of the present study is to evaluate the effects of vesperal MPH administration on nocturnal activity in ADHD children. ADHD children, (5 male, aged 7-8 years, DSM IV criteria, drug free) were recorded using continuous wrist-actigraphy (10 days and nights) completed by all-night foot-actigraphy, in their natural environment. Actigraphic monitoring was performed using Actiwatch 
•. Two MPH doses of 10 mg were administrated from day 3 at 8:00 AM and 8:00 PM. Variable analysis was performed on school days only, using ANOVA.

Results: Actigraphic index was significantly decreased after MPH administration in all ADHD children. Analysis of variance (ANOVA) shows significant differences for all types of measures (p<.002): daytime activity (p<.019), nocturnal activity (p<.013).

Table 1

Daytime actigraphic index (before and after MPH administration)

Table 2

Conclusions: High levels of activity also affect ADHD children during the sleep period. In this study, MPH (20 mg/day) reduced high levels of diurnal and nocturnal activity in all ADHD children. No behavioural sleep problems (bed time refusal, increased sleep latency) were reported by parents or children related to vesperal administration. In contradiction to previous published studies where most are based on clinical reports, our findings suggest that MPH could have a beneficial effect on activity during sleep. Actigraphy provided an interesting objective technique, well tolerated in agitated children even over a long period of time.

References:

“Sleep Spindles” During REM Sleep - A Quantitative Approach

Pradella-Hallinan M, Lopes-Conceicao MC, Laitano-Nassif S, Moreira GA, Tufik S
Sleep Institute - Department of Psychobiology - UNIFESP, Sao Paulo, Brazil

Introduction: The analysis of phasic events during sleep may legitimately be considered as a useful tool when differentiating normal sleep from its pathological form even if sleep structure appears to be within normal ranges. Atypical phasic elements during REM sleep have been described in patients with psychiatric related disorders (dysthymic patients). We report the observation of sleep spindles, a typical phasic element of NREM stage 2 sleep during REM sleep, in a case study. Our patient was a 9-year-old girl who experienced difficulties to initiate and maintain sleep coupled with a dread of sleeping itself. She had normal psychomotor development, normal average learning abilities at school and presented a thumb-sucking habit during the night.

Methods: A standard polysomnographic recording (PSG) was made with subsequent spindle description by qualitative and quantitative visual analysis. The patient was submitted to psychological evaluation (WISC and Rorschach). Polysomnographic parameters were compared with a control subject, paired for age and sex, who presented sleep respiratory disturbances (snoring). A seconde PSG recording was performed after 6 months of therapy.

Results: Psychological evaluation showed a normal WISC index range for the IQ and a Rorschach social inability index of 5 which indicated some degree of immaturity for her age. Analysis of polysomnographic recordings revealed spindle density during stage 2 sleep similar to the control patient for both the first and second recordings. The patient presented sleep spindles during REM sleep that were not observed in the control subject although this density of spindles descreased at the second recording.

Conclusions: These data highlight the importance of analysis of the phasic events and microstructure of sleep and of psychological evaluation/treatment when there is ground to suspect psychological associated disturbances.

References:

Supported by Assosciacao Fundo de Incentivo a Psicofarmacologia (AFIP).

SLEEP, Vol. 24, Abstract Supplement 2001
Polysomnographic Parameters in Mouth Breathing Children

Pradella-Hallinan M, Rizzo MC, Akaishi NM, Moreira GA, Tufik S
(1) Sleep Institute - Department of Psychobiology - UNIFESP, Sao Paulo, Brazil, (2) Department of Pediatrics - UNIFESP, Sao Paulo, Brazil

Introduction: Mouth breathing (MB) is a disfunction that causes many problems in children. The oral cavity is a functional unit in which breathing, language, swallowing and chewing mechanisms are related. The balance between these functions allows the correct development of dental arches and defence organs such as adenoids and tonsils. Nasal breathing develops from birth, by steps, and it promotes the development of orofacial muscles and joints. Mouth breathing children may have orofacial hypotonia, superior lip hypertrophy, tongue protrusion, open bite, language problems, frequent upper airway infections and sleep disturbances. There are multiple causes of MB - rhinitis, nasal septum alterations, adenotonsillar hypertrophy, nasal shell hypertrophy, tumors, ill advised habits (incorrect posture during feeding, use of pacifiers).

Methods: As part of an extended study programme that involved many professionals, we performed polysomnographic recordings, in order to study sleep parameters in a group of children with mouth breathing. The children were classified as atopic (A), atopic with obstruction (AO), obstructive (O) and functional (F). Atopy was defined as positive RAST or skin test. Children with obstructions had adenoidal and/or tonsillar hypertrophy. Children with neither adenotonsillar hypertrophy nor atopy were considered functional. The group was composed of 45 children aged 5 to 13 years, including 29 boys. Sixteen children were atopic (A), 15 had atopy and obstructions (AO), 11 had obstructions (O) and 3 had mouth breathing classified as functional (F).

Results: Between the different sleep parameters studied, the following were noteworthy: snoring was observed in 69% of A, 53% of AO, 100% of O and 100% of F children. Sleep fragmentation (augmented sleep stage shifts and/or augmented arousal index) was observed in all children; one in A group had also periodic limb movements. Apnea/hypopnea index > 5 was observed in 4 children, all belong to obstructive group. SaO2 nadir <= 90% was observed in 8 A, 4 AO and 5 O children; SaO2 nadir was 74% in a child with AO.

Conclusions: Sleep was disrupted in all children with mouth breathing with the above-mentioned clinical classifications. Most children presented snoring which probably contributed to sleep fragmentation. In general SaO2 levels were not altered and few children had life-threatening desaturations. Establishing sleep parameters may be helpful when quantifying some mouth breathing related disturbances and may be considered a tool which could enable decisions about the different treatments to be carried out.

References:

Supported by Associacao Fundo de Incentivo a Psicofarmacologia (AFIP).

The “BEARS”: Screening for Pediatric Sleep Problems in the Primary Care Setting

Owens JA, Dalzell VP
Brown University School of Medicine

Introduction: Despite numerous studies demonstrating both a high prevalence and significant impact of sleep problems in children, recent surveys suggest that most pediatric practitioners do not adequately screen for sleep problems. We present preliminary data on the use of a simple, 5-item pediatric sleep screening instrument, the BEARS (B=Bedtime Issues, E=Excessive Daytime Sleepiness, A=Night Awakenings, R=Regularity and Duration of Sleep, S=Snoring), designed to screen for the most common pediatric sleep complaints. The objective of this study was to compare the BEARS with a standard well child format that includes a single sleep prompt in identifying sleep problems in a primary care clinic population.

Methods: A convenience sample of children aged 2 - 12 years seen for well child visits in a pediatric residents’ continuity clinic had a BEARS form placed in the medical chart. Brief didactic sessions on the use of the BEARS questions as part of the well child visit were provided in advance to all residents. Two independent reviewers then compared sleep-related information recorded in the BEARS visits to information recorded at the time of each subject’s previous well child visit, with respect to: specific content in a number of sleep categories, and whether the information recorded indicated a definite problem, probable problem, no problem, or insufficient information to determine problem status.

Results: 201 children (mean age 5.57 years SD 2.84; 43.2% Hispanic/16.6% African American; 52% male) had a BEARS form filled out by their provider at a well child visit. Mean age of the sample at the pre-BEARS visit was 4.32 years, SD 2.75. 98.5% of BEARS visit charts had ANY sleep information recorded, compared to 87.9% of the pre-BEARS visits (p<.001). Table 1 compares the BEARS and pre-BEARS visits with regard to recording of specific categories of sleep information and sleep problems, respectively. No significant correlation was found in the sample as a whole between age and number or type of sleep problems.

Table 1

<table>
<thead>
<tr>
<th>Percent of visits with sleep information recorded</th>
<th>Percent of visits with sleep problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEARS</td>
<td>BEARS pre-BEARS</td>
</tr>
<tr>
<td>Bedtime Issues</td>
<td>93.5%</td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>94.0%</td>
</tr>
<tr>
<td>Regularity and Duration of Sleep</td>
<td>91.4%</td>
</tr>
<tr>
<td>Snoring</td>
<td>93.0%</td>
</tr>
</tbody>
</table>

*: p<.001  **: p<.01

Conclusions: The BEARS appears to be a user-friendly pediatric sleep screening tool which significantly increases the amount of sleep information recorded, as well as the likelihood of identifying sleep problems in the primary care setting.

Research supported by Sleep Academic Award grant, NHLBI
**Arousal Index in 100 Children: Normative Data**

Tasali EF, Mendelson WB, Spire JP, Kohrman MH
University of Chicago

**Introduction:** Arousal during sleep in children are not well characterized. The ascertainment of this data is important as disruption of sleep architecture affects daytime performance. In pediatric age group, normative data is needed to establish the significance of arousals as related to sleep disordered breathing and periodic limb movement disorder (PLMD). The purpose of this study was to describe multiple arousal variables in children and to establish these norms in our sleep laboratory.

**Methods:** We reviewed 100 consecutive polygraphic recordings out of 550 studies obtained between January 1999 and October 2000 from children aged 0-17 years (50 female, 50 male). Children had been referred to our sleep disorders center for snoring, restless sleep excessive daytime sleepiness, observed apneas and other symptoms such as mouth breathing, headache and poor school performance. The polysomnograms were interpreted as normal if these were without significant sleep apnea (RDI < 3) or PLMD (PLM index < 2). Patients were free from medications that could alter EEG characteristics. Titration studies and children with seizure disorder or tracheostomy were excluded. Arousals were manually scored by an independent scorer using the ASDA criteria (1). Multiple arousal variables were computed for each polysonmogram. Mean values and 95% confidence intervals (95% CI) were then analyzed for age, total sleep time (TST), percent sleep efficiency (%SE), respiratory disturbance index (RDI), periodic leg movement index (PLMI), PLM arousal index (PLMAI), number of arousals associated with respiratory events (Aa), and leg movements (La), number of spontaneous arousals (Sa), total number of arousals (A tot), and the number of arousals for stage 1 and stage 2 sleep (Stage 1-2 a), delta sleep (Delta a) and REM sleep (REM a). Arousal indices for age subgroups were also calculated.

**Results:** Table 1, shows the mean values and 95% CI for different variables. The mean arousal index was 7.7 (range = 3.3 to 16.2). Mean arousal index (AI) showed a tendency to increase with age (between ages 0-5= 7.2, ages 5-11=7.7, and ages 7-11= 8.0). There was no difference in AI related to gender. The highest number of arousals were observed in stage 1-2 sleep followed by REM sleep and delta sleep.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>7.7</td>
<td>0.9</td>
</tr>
<tr>
<td>TST</td>
<td>343.4</td>
<td>11</td>
</tr>
<tr>
<td>SE %</td>
<td>83.3</td>
<td>2</td>
</tr>
<tr>
<td>RDI</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>PLMI</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>PLMAI</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>AI</td>
<td>7.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Ea</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>La</td>
<td>5.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Sa</td>
<td>18</td>
<td>3.3</td>
</tr>
<tr>
<td>Stage 1-2 a</td>
<td>25.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Delta a</td>
<td>5.0</td>
<td>0.9</td>
</tr>
<tr>
<td>REM a</td>
<td>5.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Rem A</td>
<td>43.9</td>
<td>3.2</td>
</tr>
</tbody>
</table>

**Conclusions:** These normative values may contribute to a better description of arousals and sleep disruption in children. This data serves to provide a comparative baseline when assessing sleep architecture in children with sleep related breathing disorders, PLMD and other conditions causing sleep fragmentation. A larger sample is currently being obtained to validate our initial database. Further studies in multiple centers are also needed to account for local environmental and technical variability as a factor in the arousal index.

**References:**

**School Starting Time Logistcs vs. Teen Sleep Needs: Are High Schools Taking Students’ Needs into Account?**

Boyer SB, Hsieh S, Harrish MJ
Lynn Institute for Healthcare Research

**Introduction:** Recent research on adolescent sleeping patterns has focused on the shift in sleep habits that is associated with puberty. As children become teenagers they tend to experience a phase delay involving a shift to later bed and rise times. How much of this phase delay syndrome is due to psychosocial factors and how much is biological remains unclear. However, as evidence mounts for such a phenomenon, and its impact on daytime performance, it raises the question: how will this evidence affect decisions regarding high school starting times? This study is intended to be the first phase of a long-term investigation into school starting times nationwide, tracking changes across several years, in an effort to investigate if school districts are implementing recommendations made by sleep specialists.

**Methods:** School day starting times for 233 high schools across the country were obtained either from high school web pages, or through direct e-mail to webmasters or various administrators. Data was collected from 44 states. Most schools included grades 9-12, although some two-year schools, either 9-10 or 11-12, were included. Schools that included grades 7-9 or other middle school-high school combinations were not included.

**Results:** The average nationwide school starting time remains earlier than 8:00 AM, with a mean of 7:53 AM and a standard deviation of 27 minutes. The earliest school day for American high school students starts at 7:00 AM, while the latest begins at 9:15 AM. The starting time seen the most often was 7:30 AM. Starting times were broken down by state as well. States with an average starting time of 8:15 AM or later include Kentucky, Oklahoma, South Dakota, Texas, Iowa, Minnesota, Wyoming and Vermont. In contrast, Colorado, Florida, Nebraska, Nevada, Tennessee, and Virginia all had average starting times of 7:30 AM or earlier. Only 41% of states had an average starting time of 8:00 AM or later. A breakdown of average starting times by state is shown below.

**Table 1**

<table>
<thead>
<tr>
<th>State</th>
<th>N</th>
<th>Mean</th>
<th>State</th>
<th>N</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>3</td>
<td>7.50</td>
<td>Mississippi</td>
<td>10</td>
<td>7.53</td>
</tr>
<tr>
<td>Arkansas</td>
<td>3</td>
<td>8.02</td>
<td>Nebraska</td>
<td>3</td>
<td>7.53</td>
</tr>
<tr>
<td>Arizona</td>
<td>3</td>
<td>7.40</td>
<td>Nevada</td>
<td>3</td>
<td>7.23</td>
</tr>
<tr>
<td>California</td>
<td>11</td>
<td>7.44</td>
<td>Tennessee</td>
<td>6</td>
<td>7.30</td>
</tr>
<tr>
<td>Colorado</td>
<td>3</td>
<td>7.23</td>
<td>Utah</td>
<td>17</td>
<td>7.31</td>
</tr>
<tr>
<td>Connecticut</td>
<td>3</td>
<td>7.35</td>
<td>Virginia</td>
<td>11</td>
<td>7.26</td>
</tr>
<tr>
<td>Delaware</td>
<td>5</td>
<td>7.36</td>
<td>Vermont</td>
<td>3</td>
<td>8.25</td>
</tr>
<tr>
<td>Florida</td>
<td>7</td>
<td>7.29</td>
<td>Washington</td>
<td>6</td>
<td>7.41</td>
</tr>
<tr>
<td>Georgia</td>
<td>6</td>
<td>8.00</td>
<td>Wisconsin</td>
<td>7</td>
<td>7.49</td>
</tr>
<tr>
<td>Hawaii</td>
<td>2</td>
<td>8.00</td>
<td>Wyoming</td>
<td>3</td>
<td>8.15</td>
</tr>
<tr>
<td>Idaho</td>
<td>4</td>
<td>8.02</td>
<td>Pennsylvania</td>
<td>3</td>
<td>8.01</td>
</tr>
</tbody>
</table>

**Conclusions:** This survey indicates that high school starting very greatly across the United States, with a significant number of schools still starting at 8:00 AM or earlier. Furthermore, there is a lack of consensus on what is an optimal starting time, balancing sleep needs with other activities such as extracurricular activities, work, etc. Some studies show that even at 8:30 AM some adolescents’ brains are better suited for sleeping than studying, thus an optimal school starting time may not be logisti-
cally possible. The current study will continue to track trends in school starting times to assess the impact of current sleep research on school and public policy.

Research supported by Lynn Institute for Healthcare Research

369.G

Symptoms Of Sleep Disorders In Children With Attention Deficit Hyperactivity Disorder (ADHD).

Harnish MJ, Boyer SR, Kakas L, Mason P, Bowles AM, Orr WC
(1) Lynn Institute for Healthcare Research, (2) Developmental Pediatrics, (3) Center for Attention Deficit Disorders

Introduction: Previous research has demonstrated that children with sleep disorders often carry a diagnosis of ADHD until their sleep disorders are detected. Furthermore several case studies have shown that treatment of sleep disorders in ADHD children can lead to dramatic improvement in daytime behavior and discontinuation of stimulant medication. The purpose of this study was to investigate whether children with a diagnosis of ADHD have symptoms of sleep disorders more frequently and whether these symptoms are supported by objective polysomnographic data. The data present here represents our preliminary results from a large scale study of both subjective and objective sleep parameters in ADHD children. Given the lack of available control data we are comparing our results with previously published data.

Methods: 18 children (16 males, 2 females) with a confirmed diagnosis of ADHD were studied as part of an ongoing research study. The mean age was 10.3 (range = 6-14) years. All children were referred from a developmental pediatrician specializing in ADHD and were not selected on the basis of sleep complaints or symptoms of sleep disorders. 16 of the 18 subjects were on stimulant treatment for their ADHD. The parents of all subjects completed a pediatric sleep questionnaire (PSQ) during their participation as well as a one-week sleep diary. The PSQ is a validated diagnostic tool described previously. The numbers of patients responding positively to specific criteria on the PSQ were examined. Simple logistic regression was also carried out to test for association of the PSQ subscales with respiratory distress indices (RDI) measured during a follow-up polysomnographic study performed on each subject.

Results: The number and percent of patients who reported various symptoms is shown in the table below. The snoring subscale of the PSQ demonstrated a significant association with RDI (linear regression, \( p = 0.02, R^2 = .313 \)). The overall sleep related breath disorder score also showed a trend toward a significant association with RDI (linear regression, \( p = 0.06, R^2 = 0.227 \)).

<table>
<thead>
<tr>
<th>Item</th>
<th># (percent) of patients (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Habitual snoring</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>2. Always snoring</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>3. Loud snoring</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>4. Heavy breathing</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>5. Difficulty breathing</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>6. Unrefreshed in the morning</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>7. Daytime sleepiness</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>8. Difficulty waking up</td>
<td>13 (72%)</td>
</tr>
</tbody>
</table>

Conclusions: These results provide further evidence that symptoms of sleep-related disorders are very common in children with a diagnosis of ADHD. The current results are very similar to values found by previous studies investigating symptoms in this group. Given that the children studied were not pre-selected based on symptoms and that they were diagnosed with ADHD only after an extensive battery of testing, these results suggest that more comprehensive evaluation of sleep-related symptoms should be included in the ADHD diagnostic criteria. The study’s results also further validate the utility of the PSQ for predicting the existence of sleep disorders in a pediatric population.

References:

This research was supported by a grant by the Oklahoma Center for the Advancement of Science and Technology (OCAST) and an equipment donation by Grass Instruments, Inc.

370.G

Validation of the Children’s Sleep-Wake Scale (CSWS)

LeBourgeois MK, Hancock MH, Harsh JR
Sleep Research Laboratory, University of Southern Mississippi

Introduction: This is a report on the validity of the Children’s Sleep-Wake scale (CSWS). The CSWS is a parent-report questionnaire constructed to permit convenient study of children’s sleep. It is based on a model that identifies five behavioral dimensions of sleep in preschool and early school-aged children: Going to Bed (GTB), Falling Asleep (FA), Awakening/Arousing (AA), Reinitiating Sleep (RS), and Returning to Wakefulness (RTW). Developmental procedures and reliability information for the CSWS are presented in a companion abstract. In this study, parents were asked to evaluate their children’s sleep along each of the five behavioral dimensions. Their ratings were then compared with the respective subscale scores of the CSWS.

Methods: Participants were caretakers of children (n = 485), ages 2 to 8 years (mean = 4.9; SD = 2.0) recruited from local shopping malls, daycare centers, and community activities. During this face-to-face contact, potential participants were asked to complete a short information form requesting their name, telephone number, preferred interview times, and the age(s) and sex of their children. Using this information, student researchers contacted caretakers by telephone and administered the CSWS. These interviews were about 10 minutes in duration. Response rate was 89%.

Results: Mean subscale scores were lower for children whose parents described them as having a problem on the respective sleep dimension (p< 0.001). Parental ratings of problem severity of each dimension were most highly correlated with the scores for the CSWS subscale assessing that dimension (r=-.315 to -.569; p<0.001; see Table 1). Coefficients in bold print represent the correlations between specific validity items and the subscales intended to measure the behavioral dimension addressed by that item.
Spearman’s correlation coefficients assessing correspondence between CSWS subscale scores and parental rating of problem severity for the respective behavioral dimension as well as all other dimensions.

<table>
<thead>
<tr>
<th>Parental rating of severity</th>
<th>CSWS Subscale</th>
<th>Total Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>bedtime resistance</td>
<td>.408**</td>
<td>.479**</td>
</tr>
<tr>
<td>difficulty falling asleep</td>
<td>.269**</td>
<td>.468**</td>
</tr>
<tr>
<td>nocturnal awakenings</td>
<td>.289**</td>
<td>.268**</td>
</tr>
<tr>
<td>difficulty remaining awake</td>
<td>.192**</td>
<td>.453**</td>
</tr>
<tr>
<td>difficulty returning to sleep</td>
<td>.425**</td>
<td>.362**</td>
</tr>
<tr>
<td>overall sleep problem</td>
<td>.576**</td>
<td>.374**</td>
</tr>
</tbody>
</table>

*p<0.01  *p<0.05  All correlation coefficients are negative (signs were excluded from the table for the purpose of simplicity and readability).

Conclusions: CSWS subscale scores are congruent with parental perceptions of the existence of a sleep problem. Furthermore, the greater the perceived problem severity, the lower the score on the relevant subscale. These data provide evidence of the construct validity of the CSWS. This instrument may be useful in the investigation of normal and abnormal sleep in young children.

Research supported by Aubrey K. and Ella Ginn Lucas Endowment for Faculty Excellence

371.G

Preliminary Development of the Pediatric Daytime Sleepiness Scale

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Introduction: Sleep need changes throughout one’s life span. Research suggests that, in adolescents, sleep need is greater than 8 hours per night and when the sleep of adolescents is reduced below 8 hours per night performance is impaired. However, survey data has shown that high school students report obtaining less than 8 hours of sleep per night on weekdays. Evidence suggests this age group may be chronically sleep deprived. Indeed, high school students with poor grades report getting fewer hours of sleep, later bedtimes, and irregular sleep schedules compared with higher achieving students (1). However, few studies have examined the relationship between sleep habits, sleepiness and educational achievement in younger adolescents (11 to 15 year olds). The present study examined the relationship between self-reported sleep patterns, sleepiness and school achievement in middle school age children.

Methods: Four hundred fifty-two students aged 11-15 participated (230 males, 215 females). The sample included students from grades 6 (173), 7 (125), and 8 (144) within an elementary school in rural Ohio. The sleep questionnaire included 32 items related to daily sleep patterns, school achievement, mood, sleepiness, and extra curricular activities. Thirteen candidate questions regarding sleep related behaviors were identifiend for inclusion in a daytime sleepiness scale. Factor analysis using unweighted least squares extraction method with promax rotation was used to examine scale structure.

Results: Factor analysis yielded three factors. The first factor accounted for 28% of the total variance. Questions related to daytime sleepiness loaded highly on this factor (.4 to .7). Two other factors were present but accounted for less than 10% of the remaining variance. Items loading above .4 on factor 1 (daytime sleepiness) were included as scale items for further analyses (8 items). Internal consistency (Chronbach’s alpha) for the total 8 item scale was .80. Scale scores were calculated for each individual in order to examine relationships between daytime sleepiness and school achievement (overall mean = 13.57 ± 5.62). Separate one way ANOVAs were performed comparing mean sleepiness scores at the five different levels of total sleep time, school achievement, mood, anger, school attendance, illness, extra curricular activities, and others (3 for grade level). Post hoc Tukey comparisons were performed where significant relationships were identified (Table). Significant linear effects were also present for each variable in the expected direction. Specifically, adolescents who reported low school achievement, higher rates of absenteeism, lower school enjoyment, lower total sleep time, more illness, and lower school enjoyment also report significantly higher levels of daytime sleepiness.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anova</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Lev.</td>
<td>6</td>
<td>12.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Absent</td>
<td>Never</td>
<td>11.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Enjoy Sch.</td>
<td>Always</td>
<td>9.3</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Conclusions: The scale developed in the present work appears to be suitable for this younger age group and may be useful in further research given its sound psychometric properties. Higher daytime sleepiness was related to reduced educational achievement and other school related outcomes. However, the causal variable(s) mediating this association have yet to be determined.

References:

372.G

Risk Factors for Apparent Life Treating Events (ALTE) in Infants: Clinical and Polysomnographic Evaluation

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(1) Sleep Disorders Center, IRCCS H San Raffaele, Milan, Italy, (2) Pediatric Dept., Insubria University, Varese, Italy

Introduction: Sudden infant death, apparent life treating events (ALTE) and regurgitation occur mostly during the first 6 months of life making very tempting to suspect a relation between these phenomena. According to epidemiological data, the role of gastro-esophageal reflux in the aetiology of ALTE is unclear (1). Previous studies indicated that episodes of apnea were seldom associated with gastro-esophageal reflux; the predominant sequence of events was obstructive apnea as terminal event (2). Whether or not an obstructive apnea is the primary event is unknown. However, there have been well documented case of ALTE infants who in time developed the symptoms of OSA (3). Aim of our study was to investigate whether anamnetic information and objective data (esophageal pH monitoring, polysomnography) could identify infants at high risk for ALTE. Highy suspected risk factors could be considered as a possible way of prevention in order to decrease the incidence of this life-treating syndrome.

Methods: We studied 50 patients (30F, 20M; median age 62.6 years) who had experienced ALTE and 50 age-matched controls (23F, 27M; median age 77 years). A complete clinical investigation was performed in all infants; this included information on anthropometric data, family history, exposition to risk factors (passive smoking, alcohol, drug intake),
delivery modality, Apgar score, prematurity, growth, specific circumstances of ALTE episodes, neurologic evaluation. All patients underwent extensive emathological and serologic tests and instrumentation monitoring that included pH-recording and nocturnal polysomnography. All collected variables have been statistically analysed in order to find the best predictive factors for ALTE.

Results: Our data showed that the major risk factors involved with ALTE were: gastrointestinal diseases (p=0.0005), smoking in pregnancy (p=0.0004), family history of ALTE (p=0.2), type of delivery (p=0.006), previous ALTE (p=0.0001), Apgar 1 score (p=0.005), Apgar 5 score (p=0.02), 24-hours esophageal pH monitoring reflux index (0.003) and number of refluxes (p=0.0001). No significant differences were observed in any of the following variables between ALTE patients and controls: total sleep time, delay in sleep onset, time of awake, percentage of REM and non-REM sleep, density and duration of apneas. An infant with a low Apgar score, premature birth, distocic delivery and severe gastro-esophageal reflux resulted at high risk for ALTE. None of the polysomnographic findings were predictive for ALTE in our population.

Conclusions: Our results showed that a detailed anamnestic investigation and pH recording seem to be more useful than polysomnography in detecting infants at high risk for ALTE.

References:

373.G

Long-lasting Effects of Iron Deficiency Anemia in Infancy on Sleep Autonomic Nervous System Functioning in Childhood

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Introduction: Our previous studies indicate that iron-deficiency anemia (IDA) in infancy disrupts the functional development of the autonomic nervous system (ANS) during sleep (Médigue et al 1996, 1997). The pattern of ANS balance suggested a delay primarily in vagal tone. Alterations in the functioning of several central neurotransmission systems and/or neuronal metabolism may be involved in the ANS imbalance. However, consistent with iron’s essential role in quantity and quality of myelin, we suggested disruptions of myelination processes as a promising explanation. Myelination of the vagus in the human is partly postnatal, and parasympathetic functional maturation follows that of the sympathetic system. To determine whether ANS changes are long-lasting, we evaluated heart rate and their variabilities as a function of sleep states in former IDA children aged 3-4 years.

Methods: All-night polysomnographic recordings were done in a group of healthy 3- to 4-year-old chilean children who were treated for IDA (n=24) or were nonaneic (controls, n=26) in infancy. The following variables were simultaneously recorded: EEG, EOG, EMG, cardiac, respiratory and motor activities, and oximetry. The ECG signal was processed off-line by a signal-to-noise ratio algorithm that detected the peak of the R wave for each heart beat and quantified sequential RR intervals in ms. Another algorithm based on the Fast Fourier Transform provided the spectral amplitude (in ms) in frequency bands: high, mid, and low-frequency HRV, corresponding to variations of RR intervals within periods of 3-8, 10-25, and 30-100 heart beats, respectively. Sleep was scored according to R&K criteria; NREM stages III and IV were grouped as SWS. For the individual child, means for RR interval and each HRV were computed over each REM, NREM stage 2, and SWS, and then analyzed according to the successive thirds of the night.

Results: The nocturnal organization of RR intervals and their variabilities within sleep states differed between groups (Table 1). In controls, RR intervals were longer in all states and lengthened during the 2nd third of the night in NREM stages. In former IDA children, HR values remained similar in all thirds. The extent of high-frequency HRV was higher in controls especially during the first two thirds of the night in all sleep states. A similar temporal pattern of differences between groups was present for low-frequency HRV in REM and NREM stages, except for SWS in which differences appeared by the end of the night.

Conclusions: Our results indicate that early IDA is associated with long-lasting alterations in the ANS functioning in both REM and NREM sleep. They also emphasize the role of iron in establishing the pattern of temporal organization in ANS balance. The results are provocative due to the role of ANS system balance and/or parasympathetic tone in children’s neurodevelopment, including visual recognition memory, vulnerability to stress and self-regulatory and exploratory behaviors. Since related physiologic and behavioral processes depend on the functional integrity of the ANS, we suggest that long-lasting IDA effects on the temporal organization of the ANS may help understand other developmental outcomes in childhood.

Research supported by Grants from NICHD (HD33487), Fondecyt (CONICYT, Chile 1000657) and Fogarty (TW00035)

374.G

Increasing Sleep Time Effectively Reduces Sleepwalking and Sleep Terrors in Children

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Introduction: Sleepwalking (SW) and sleep terrors (ST) are partial arousal parasomnias involving sudden arousal from slow wave sleep. There is considerable overlap in the pathophysiology and presentation of SW and ST, suggesting that they may represent variable expressions of the same clinical entity. Because physicians and parents are reluctant to prescribe medications for young children, researchers have turned their attention to behavioral interventions.1,2 The majority of studies have evaluated Scheduled Awakenings, which can be cumbersome for parents to carry out.1,2 Many sleep experts have noted that children exhibiting SW/ST present with daytime sleepiness and excessive sleep pressure. One suggested introducing daytime naps to decrease depth of sleep and reduce ST/SW events.3 The purpose of the present study was to evaluate

Table 1

<table>
<thead>
<tr>
<th></th>
<th>FORMER IDA</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st</td>
<td>2nd</td>
</tr>
<tr>
<td>REM SLEEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval (ms)</td>
<td>593</td>
<td>616</td>
</tr>
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<td>High-freq. HRV (ms)</td>
<td>16.0</td>
<td>16.3</td>
</tr>
<tr>
<td>Low-freq. HRV (ms)</td>
<td>15.3</td>
<td>16.3</td>
</tr>
<tr>
<td>NREM STAGE 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval (ms)</td>
<td>635</td>
<td>636</td>
</tr>
<tr>
<td>High-freq. HRV (ms)</td>
<td>23.7</td>
<td>19.2</td>
</tr>
<tr>
<td>Low-freq. HRV (ms)</td>
<td>14.3</td>
<td>13.4</td>
</tr>
<tr>
<td>SWS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval (ms)</td>
<td>645</td>
<td>671</td>
</tr>
<tr>
<td>High-freq. HRV (ms)</td>
<td>26.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Low-freq. HRV (ms)</td>
<td>12.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>
the effect of increasing total sleep time (TST) in children with frequent ST and SW events.

**Methods:** Participants were ten children (8 male; 2 female, 2½ to 9 yrs.) referred to a Behavioral Pediatric Sleep Clinic for frequent sleepwalking or sleep terrors. All children were screened for medical pathology and physician referred. They met ICSD criteria for sleepwalking or sleep terrors and displayed typical clinical characteristics (e.g., childhood onset, positive family history, occurring first third of night, amnestic for event, noninjurious automatistic behaviors). Parents maintained a daily sleep diary and recorded instances of SW/ST activity, including a narrative description of the events to ensure that the clinical characteristics were consistent with ST or SW. The goal of the intervention was to increase each child’s total sleep time. Specific procedures to accomplish this goal varied, but generally involved well-established interventions described in the pediatric sleep literature. Examples include teaching appropriate sleep onset associations, addressing sleep hygiene (e.g., removing TV from bedroom), re-instituting a daily nap or adding time in bed.

**Table 1**

<table>
<thead>
<tr>
<th>Subj</th>
<th>Pre-TST</th>
<th>Post-TST</th>
<th>Pre-Freq</th>
<th>Post- Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>9</td>
<td>8</td>
<td>0</td>
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<tr>
<td>2</td>
<td>9.0</td>
<td>10.1</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>10.5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>11.2</td>
<td>10.3</td>
<td>6.9</td>
<td>6.6</td>
</tr>
<tr>
<td>5</td>
<td>9.9</td>
<td>10.75</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>9.1</td>
<td>10.25</td>
<td>n.a</td>
<td>n.a</td>
</tr>
<tr>
<td>7</td>
<td>8.5</td>
<td>9.4</td>
<td>30</td>
<td>4.6</td>
</tr>
<tr>
<td>8</td>
<td>10.0</td>
<td>10.5</td>
<td>n.a</td>
<td>0</td>
</tr>
<tr>
<td>9*</td>
<td>9</td>
<td>10.2</td>
<td>12.8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>10*</td>
<td>9.4</td>
<td>10.6</td>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

Pre and Post-Freq = number of SW/ST events per month
n.a. = data not returned or not available
* = Scheduled Awakenings were added

**Results:** Pre-treatment sleep diaries indicated that all ten children fell below published developmental norms for total sleep time (group mean = 2.25 hrs. less than norms). All seven children for whom the genetic history was known had a positive family history of parasomnias. Six of ten children presented with a behavioral sleep disorder (bedtime struggles, frequent night-waking, refusal to nap, poor sleep hygiene) in addition to partial arousals. With behavioral intervention, nine of ten children/families successfully increased the child’s TST (avg = 1.25 hrs. range = .5 to 4.0 hrs.). Post-Treatment data on event frequency were returned by eight families. All eight children who increased TST showed clinically significant decreases in SW or ST events (see Table 1). All four children who presented to clinic on prescription medication for sleep were successfully tapered off. The only child who did not increase his TST displayed no change in SW/ST events. The addition of Scheduled Awakenings was necessary to eliminate SW/ST events for two children who either had difficulty maintaining sufficient TST because of school/extracurricular activities, or because increasing TST failed to fully eliminate SW/ST events. Interestingly, one of these children failed to respond to a previous trial of Scheduled Awakenings before increasing his TST.

**Conclusions:** The results of this study should be interpreted with caution as they represent initial pilot data with few methodological controls. These data do, however, suggest that a substantial number of otherwise healthy children with sleep terrors and sleepwalking may be sleep deprived. Our clinic successfully helped children increase their total sleep time through practical behavioral recommendations. Those children who successfully increased their total sleep time (sometime as little as ½ hour per day) demonstrated rapid and clinically impressive reductions in the frequency of sleep terrors and sleepwalking events.

**References:**

375.G

**OSAS in Children is Associated with Changes in Sleep Architecture**

Tayag-Kier CE, Pillai M, Slintak C, Chopra A, Maczaj M.
Center for the Study of Sleep and Waking; University Hospital SUNY at Stony Brook

**Introduction:** Poor sleep quality has been reported in children with OSAS. To the best of our knowledge, the extent and type of sleep architecture disturbance has not been described polysomnographically.

**Methods:** Our sample included every child that was diagnosed with OSAS at our center between 1/97 and 11/00 (n=83). The ages of the children ranged between 7 months and 18 years. median age was 7. There were 48 boys and 35 girls. OSAS criteria was defined as RDI=>1/hour. The RDI included both apneas and hypopneas that were associated with 4% or greater arterial oxygen desaturations and disturbed respiratory events which appeared to be apneas/hypopneas but were not associated with a 4% or greater arterial oxygen desaturation. All disturbed respiratory events were of at least two respiratory cycles in duration. Disturbed respiratory events were counted even if they were not associated with an arousal. We compared our sleep architecture findings to published values for normal children (1,2). We separated our children into five age groups (ages 3-5; 6-9; 10-12, 13-15, and 16-19) and divided them by gender for more exact comparison to the published values.

**Results:** Significant (p ≤ 0.05) sleep architecture changes were as follows: TST was decreased, SE% was decreased, REM% was decreased. These findings were found in all age groups except in the 16-19 years age group in which REM% was not statistically different. Average TST in our OSAS children was 374.12 min.; average SE% was 86.22; average REM% was 13.41.

**Conclusions:** Our findings of a shorter TST may perhaps be due to a sleep lab imposed sleep restriction (delayed bedtime). The findings of a poor sleep efficiency may be due to difficulty sleeping in a new environment, though this is doubtful. The finding of a markedly lower REM% is not easily explained –it may be a direct result of the OSAS. Interestingly, SWS% was preserved despite the majority of the disturbed breathing events occurring in NREM sleep. Since approximately 23% of our OSAS sample had symptoms of hyperactivity, we eliminated this group to exclude the possibility of hyperactivity confounding the results. Exclusion of the hyperactive sample did not affect the sleep architecture changes in the non-hyperactive OSAS sample. Exclusion of 8 cases with congenital abnormalities also did not affect the outcome of our findings. Our data suggest that the sleep architecture changes are associated with one or more of the underlying processes of OSAS, possibly the number or frequency of the apneas/hypopneas or changes in arterial oxygen saturation. We plan to further analyze our data to establish what features of the OSAS may be responsible for the aforementioned sleep architecture changes.

**References:**
376.G

Monitoring Home-based Experimental Sleep Manipulation in Children with Actigraphy

Fallone GP, Acebo C, Seifer R, Carskadon MA
Bradley Hospital Sleep Research Laboratory

Introduction: Children appear to be at increasing risk for inadequate sleep, but those who sleep poorly often have comorbid medical/psychological problems confounding interpretation of inadequate sleep. Experimental sleep deprivation in healthy children may aid understanding of effects of poor sleep. Home-based protocols increase opportunities for prolonged sleep manipulation in children and assessment may be possible using actigraphy. We examined healthy children in a three-week home-based protocol under conditions of self-selected, optimized, and restricted sleep. We used actigraphy to describe self-selected sleep patterns and to monitor compliance with experimental schedules and report here on participants’ success in maintaining the sleep schedules.

Methods: 36 boys and 32 girls screened for medical and psychological health participated in the three-week study. Participants had a self-selected school-night schedule at home during week 1 and followed assigned schedules for 6 consecutive nights during weeks 2 and 3. Restricted schedules limited sleep to 6.5 hours in children grades 3-7 (ages 8.6-12.8; n = 57) and to 7 or 8 hours in grades 1 and 2 (ages 6.5-8.2; n = 11); usually by delaying bedtime. Optimized schedules advanced bedtime to provide at least 10 hours to sleep, longer in children who manifested longer usual sleep times. Participants were monitored with actigraphy, completed a daily diary, and left a time-stamped phone message at bedtime and wake time. Actigraphy records from Self-selected and Optimized conditions were examined using standard laboratory procedures. Measures of compliance to the Optimized schedule were minutes between bedtime and scored sleep onset (sleep compliance) and minutes between scored sleep offset and risetime (wake compliance). Actigraphy from the Restricted condition was examined for scored sleep during scheduled sleep opportunity, sleep within 165 minutes prior to assigned bedtime (mean difference of Restricted & Self-selected bedtimes), and 120 minutes following assigned wake time. Compliance to Restriction was assessed as minutes scored as sleep in the pre-bedtime and post-waketime periods.

Results: Table 1 provides the overall values for actigraphically estimated total sleep demonstrating lowest sleep during Restriction and highest during Optimized. Table 2 shows the compliance variables. In general, participants were able to comply with Optimized sleep and wake times within thirty minutes and had less than 10 minutes of scored sleep prior to Restricted bedtime or following risetime. ANOVA revealed a significant difference between younger and older participants for wake compliance (F(1.67) = 7.02; p<.05). No other age-related differences were noted for compliance variables.

Table 1: Total Sleep Time (TST) from Actigraphy (minutes)

<table>
<thead>
<tr>
<th>Group</th>
<th>Self-selected TST x (sd)</th>
<th>Optimized TST x (sd)</th>
<th>Restricted TST x (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-2nd Graders</td>
<td>482 (58)</td>
<td>502 (73)</td>
<td>395 (61)</td>
</tr>
<tr>
<td>3rd-7th Graders</td>
<td>480 (47)</td>
<td>509 (43)</td>
<td>355 (27)</td>
</tr>
</tbody>
</table>

Table 2: Compliance Variables (minutes)

<table>
<thead>
<tr>
<th>Group</th>
<th>Optimized Sleep</th>
<th>Restricted Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bedtime compliance</td>
<td>Wake time compliance*</td>
</tr>
<tr>
<td>1st-2nd Graders</td>
<td>29 (19)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>3rd-7th Graders</td>
<td>25 (14)</td>
<td>14 (15)</td>
</tr>
</tbody>
</table>

*p < 0.05

Conclusions: These data demonstrate that healthy children can comply with significant home-based sleep manipulation over a prolonged period. Though results of this protocol are very encouraging, some children clearly had difficulty with the schedules and this difficulty may be more pronounced if similar methods were applied to a clinically at-risk sample.

References:

Research supported by NR04279 and MH01358

377.G

Disturbed Sleep Architecture in Children with OSAS is Associated with Oxygen Saturation Changes

Maczaj M, Tayag-Kier C, Pillai M, Slintak C, Chopra A
Center for the Study of Sleep and Waking, University Hospital SUNY at Stony Brook

Introduction: Disrupted sleep has often been referred to in children with OSAS. We evaluated the sleep architecture findings of 83 consecutive children diagnosed with OSAS who were studied in our center between 1/97 and 11/00. Sleep architecture changes revealed significantly shortened TST, decreased SE%, and decreased REM% compared to published norms for children. We analyzed our data to see what features of the OSAS may be responsible for the sleep architecture changes.

Methods: Our sample included every child that was diagnosed with OSAS at our center between 1/97 and 11/00 (n=83). The ages of the children ranged between 7 months and 18 years. Median age was 7. There were 48 boys and 35 girls. OSAS criteria was defined as RDI=>1/hour. The RDI included both apneas and hypopneas that were associated with 4% or greater arterial oxygen desaturations and disturbed respiratory events which appeared to be a pneumonia or hypopneas but were not associated with a 4% or greater arterial oxygen desaturation. All disturbed respiratory events (including apneas and hypopneas) were of at least two respiratory cycles in duration. Disturbed respiratory events were counted even if they were not associated with an arousal. Baseline arterial oxygen saturation was calculated five minutes after sleep onset. We performed multiple regression analysis on the following variables: Predictors (respiratory variables): Number of apneas/hypopneas (associated with =>4% desaturations) RDI (includes all disturbed respiratory events with and without desaturations). Baseline arterial oxygen saturation. Average maximum arterial oxygen saturation associated with the respiratory disturbances. Average minimum oxygen saturation. Minimum arterial oxygen saturation. Dependent variables (Sleep architecture values): TST; SLSE%; REM latency; REM%; SWS%; WASO.

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Center for the Study of Sleep and Waking, University Hospital SUNY at Stony Brook

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Methods: Our sample included every child that was diagnosed with OSAS at our center between 1/97 and 11/00 (n=83). The ages of the children ranged between 7 months and 18 years. Median age was 7. There were 48 boys and 35 girls. OSAS criteria was defined as RDI=>1/hour. The RDI included both apneas and hypopneas that were associated with 4% or greater arterial oxygen desaturations and disturbed respiratory events which appeared to be a pneumonia or hypopneas but were not associated with a 4% or greater arterial oxygen desaturation. All disturbed respiratory events (including apneas and hypopneas) were of at least two respiratory cycles in duration. Disturbed respiratory events were counted even if they were not associated with an arousal. Baseline arterial oxygen saturation was calculated five minutes after sleep onset. We performed multiple regression analysis on the following variables: Predictors (Respiratory variables): Number of apneas/hypopneas (associated with =>4% desaturations) RDI (includes all disturbed respiratory events with and without desaturations). Baseline arterial oxygen saturation. Average maximum arterial oxygen saturation associated with the respiratory disturbances. Average minimum oxygen saturation. Minimum arterial oxygen saturation. Dependent variables (Sleep architecture values): TST; SLSE%; REM latency; REM%; SWS%; WASO.

References:

Research supported by NR04279 and MH01358

377.G

Disturbed Sleep Architecture in Children with OSAS is Associated with Oxygen Saturation Changes

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Center for the Study of Sleep and Waking, University Hospital SUNY at Stony Brook

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Sleep And Memory T Lymphocytes In Alzheimer’s Caregivers

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Introduction: Previous research indicates that disturbed sleep increases with age, and that such sleep disturbances, including frequent awakenings, insufficient total sleep time, and sleep-disordered breathing, may be associated with cardiovascular disease, hypertension, and other health indicators (1). Previous research by our group with other elderly populations also revealed that disordered sleep is accompanied by increases in circulating catecholamines (2), that may be associated with a deficit in memory T cells (3). Given that both sleep loss and stress have profound effects on the immune system, and that Alzheimer’s caregivers are likely to have interrupted and fragmented sleep by virtue of their caregiving role, we performed a pilot study to examine the relationship between sleep and circulating memory T lymphocytes in caregivers.

Methods: Nine older vulnerable caregivers of patients with Alzheimer’s Disease and four age/gender matched non-vulnerable controls (mean age 73 years) served as subjects. Vulnerable caregiving was defined as a severe mismatch between the number of care the caregiver needed to provide versus amount of respite available. Subjects received three-day at-home sleep/wake activity monitoring with the Actillume (Ambulato-

Results: Statistically significant associations (p ≤ 0.05) were found between TST, SE%, REM%, WASO and the following respiratory predictors: baseline arterial oxygen saturation, average max. arterial oxygen saturation, average min. arterial oxygen saturation, (TST beta=0.293 for baseline O2; 0.342 for average max. O2; SE% beta=0.272 for baseline O2; 0.421 for average max. O2; REM% beta= 0.300 for baseline O2; average max. O2 and average min. O2 were not statistically significant for this measure; WASO beta= -0.260 for baseline O2, -0.368 for average max. O2 and -0.264 for average min. O2. No significant association was found between sleep architecture changes and the number or frequency of disturbed breathing events.

Conclusions: This data supports the concept that low oxygen saturation and not the number of disturbed breathing events is responsible for sleep fragmentation and decreased REM% in children with OSAS.

References:
(1) Ancoli-Israel, S. et al. Sleep Medicine Reviews 1:3-17, 1997.

Supported by MH42840, HL44915, HL57265, NIA AG02711, NIA AG08415, NCI CA85264, the Department of Veterans Affairs VISN-22 MIRECC, the UCSD Cancer Center and the Research Service of the Veterans Affairs San Diego Healthcare System.

378.H

Sleep In Postmenopausal Women A Double Blinded Study, Placebo-Controlled Using Hormone Replacement

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Introduction: The menopause is the cessation of cyclic ovarian function as manifested by the occurrence of the final menstrual period. Women typically live over one-third of their life after the onset of the climacteric and the occurrence of menopause wherein they may suffer from a number of symptoms. The symptoms are thought to be due to decreased levels of circulating estrogen and progesterone. These symptoms which are variably present frequently include alterations in sleep such as insomnia and night sweats and a number of non-sleep related symptoms including: hot flushes paresthesia, vaginal dryness, dyspareunia, urinary frequency, palpitations, headache, vertigo, anxiety, and so on. There is a lack of literature on diagnosis, treatment and pathophysiology of sleep difficulties in women in peri and post menopausal periods, that’s why we decided to start this study. The aim of this survey was to study the sleep in post menopause: to see the incidence of sleep disturbance and to compare the register of the polysomnography in postmenopausal women before and after using hormone therapy.

Methods: Thirty-three women in postmenopause were selected to join the group. None of them had any contraindications for the use of hormone therapy. They were not using either hormone therapy or hypnotic drugs. All of them had a basal polysomnography after what they had been divided in two similar groups. Nineteen women joined our control group (Group B). The other fourteen women formed our tested group. (Group A). The patients from group A received estrogen whereas those from Group B received placebo. Patients of both groups had another polysomnography after three months of drug administration. Then Group A used estrogen plus progesterone and Group B placebo plus progesterone for three months and all of them did the final polysomnography.

Results: The polysomnography exhibit 12% patients with an increased sleep latency. The final latency was increased in 24% and 66% showed an increased percentage of stage 0. As a consequence of this, 42% had a lower percentage of sleep efficiency. Hormone therapy was found to result in an increase in the total time sleep. As concerning sleep quality we can state that it also got better after hormone replacement since the percentage of stages 3 and 4 (which was decreased in 30% patients) and of REM (which was decreased in 15%) experienced normal percentage in the end of the treatment. 75% of the patients showed snoring (11 in group A and 14 in group B). The absence of snoring was observed in 70% of the patients from group A whereas 50% of the patients from group B continued showing snoring after hormone therapy. The apnea
hypopnea index was positive in 39%. Only two in Group B didn’t have it lowered after drug administration.

Conclusions: Postmenopausal women exhibit a poor sleep quality and a low sleep efficiency. Most of them had a good response to hormone replacement. The respiratory events had a great result after the use of estrogen progesterone association.

Research supported by Associacao Fundo de Incentivo a Psicofarmacologia

380.H

Objectively Measured Sleep Behaviors and Vigilance in Community Residing Elderly With and Without Complaints of Daytime Sleepiness

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Introduction: As part of our recently completed case-control study of excessive daytime sleepiness (EDS) in community residing elderly (1), a number of factors including sleep apnea (AHI>=20) were implicated. Additionally, subjects wore wrist actigraphy and underwent portable psychomotor vigilance testing (PVT). Thus, this case-control study provides an opportunity to characterize differences in objectively measured sleep patterns and functional performance between community residing elderly with and without complaints of excessive daytime sleepiness.

Methods: Subjects were recruited from continuing care retirement communities supplemented by recruitment of community dwelling African-Americans (Mean age = 78yrs). EDS cases were identified by subjective reports of problems with daytime sleepiness at least 3-4/wk while controls reported no problems with daytime sleepiness and not falling asleep in active or passive situations more than twice the previous month. Eligibility required that subjects were neither depressed (Geriatric Depression Scale<11) nor cognitively impaired (Short Blessed Exam<7). Actigraphy was used to obtain daily estimates of sleep duration, nocturnal awakenings, daytime naps, etc (2) over a one-week period. Then, subjects underwent polysomnography and psychomotor vigilance task (PVT) testing (3). The PVT, a test of behavioral alertness, uses simple reaction time (RT) to evaluate abilities to sustain attention and respond in a timely manner. PVT outcomes included: (1) median response time (ms); (2) frequency of lapses (RT>499ms); (3) duration of lapse domain (reciprocal of 10% slowest RTs); (4) optimum response times (10% fastest RTs); and (5) the fatigability function (least squares slope of vigilance decrement function across time on task). Subjects had a PVT practice session the night prior to PSG and 2 PVT sessions the next day. Time from first to last nocturnal sleep epoch (hr)

Results: The table summarizes comparisons between groups. Subjects with EDS had significantly shorter times between the first and last epoch of nocturnal sleep, greater nocturnal time awake after sleep onset, less nocturnal sleep time, but more daytime napping (all p<0.009). Subjects with EDS had significant PVT slowing as demonstrated by shifts in the right side of the RT distribution (i.e., slowest 10% and lapses). Vigilance lapses were elevated by 40% relative to controls. There were no differences in fastest RTs. The partial correlations of total nocturnal time spent awake with PVT lapses and with 10% slowest RTs were statistically significant (|r|>0.19, p<0.008).

Table 1

<table>
<thead>
<tr>
<th>Actigraphy</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>time from first to last nocturnal sleep epoch (hr)</td>
<td>7.64</td>
<td>0.84</td>
<td>7.96</td>
<td>0.94</td>
<td>0.008</td>
</tr>
<tr>
<td>nocturnal time awake (hr)</td>
<td>0.65</td>
<td>0.69</td>
<td>0.44</td>
<td>0.49</td>
<td>0.009</td>
</tr>
<tr>
<td>nocturnal time asleep (hr)</td>
<td>0.99</td>
<td>1.17</td>
<td>7.53</td>
<td>1.10</td>
<td>0.0006</td>
</tr>
<tr>
<td>daytime nap sleep time (hr)</td>
<td>0.49</td>
<td>0.39</td>
<td>0.32</td>
<td>0.35</td>
<td>0.0006</td>
</tr>
<tr>
<td>total 24 hr time asleep (hr)</td>
<td>7.50</td>
<td>1.28</td>
<td>7.88</td>
<td>1.18</td>
<td>0.024</td>
</tr>
<tr>
<td>PVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean of 1/RT for 10% slowest RTs</td>
<td>248.2</td>
<td>50.5</td>
<td>246.1</td>
<td>87.4</td>
<td>0.819</td>
</tr>
<tr>
<td>mean of 10% fastest RTs</td>
<td>334.9</td>
<td>88.5</td>
<td>325.6</td>
<td>141.1</td>
<td>0.53</td>
</tr>
<tr>
<td>mean of 1/RT for 10% slowest RTs</td>
<td>1.75</td>
<td>0.59</td>
<td>1.94</td>
<td>0.62</td>
<td>0.015</td>
</tr>
<tr>
<td>frequency of lapses</td>
<td>11.70</td>
<td>15.15</td>
<td>8.42</td>
<td>13.80</td>
<td>0.067</td>
</tr>
<tr>
<td>snore freq. (1/sqrt) + (sqrt+1)</td>
<td>5.95</td>
<td>3.58</td>
<td>4.82</td>
<td>3.37</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: Objectively measured differences in sleep behaviors and daytime vigilance performance were found between elderly individuals who complained of excessive daytime sleepiness and those who did not. Elderly subjects with such complaints tended to have shorter nocturnal sleep durations and poorer daytime performance. Thus, complaints of EDS from elderly individuals must be taken seriously as they reflect true behavioral differences rather than simply differences in their propensity to complain.

References:

Research supported by HL-50051, AG-03934, HL-60287, RR-00040.

381.H

Effects of Aging on Light-induced Per1 &Per2 Expression in the Syrian Hamster Suprachiasmatic Nucleus

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Introduction: In mammals, the suprachiasmatic nucleus (SCN) of the hypothal-amus has been shown to be a primary circadian pacemaker for most, if not all, circadian rhythms. Recent studies on the molecular aspects of clock genes have produced a functional model of circadian rhythms, and have indicated that number of genes are involved in the generation of circadian rhythm. In particular mPer1, mPer2, and mPer3, cloned as mouse homologs of the Drosophila gene Period (Per), exhibit circadian rhythmic expression in the SCN. Brief exposure to light during subjective night results in a large and rapid induction of mPer1 and mPer2 expression. Aging is associated with changes in several basic parameters of circadian rhythms in mammals, including changes in period length under free-running conditions, amplitude, and the phase angle of entrainment to the light-dark cycle. Furthermore, some studies have demonstrated that aging alters the effects of light on c-fos expression, and phosphorylation of CREB in the SCN as well as on the phase shifting effects of light on the rhythm of activity. The purpose of this study was to determine the effects of aging upon light-induced Per1 and Per2 expression in the SCN.

Methods: Male golden hamsters purchased from Charles River at the ages of 8 to 9 weeks or 6 to 7 months were group housed and maintained in active or passive situations more than twice the previous month.
on a 14:10 light dark cycle. After hamsters reached the age of three to four months (“young”) or 18-22 months (“old”) the animals were transferred to individual cages equipped with running wheels for continuous recording of locomotor activity with an on-line computer system (Chronobiology Kit, Stanford Software Systems). Two weeks later, the animals were transferred to constant darkness. After 10 days in constant darkness animals were exposed to a 5 min monochromatic light pulse (503nm) at one of four irradiance levels [7.5 x 10 9, 1.5 x 10 11, 8.6 x 10 12 or 2.6 x 10 14 photons/cm2/s] at circadian time (CT) 19. Control animals were handled in the same manner but were not exposed to light. After 70 min, each hamster was killed for the quantitative study. In situ hybridization using 33P-labeled probes was used to determine the quantity of Per1 and Per2 mRNA levels in coronal sections of the hypothalamus. Significant differences between the response of individual groups were determined using ANOVA or Dunnet’s test. The 0.05 level of probability was used as the minimum criterion of significance.

Results: Per1 and Per2 mRNA expression of both young and old hamsters were increased with increased irradiance. According to the two-way ANOVA, the main effect of irradiance level was significant. There was a significant main effect of age on Per1, but not Per2, expression. Light induced Per1 levels were significantly greater in the young than the old animals at one light intensity (8.6 x 10 12 photons/cm2/s).

Conclusions: These data indicate that there are dramatic changes in light activated molecular responses in the suprachiasmatic nuclei of old hamsters, and suggest that these molecular changes, particularly Per1, may underlie age-related changes in the effects of light on the circadian clock system.

Research supported by AG11412-07 Project 3

382.H

Effects of Age on Cardiac Autonomic Nervous System Activity During Sleep

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Introduction: Measurements of heart rate variability (HRV) are increasingly being used as markers of cardiac autonomic function. Power in the high frequency (HF) component has been associated with the presence of respiratory sinus arrhythmia (RSA), which is primarily vagally mediated. Although, less well-defined, power in the low frequency (LF) component has been associated with sympathetic tone. These and other measures have indicated that during sleep, cardiac parasympathetic nervous system (PNS) activity increases and sympathetic nervous system (SNS) activity decreases. In the elderly sleep fragmentation is a common sleep complaint. One alleged cause of sleep deterioration is increased activity of the SNS as indicated by raised plasma norepinephrine levels. To date, there has been no study that has used HRV to determine the effect of age on autonomic variables during sleep. The aim of the current study was to assess the possible relationship between autonomic balance and age-related sleep disturbances.

Methods: 14 young adults (mean age = 21 + 6.22 yrs) and 20 older adults (mean age = 74.31 + 6.56) each spend two non-consecutive nights in the sleep laboratory. All subjects were neurologically and medically healthy and were not taking any medications that are known or suspected to impact on the integrity of the central nervous system or sleep. For each recording session all movement and artefact free 2 minute epochs were identified, beginning 2 hours before sleep onset and until morning awakening. Epoch values were obtained for each measure and the data binned into 30 minute intervals. The cardiac variables measured were: heart rate (HR) and LF and HF components of HRV. The two HRV components were calculated as both absolute values and as a proportion of total power.

Results: The HF component, when expressed as absolute power, increased in both young and elderly groups during sleep. In contrast, absolute LF power also increased in the elderly, but decreased slightly in the young. However, the pattern was different when the components were expressed as a proportion of total power. In this case the HF component increased during sleep in the young, but not in the elderly, while LF power was not different between the groups during sleep.

Conclusions: These results are consistent with previous studies reporting changes in autonomic activity from wake to sleep in young adults. The data also suggest that the balance between parasympathetic and sympathetic activity change with age, such that sleep in the elderly is characterised as a period of relative sympathetic domination, or parasympathetic inhibition, as opposed to the more parasympathetically determined NREM sleep of young adults. This supports the view that relative sympathetic hyperarousal may be a cause of age-related sleep disturbance. However, the data is ambiguous as to whether this aging effect is related to sympathetic, or parasympathetic modulation.

383.H

The Effects of Normal Aging on Phasic Events During Sleep

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Introduction: Sleep spindles and K-complexes are the hallmarks of Stage 2 sleep. Despite a relatively large body of literature describing the characteristics of these two phasic events in young adults, relatively little research has been conducted in older adults, particularly normal aging. The general consensus from the few studies that have addressed this issue is that there is a consistent decrease in the number of spindles and K-complexes, although there is a large intra-individual variation (1). Whether or not changes in the characteristics of these phasic events is an inevitable consequence of the aging process can be address by studying healthy older adults who provide an example of the effects of age independently of those of disease.

Methods: We studied 14 young adults (mean age = 21 + 6.22 yrs) and 20 older adults (mean age = 74.31 + 6.56). All subjects were neurologically and medically healthy and were not taking any medications that are known or suspected to impact on the integrity of the central nervous system or sleep. Scoring of sleep records was performed on 30 second epochs according to Rechtschaffen and Kales criteria. Sleep spindles were detected algorithmically from C3 EEG data bandpass between 12 and 16Hz. K-complexes were visually scored according to conventional criteria. For each subject a number of characteristics were determined including the number, density (SS/min), amplitude and frequency of all spindles as well as the number and density of K-complexes (KC/min).

Results: Results indicated that spindle number, density and duration as well as K-complex number and density were all significantly lower in the elderly compared to the young adults. The difference between the two groups in terms of spindle frequency was slight and not statistically significant. In addition, there was a sex difference: both older and young females were producing almost twice as many spindles and K-complexes as men. Sleep efficiency displayed significant positive correlations between sleep spindle number and density and K-complex number and density and a negative correlation with age.

Conclusions: The age-related decrease in sleep spindle and K-complex
density is consistent with previous reports and may be interpreted as an age-related disturbance of thalamocortical regulatory mechanisms. The presence of the effect in neurologically healthy subjects would argue that this is a true aging effect and not the result of a confounding illness. The apparent link between sleep spindles, K-complexes and sleep efficiency is congruent with the notion that these phasic events have a sleep protective role. In summary, characteristics of these phasic events may be a good biological marker of the changes in sleep that occur with age.

References:
(3) Van Someren, E. J. Circadian rhythms and sleep in human aging.

384.H

Effect of Regular Training Program on Sleep, Circadian Rhythms and Performance on Driving Simulator in the Elderly.

Gruau S,1 Denise P,1 Normand H,1 Sesboüé B,1 Davenne D2 (1) Laboratoire de Physiologie Faculté de Médecine CHU Caen France, (2) Centre de Recherches en Activités Physiques et Sportives Université de Caen France, (3) Institut Régional de Médecine du Sport CHU Caen France

Introduction: Aging is associated with changes in both sleep and circadian rhythms. The most important changes in sleep disorders with aging are reduction in sleep efficiency, increased latency of onset of sleep, increased number and duration of awakenings and increased frequency of daytime napping (1). Obviously, the reduction in sleep quality experienced by many older people has numerous implications for their daytime functioning and thus their quality of life. Daytime sleepiness may be greater with aging and such sleepiness could lead to an increased number of accidents (2). Alteration of circadian rhythmicity include a decrease in the amplitude, a phase advance and a shortening in the period (3).

Methods: The study involved 20 subjects (aged 65.7 ± 1.7 years) divided into two groups : a control group and an experimental group. The experimental group were enrolled in a moderate fitness training program for 4 months. To quantify the effectiveness of the training, VO2max was assessed using a maximal test on a bicycle ergometer. Oral temperature circadian rhythmicity, sleep objectives parameters and performance on driving simulator were assessed before and after the training program.

Results: Moderate fitness training significantly affects all parameters. While no between-group differences were seen at baseline for all parameters, exercisers showed significant improvement in the VO2max, the amplitude of temperature cycle, the index quality of sleep with actigraphy, the objectives sleep measures and showed significant decrease in mean variance of lateral position, an index in vehicle control.

Conclusions: These results confirm the sleep quality and the amplitude of normal circadian rhythms are altered with aging. Also they demonstrate that the elderly can engage in moderate-intensity exercise program are important as exercise may counteract this phenomenon and enhanced driving performance. Thus may be helpful in elderly people suffering from sleep problems and daily altered performance related to circadian rhythms disturbances.

References:
(3) Van Someren, E. J. Circadian rhythms and sleep in human aging.

385.H

Self-Reported Sleep Patterns and Sleep-Related Characteristics of ‘Young-Old’ and ‘Old-Old’ Community Dwelling Seniors

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Introduction: The range of ages qualifying an individual as an older adult can span 30+ years. As a result, aging researchers often divide their samples into ‘young old’ and ‘old old’ (75+) groups. Although sleep researchers rarely utilize this distinction, evidence that sleep worsens with age suggests such distinction may help elucidate the nature of sleep in aging. The present study examines sleep and factors associated with age-related increases in sleep difficulties (health, medication, psychological distress) in young old and old old elderly.

Methods: Random-digit dialing was used to recruit at least 50 males and 50 females in each decade (20-80+). Participants completed 14 sleep diaries and several sleep-related questionnaires. A subset of 322 older individuals from this normative sample were divided into young old (60-74 years; n = 175; 76 M & 79 F) and old-old (75-98 years; n = 147; 75 M & 72 F) groups.

Results: ANOVA (see table) and regression analyses were used to compare the young old and old old groups on eight sleep variables, two psychological measures, and two health items. Sleep variables included: SOL, NWAK, WASO, TST, SE, TIB, quality, and naps. Psychological measures included: State-Trait Anxiety Inventory, Trait-STAI and Beck Depression Inventory-BDI. Health-related items included: number of medical conditions and number of medications. Sleep Variables. Significant group differences were found for all sleep variables except sleep quality and WASO. Young old took less time to fall asleep, slept more efficiently, awoke less, and napped less than old old. Interestingly, both age groups rated their sleep quality as fair and had about 30 minutes of unwanted nightly awake time. Psychological Measures. Young old reported significantly less depression than old old; the two groups did not differ in anxiety. Health Items. Significant group differences were found for number of medical conditions but not for number of medications. On average, old old reported more medical conditions than did young old. Medication usage did not differ with both groups taking only 2-3 medications on average. Because SE provides a good overall estimate of an individual’s sleep, a stepwise regression analysis was performed with SE as the dependent variable and the sleep-related measures and several demographic variables as independent variables. For young old, anxiety accounted for 10.7% of the variance in sleep efficiency followed by gender (4.1%) and history of mental health problems (3.6%). For old old, number of medical conditions accounted for 15.0% of the variance in sleep efficiency followed by gender (4.1%) and anxiety (3.0%).
Sleep Disorders in Ambulatory Seniors

Rigato CB, Silva AB, Prado GF, Masuko A, Carvalho LC, Capucho C, Ramos LR, Miranda RD, Lopes EA

Sector of Sleep Disorder of Neurology/Neurosurgery, Internal Medicine and Geriatric Departments of Federal University of São Paulo

Introduction: The sleep main function is to restore the energy, intellectual or motor, spent during the day and to attach the learned information. All the organism functions, like physical, emotional and intellectual development depend on the cycle awake-sleep. Adult needs to sleep less than the teenager and more than senior does. In the old age, the sleep architecture has significant changes: decrease in stages 3, 4 and 5, and increase of nocturnal awakenings and diurnal sleepiness. These alterations favor the naps that reduce the nocturnal sleep. The social-economic condition of the senior is synonymous of solitude, for he is left aside by the family because of his diseases, doubting whether he is capable to take care of himself. He is afraid of sleeping because he thinks he cannot awake anymore. The situation is enough to cause Sleep Disorders and bad sleep quality, reducing the social and productive activities. Verifying sleep disorders and their treatment can help to improve the individual life quality. Objective: verify Sleep Disorders in Senior and their associations with other diseases common in seniors, diagnosed by a clinician of the Geriatrics Ambulatory.

Methods: We are going to evaluate 100 female patients, with average age 74.7 years, in the Geriatric Ambulatory of UNIFESP-EPM, São Paulo, Brazil. The Geriatric Ambulatory takes care of patients above 65 years old with some cardiac, endocrine or psychiatric diseases. Assessment of sleep disorder by Sleep General Inquiry (adapted of Bruni et al., 1996) applied individually by a psychologist. Independent variables: disorder of initiating and maintaining sleep, sleep breathing disorders, parasomnias, narcolepsy, excessive somnolence.

Results: 54% of the patients showed disorder of initiating and maintaining sleep, 37% of excessive somnolence, 53% sleep breathing disorders, 19% narcolepsy, 6% parasomnia. Among these patients, 15% showed BMI > = 30, 65% had arterial hypertension, 32% has diabetes mellitus and 30% had depression.

Conclusion: Sleep Disorders in senior were verified in 54% of the patients. 65% of these patients had arterial hypertension, 32% has diabetes mellitus and 30% had depression.

References:

387.H

Age and Gender Effects in Body Temperature Minimum Estimated in a 90-min Day

Bliwise DL, Sanders DD, Bailey ET, Keefe J, Ansari FP, Albers HE, Pratt L, Murphy S

(1) Emory University School of Medicine, (2) Georgia State University

Introduction: Age effects in relation to the estimated body temperature minimum (BTmin) as a marker of endogenous phase vary by experimental protocol. Under entrained conditions and constant routines, phase advances with age have been reported, whereas forced desynchrony protocols with long enforced wake periods (28 hr day) have reported virtual absence of age differences. Gender interactions with aging in these protocols have been underexplored. We report here age and gender effects on BTmin derived from a forced desynchrony protocol of low homeostatic drive (90 min day).

Methods: Subjects were 70 adults (37 M, 33 F) representing a broad age range (18-82) screened for excellent health and absence of sleep disorders. Pre-menopausal women had regular menstrual cycles and were studied during follicular phase; post-menopausal women included those on/not on HRT. All kept sleep logs for two weeks prior to entering the study. Following a Baseline night of uninterrupted sleep and MSLT, subjects underwent 32 90 min cycles (30 min sleep/60 min awake) commencing at 2000 during which oral temperatures were taken every 30 minutes. Subjects did not undergo strict temporal isolation. Meals were provided ad lib but activity and exposure to outdoor light were controlled. Temperature data were subjected to a 5-point moving average and then curve fit to a quadratic function using least squares regression. Subjects’ temp data were retained for further analyses if r-squared values exceeded .50 (n = 23 men; n = 26 women). BTmin was derived from the clock time associated with the minimum of the fitted temperature curve.

Results: Age was associated with earlier bedtime and wake-up times for both men (rho = -.85 and -.81, both p < .0001, respectively) and women (rho = -.55, p < .002 and -.48, p < .02, respectively). X (SD) BTmin occurred earlier in women than in men (0609[130 min] vs 0728[92 min], t = 2.42, p < .02) without gender differences in age. Across the entire age range, estimated BTmin for men and women were uncorrelated with age (rho = -.08 and -.16, NS). In pre-menopausal women (ages 18-47) BTmin was negatively correlated with age (rho = -.88, p < .0001) whereas in post-menopausal women (ages 49-73) BTmin was positively correlated with age (rho = + .60, p < .02). HRT did not impact correlations in the post-menopausal women.
Conclusions: Across a broad age range in men and in women, estimates of BTmin derived from a 90 min day protocol showed no associations with age, despite the predictable earlier bedtimes/wakeup times in the elderly. In women, reproductive status exercised a huge and unexpected effect on timing of BTmin. In pre-menopausal women studied under follicular phase, middle age was associated with the predictable phase advance in BTmin. In post-menopausal women, older age was associated with a phase delay and was independent of HRT. These results suggest interactions between reproductive status and estimates of BTmin derived from the 90-min day and may also imply important species differences, since, in rodents, estrogen has long been known to induce phase advances in the circadian system.

Supported by AG-10643

388.H

Normal Elderly Maintain Delta Conservation Across Naps and Post-Nap Sleep

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Introduction: Evidence that NREM delta intensity and amounts are proportional to prior waking duration provides the cornerstone of homeostatic sleep models. These models are further supported by the phenomenon of delta conservation: delta expressed in a daytime nap is subtracted from the delta in post-nap sleep to maintain an approximately constant 24-hour total. (Such conservation is notably absent for REM.) Thus far delta conservation studies have been limited to young adults. It is not known whether normal elderly, who manifest decreased levels of delta and spindles and increased awakenings retain delta conservation. We addressed this question by studying delta conservation for naps taken at 4 different times in young adult and normal elderly subjects (Ss).

Methods: Twenty healthy young adults (20-26 yrs) and 17 healthy elderly (65-80 yrs) subjects passed health, psychiatric, and two night sleep EEG screening. Recording blocks for each of 4 nap times (0900, 1200, 1500, 1800) consisted of a baseline night, a daytime nap (Ss in bed for 2 h, >25 min sleep required), and a post-nap night. Amplified and filtered EEG (C3, C4, O1) and EOG signals were digitized and analyzed with PassPlus (Delta Software, St. Louis) period amplitude and FFT routines. Using onscreen display of the digitized data, each 20-sec epoch was scored for vigilance states and artifacts. Delta conservation was evaluated by testing the prediction that NREM delta (0.3-3 HZ) integrated amplitude (IA) or FFT power summed across nap and post-nap sleep would equal total IA or power on the baseline night.

Results: The results presented here are preliminary as cycle and rate (e.g. IA/epoch) analyses have not been completed. In young adults, delta IA summed for the nap and post nap night (PNN) slightly exceeded delta IA on the baseline night (BN) particularly for the earlier naps (Fig 1). Baseline night delta IA in the elderly group was roughly half that of the young adults. However, the delta conservation in the elderly was equal to that of the young adults (Fig 2). FFT analysis (not shown) gave similar results. A further finding of interest is the delta growth curve as a function of prior wake duration. In young adults, delta IA (and FFT power) showed a simple linear increase. The curve for the elderly initially increased at 900 h, was flat across the 1200 and 1500 h naps, and increased further at 1800 h.

Conclusions: Our main finding thus far is that normal elderly, in spite of markedly reduced levels of delta, maintain delta conservation across naps and post-nap sleep as effectively as young adults do. Taken in association with the similar response of young and elderly Ss to sleep deprivation, these findings support the generality of the homeostatic model of NREM delta. Although the data must be considered preliminary since no statistical analyses have been conducted, the delta growth curves differ for young adults and elderly and differ from previously published observations of exponential or S-shaped growth.

This work was supported by RO1-MH50741.

389.H

Relationship Between Activity and Circadian Rhythms in Patients with Alzheimer’s Disease

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Introduction: Circadian rhythms are known to deteriorate in patients with Alzheimer’s Disease (AD), which may be due to a loss of neuronal tissue in the SCN. Weak circadian rhythmicity may also be related to a decrease in zeitgebers such as light exposure and regular social cues that would facilitate entrainment. Regular activity can also act as a zeitgeber. A subset of AD patients display agitated behavior in the form of continual pacing or wandering. It was hypothesized that the increased activity seen in this subgroup may serve to enhance their circadian rhythmicity compared to sedentary AD patients at comparable stages of dementia. The purpose of these analyses was to compare the circadian rhythms of these two groups of AD patients.

Methods: These data are part of a larger study of sleep and agitation in institutionalized patients with AD. Data were collected on 26 men and
Results: There were no statistically significant differences in circadian rhythm parameters between wanderers (n=39) and non-wanderers (n=33). The extended cosinor model provided a significant fit of the circadian rhythms of both groups. The degree of fit was better for the wanderers, although this difference was not significant (F=72.9 vs. 54.3).

Conclusions: There results did not support the hypothesis that AD patients with greater activity levels would have more robust circadian rhythms than those who were more sedentary. There was significant rhythmicity in activity for both groups but no difference between them. These findings suggest that there was not a clear deterioration in rhythms of activity for these patients, despite their suffering from severe dementia. These results may help to explain the results of studies that failed to find improvements in circadian rhythms following exercise interventions. In order to better understand the relationship between activity and circadian rhythms, future research should utilize strategies to reduce masking effects.

References:

Research supported by NIA AG02711, NIA AG08415, NHLBI HL44915, the Research Service of the VAMC, VA VISN22 MIRECC 390.H

Variation of Sleep Architecture with Sleep Disordered Breathing (SDB) in Very Old Japanese-American Men

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Introduction: Normative data about sleep architecture in the elderly have not been well characterized. We describe sleep architecture and its variation with sleep disordered breathing among survivors of the Honolulu Heart Program who participated in the Honolulu-Asia Aging Study (HAAS) of Sleep Anea.

Methods: Between Aug. 1999 and July 2000, sleep studies were performed on 718 Japanese-American men ranging from 79 to 97 years of age, a sample that represented approximately 50% of the survivors of the HAAS. Studies were conducted in the home using polysomnography (Compumedics PS-2, Abbotsville AU), consisting of measurement of C3/A2 and C4/A1 electroencephalograms, electrooculogram, airflow (by thermocouple), chest and abdominal excursion (by respiratory inductive plethysmography), chin electromyogram, heart rate, oximetry, body position, and ambient light. Analyses were restricted to 661 individuals whose sleep studies captured the entire sleep period and produced satisfactory EEG readings for sleep staging. Sleep staging, arousals, apneas, and hypopneas were scored using standardized criteria identical to the approach of the Sleep Heart Health Study (1). Apnea hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep, each event of ≥ 10 seconds duration associated with ≥ 4% desaturation.

Results: In this population, the average sleep time was 5.5 ± 1.3, SD hours. Sleep distribution showed 7.3 ± 6.1% time in Stage 1, 67.1 ± 10.3% in Stage 2, 9.5 ± 9.4% in Stage 3-4, and 16.1% ± 6.3 in REM sleep. Stage 3-4 was absent in 5.8% of subjects. Where sleep latency could be ascertained (n=420), the mean time to fall asleep was 26.4 ± 24.4 minutes and sleep efficiency was 68.6% ± 13.0. The median AHI was 10.7 events per hour (4.3-22.4 IQR), and 39.6% of subjects had an AHI ≥ 15. Average number of arousals per hour of sleep was 24.4 ± 11.6. Sleep architecture, arousal index, and sleep efficiency varied by level of AHI. For example, men with an AHI ≥ 30 (18% of the sample) spent an average of 14.0% of their sleep time in REM sleep and 5.7% of their sleep time in stage 3-4, while men with an AHI < 5 (30% of the sample) spent 16.6% of their time in REM sleep and 11.1% of their time in stage 3-4.

Conclusions: This community-based sample of elderly men demonstrated relatively poor sleep efficiency. We observed more stage 2 and less stage 3-4 and REM sleep in this cohort of very old men, compared to the sleep architecture data from another large, but somewhat younger cohort studied with the same methodology (Sleep Heart Health, age 63 years)(1). SDB was prevalent and sleep architecture, measured by sleep staging, sleep efficiency, and arousal index, all varied with level of AHI. These data suggest that inefficient sleep and decreased amounts of deep sleep are common in the oldest old, especially among individuals with sleep disordered breathing.

References:

Research supported by NIA contract number NO1-AG-4-2149 and NHLBI contract number NO1-HC-05102. 391.H

The Sleep and Mental Health of Older Wife Caregivers for Spouses With Dementia

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Introduction: Female spouse caregivers exhibit poorer mental health outcomes of caregiving than other types of family caregivers, such as daughters or husbands of the patient. Caregivers frequently report problems concerning stress and sleep, but knowledge regarding caregiver sleep is limited. This descriptive study: (a) compared the mental health and sleep of older wife caregivers for spouses with dementia with non caregiving wives; and (b) examined the relationship of selected caregiving variables and appraisal variables (reaction and burden) to the outcomes mental well-being and sleep. A stress and appraisal process model of caregiving guided this study.

Methods: A convenience sample of 37 wife caregivers of community-
drowning spouses diagnosed with dementia was compared with a control group of 37 non-caregiving wife subjects who were at least 60 years of age. The subjects were matched within five years. Data collection included: background data, the Patient Memory and Behavior Problems Checklist and Reaction Measure, the Caregiver’s Activity Time Survey, number of years caregiving, the Burden Interview, the Mental Health Index (subscales: anxiety, depression, positive affect and feeling of belonging), and the Daily Sleep Diary (Morin, 1993). The sleep diary was completed for seven consecutive mornings. The findings were analyzed using descriptive statistics, t-tests, ANOVA, correlations, multiple regression procedures and specifically hierarchical regression.

Results: In this sample of 37 wife caregivers and 37 noncaregiving wives, caregivers scored significantly more poorly on measures of mental health (t = 15.3, p < .001). Caregivers reported poorer sleep efficiency (F[1] = 28.60, p < .0001). All other sleep scores, such as total sleep time, sleep onset latency, number and duration of awakenings, medication intake as a sleep aid, sleep quality and feeling upon arising, except daily nap scores, were poorer for caregivers. Neither group and sleep efficiency, nor group and mental health behaved interactively, but rather in an additive manner. The caregiving and appraisal variables showed direct and indirect effects, with appraisal being the better predictor of mental health. In the prediction of sleep efficiency, direct and indirect effects were present. The reaction variable, and not burden, added the greater indirect explanation to the prediction of sleep efficiency.

Conclusions: The results of this study show that caregivers should be taught to assess their mental health and sleep needs. Counseling on the stressors of caregiving and on strategies of caregiving may facilitate their performance in this role. Also, knowledge of and use of healthful living strategies may enable the caregiver to reappraise these stressors as less threatening and therefore improve these outcomes of caregiving.

References:

Research supported by Mayo Clinic Alzheimer’s Disease Center (AG80331), University of Nebraska-Medical Center, Minneapolis Veterans Affairs Medical Center.

392.H

Effect of Menstrual Status and Vasomotor Symptoms on Self-reported Sleep Complaints and Depression

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Introduction: Sleep complaints are reported to increase among peri- and post-menopausal women. One hypothesis is that the reduction in sex hormones during peri-menopause leads to vasomotor symptoms (hot flashes), which cause insomnia, poor sleep maintenance, and restless sleep. Previous studies have not tested the influence of symptoms independent from other changes associated with menopause. Furthermore, aging and menopause do not occur independently, and there have been few attempts to investigate these factors separately. To determine whether the menopausal transition and vasomotor symptom severity are independently associated with increased self-reported sleep disturbances, we analyzed data from women at risk for menopause enrolled in the Women’s Sleep Study (WSS), a subset of an on-going prospective study (Sleep Cohort Study). Participants fill out monthly diaries on menstruation, medications (including OC’s, HRT, and sleep aids), menstrual cycle changes, feelings of depression and record daily the occurrence of hot flashes (day and night), and sleep complaints. Using this information, we explored the independent associations of hot flashes, menstrual status along with HRT use, and age with sleep complaints of difficulty getting to sleep, difficulty maintaining sleep, restless sleep, and feelings of depression.

Methods: Participants included 184 women aged 35.7 to 62 years (mean = 50.3 years) with 1403 diaries. Participants’ menstrual status at the time of diary completion was classified as: regular cycles without HRT (N = 598), HRT use (N = 372), and irregular or no cycles without HRT (N = 433). We analyzed data from 1-11 monthly diaries for each woman spanning up to 4 years. Risk factors for sleep complaints and depression such as age, menstrual status, and hot flashes were modeled using multiple linear regression with appropriate techniques to adjust for correlation within women (Proc Mixed, SAS Institute). Hot flashes were recorded as either occurring during the daytime or nighttime. Analysis showed that reported daytime hot flashes were not strong significant predictors alone and not significant at all when in combination with nighttime hot flashes.

Results: The results (Table 1) show that nighttime hot flashes are related to sleep complaints. Women who report > 10 nighttime hot flashes/month have on average 5 more nights of restless sleep and 4 more nights of difficulty maintaining sleep and 1 more night of difficulty initiating sleep, than women reporting no nighttime hot flashes. Having < 10 nighttime hot flashes is not strongly related to sleep complaints. At most only a slight relationship between age and these sleep complaints exists. HRT users had a mildly elevated frequency of restless sleep compared to women who reported regular periods. Reported nighttime hot flashes had no significant effect on reported feelings of depression.

Table 1

<table>
<thead>
<tr>
<th>Linear regression relating age, menstrual status, and nighttime hot flashes to number of sleep complaints per month</th>
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</thead>
<tbody>
<tr>
<td>Model Terms</td>
</tr>
<tr>
<td>Restless Sleep</td>
</tr>
<tr>
<td>Age, 5 yr</td>
</tr>
<tr>
<td>Menstrual Status (vs. regular periods)</td>
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*p < 0.05 *p < 0.10

Conclusions: Our findings support the hypothesis that nighttime hot flashes lead to increased frequency of sleep problems during menopause, independent from other aspects of menopause and aging.

Supported by NIH and NIA grants R01HL62252, RR03186, and R01AG14124

393.H

Alterations in the Homeostatic Mechanisms of Sleep in β-amyloid Precursor Protein Transgenic Mice

Huitron-Resendiz S, Sanchez-Alavez M, Criado J, Gutierrez T, Stobbs SB, Carr J, Gallegos R, Wills D, Games D Henriksen SJ

Introduction: Alzheimer’s Disease (AD) is the most prevalent form of age-related neurodegenerative disorder. Similar neuropathology to that seen in human AD brain has been observed in the PDAPP mice that overexpress a mutant human amyloid precursor protein (Games et al., 1995). In previous studies we have reported alterations in the sleep/wake...
cycle and circadian rhythmicity of PDAPP transgenic mice (Huitron-Resendiz et al., 2000). However, the homeostatic regulation of sleep in this animal model of AD remains unknown. To determine whether the overexpression of APP affects the homeostatic regulation of sleep, we compared sleep in PDAPP transgenic mice and their nontransgenic littermates under baseline conditions and recovery from 24 h of sleep deprivation.

Methods: Female PDAPP transgenic mice and nontransgenic littermates (5-7 and 20-24 month old) were anesthetized with 1.0 % halothane and implanted for chronic sleep recordings. One week after surgery, mice were habituated to the recording conditions for 96 h. Once the habituation period was completed, animals were recorded during 24 h without disruptions (control recordings) and hand-deprived during 24 h beginning in the light onset. After sleep deprivation mice were recorded during 24 h. Sleep recordings were visually scored and three stages were determined: wakefulness (W), slow-wave sleep (SWS), and rapid eye movement (REM) sleep. Results were analyzed using one way ANOVA. During the experiment mice were housed individually, with ad libitum access to food and water and maintained on a normal 12-h light cycle (on 06:00 h, off 18:00 h).

Results: No difference was found in the effect of sleep deprivation on the vigilance states between the young transgenic mice and their nontransgenic littermates. After sleep deprivation both groups of young mice showed a significant increase in SWS and REM sleep during the first 3 h and 6 h, respectively (p ≤ 0.01). In contrast, aged PDAPP transgenic mice showed a significant reduction of SWS 3 h after sleep deprivation and a significant increase of SWS 15 h after sleep deprivation (p ≤ 0.01). On the other hand, REM sleep was significantly increased 12 h after deprivation (p ≤ 0.01).

Conclusions: The homeostasis of sleep is manifest for the propensity for sleep after a longer wake periods (Borbely, 1982). Our results show that this propensity for sleep is altered in aged PDAPP transgenic mice and that the sleep pressure is delayed in those mice, indicating that the homeostatic mechanisms of sleep in the aged transgenic mice are disrupted.

References:

394.1H
Ethnic Differences in Self-Reported Sleep Problems in Older Adults

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Introduction: While advances in the medical sciences have remarkably increased human lifespan, sleep disturbance among older adults remains a significant problem. According to the 2000 Omnibus Sleep in America Poll 64% of adults 365 years old reported symptoms of insomnia a few nights a week. Whereas ample evidence demonstrates the relationships of physical health and depression to sleep problems in the elderly, little has been done to investigate racial or ethnic influences on sleep patterns. This study explored ethnic differences in reported sleep complaints using data of a population-based study of older adults living in Brooklyn (New York).

Methods: Volunteers (62% female) were urban community-residing European-Americans (EA) and African-Americans (AA) recruited with a stratified, cluster sampling technique. Trained interviewers of the same race as the respondents gathered data during face-to-face interviews conducted either in the respondent’s home or another location of their choice; interviews lasted approximately 1.5 hours. A total of 1118 respondents (ages: 65-86 years, mean = 74 ± 6; BMI: mean = 28 ± 10) provided valid data and received $20 for their participation. In a standard order, several scales/questionnaires were administered. Measures for the present analysis included demographic and health risk factors: age, sex, ethnicity, education, income, weight, height, smoking status, and alcohol consumption. Physical health was measured with the Comprehensive Assessment and Referral Evaluation; five sub-scales were included: heart disease, respiratory disease, arthritis, sleep disorder, and hypertension (Cronbach alpha = 0.89; 0.64; 0.86; 0.92; and 0.91, respectively). Social support was assessed with the Network Analysis Profile (α = 0.89). Emotional experience was assessed with a trait version of the Differential Emotions Scale, version III; two sub-scales were examined: sadness and fear (α = 0.85; and 0.85, respectively).

Results: A stepwise multiple linear regression analysis was performed with a severity index of sleep disturbance, based on the five sleep questions, as the criterion and demographic and health-related factors as explanatory variables. As shown in Table 1, EA ethnicity was the most significant predictor of sleep disturbance (F(1, 1094) = 82.40, p < 0.001). Ethnic differences in reported sleep complaints are reported in Table 2, using Chi Square test. Compared to African-Americans, a greater proportion of European-Americans reported respiratory problems (64% vs. 32%), heart diseases (69% vs. 53%), and arthritis (83% vs. 67%); equal proportions reported hypertension (54% vs. 53%). EA indicated greater sadness and stress than did AA respondents (Md. = 8 vs. Md. = 5; Md. = 8 vs. Md. = 5, respectively).

Table 1

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>European-American Ethnicity</td>
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<td>Sadness</td>
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<td>Arthritis</td>
<td>.24</td>
<td>5.30*</td>
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<tr>
<td>Heart Disease</td>
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<td>4.94*</td>
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<tr>
<td>Respiratory Disease</td>
<td>.12</td>
<td>2.97*</td>
</tr>
<tr>
<td>Stress</td>
<td>.11</td>
<td>2.67*</td>
</tr>
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(*p < 0.01)

Table 2

<table>
<thead>
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<th>EA (40%)</th>
<th>χ²</th>
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<tr>
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<td>41</td>
<td>98*</td>
</tr>
<tr>
<td>Maintain Sleep</td>
<td>37</td>
<td>75</td>
<td>162*</td>
</tr>
<tr>
<td>Wake Up Early</td>
<td>17</td>
<td>46</td>
<td>116*</td>
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<tr>
<td>Daytime Sleep</td>
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<td>0.07</td>
</tr>
<tr>
<td>Sleep Medicine</td>
<td>3</td>
<td>17</td>
<td>72*</td>
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</tbody>
</table>

(*p < 0.01)

Conclusions: Ethnicity was the most significant predictor of reported difficulty sleeping in our sample. Consistent with population-based study of sleep complaints, African-Americans reported less sleep complaints than did European-Americans. We note that difficulty sleeping among AA was similar to previous observations using both AA and EA elders, but EA reported substantially more complaints than AA and EA in previous studies. That AA reported better sleep could be explained in
part by less self-perceived health problems. However, based on epidemiologic and vital statistics data, showing worse health outcomes for AA, one would have expected to find greater sleep complaints among AA elders. It is important to determine whether AA, reporting less sleep complaints, are in fact characterized by relatively greater positive reappraisal than EA. According to appraisal and coping theories, older AA might have developed effective strategies to deal with hardships due to poverty, racism, segregation, and other life stresses. These, over time, would have fostered effective reframing of difficult life experiences that could not be easily changed. Conceivably, the same processes might provide a positive context for accepting sleep-related difficulties as part of the aging process. There is a body of research showing that some self-described normal sleepers may endure significant sleeping difficulty with no corresponding reports of sleep complaints. Understanding of ethnic and cultural differences between AA and EA may be critical in interpreting subjective health-related data.

References:

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395.H

Impact of Gender and Estrogen Replacement Therapy on Sleep Quality and Sleep-related Hormone Secretion in Older Adults

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Introduction: Aging is associated with alterations of sleep and hormonal profiles. Slow wave activity (SWA) is relatively better preserved in women than in men and estrogen replacement therapy (ERT) may have beneficial effects on sleep in women. Whether gender differences in sleep are associated with differences in sleep-dependent hormones is not known. The present study examines the impact of gender and ERT on sleep and secretory profiles of growth hormone (GH) and prolactin (PRL) in the older population.

Methods: Three groups of healthy non-obese subjects were studied: 11 men (59 ± 2 years, mean ± SEM), 7 women on ERT (60 ± 3 years), and 9 women not on ERT (65 ± 2 years). Following one night of habituation, subjects spent 2.5 days in the Clinical Research Center. Sleep was recorded and a spectral analysis of the EEG performed in the delta band (0.5-4.0 Hz). Blood samples were collected during a 24-h period. The Stanford Sleepiness Score and Visual Analog Scales for vigor and affect were administered hourly. Subjects completed the Pittsburgh Sleep Quality Questionnaire.

Results: Subjective quality of sleep was not significantly different among the groups. There were no differences in daytime sleepiness, global vigor and global affect. There was no significant impact of ERT on any of the sleep parameters, and therefore data from both ERT and non-ERT women were pooled. Men had shorter total sleep durations than women (363 ± 15 min vs. 400 ± 8 min, p<0.05). They had also more shallow and fragmented sleep as evidenced by higher percentages of wake and stage 1 (p<0.05). There was no gender difference in SW sleep. Over the first 6 hours of sleep, men had less total delta activity than women (21265 µV² vs. 40638 µV², p<0.05). In women, total delta activity over the first 6 hours of sleep was not affected by ERT. However, a “normal” temporal pattern of SWA (highest SWA in the first sleep cycle, followed by progressive decline across subsequent cycles) was apparent in ERT women, but not in untreated women. Men had lower mean levels of PRL during sleep (10.0 ± 0.8 ng/ml, women on ERT 18.6 ± 2.8 ng/ml, women not on ERT 15.0 ± 1.1 ng/ml, p<0.002) but differences in mean levels during wake failed to reach significance. Daytime GH secretion did not differ significantly across the 3 groups of subjects. In contrast, GH secretion during sleep was lower in women not on ERT than in women on ERT (52 ± 11 µg vs. 176 ± 36 µg, p<0.01). Men had values that were higher than those in non-ERT women (131 ± 26 µg; p<0.01) and slightly, but not significantly, lower than those in ERT women.

Conclusions: There are marked gender differences in sleep quality in older adults, with men having more shallow sleep and lower SWA than women. Gender differences in secretion of GH and PRL are clearly apparent during sleep, but not during wake. ERT appears to normalize the temporal pattern of SWA in women and to be associated with increased GH and PRL secretion during sleep.

Research supported by grant DK-41814 and AG-11412 from the National Institutes of Health and by the MacArthur Foundation. The University of Chicago Clinical Research Center is supported by NIH grant RR00055.

396.H

Relationship Between Sleep Complaints and Reported Visual Impairment in The Elderly.

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Introduction: Visual impairment increases with age and is associated with a reduction in quality of life. Research has shown that several disorders contribute to the report of visual impairment among older adults. They include macular degeneration, cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy. It has been documented that blind individuals experience difficulty sleeping, which may be linked to a desynchronized circadian clock. However, little is known about how much visual impairment (with persisting light perception) might contribute to sleep disturbance in older adults. This study examined the relationship between sleep complaints and reported visual impairment among urban community-residing elderly.

Methods: A total of 1118 volunteers from a biracial cohort participated in the study (mean age = 74 ± 6; mean BMI = 28 ± 10). Sixty percent were African-Americans and 40% were European Americans; 62% were women. Volunteers were recruited using a stratified, cluster sampling technique and those that provided valid data were paid $20 for their participation. Trained interviewers gathered data during face-to-face interviews conducted either in the volunteers’ homes or another location of their choice. In a standard order, several questionnaires were administered, soliciting information on socioeconomic status, physical health, social support, and emotional experience. The physical health questionnaire included questions on whether or not the volunteer experienced sleep disorder, visual impairment, heart disease, respiratory disease, arthritis, and hypertension. In this report, we present data on the prevalence of reported sleep problems and visual impairment among older
adults.

**Results:** Of the total sample, 9% used sleep medicine, 25% reported difficulty falling asleep, 52% indicated experiencing difficulty maintaining sleep, 28% reported waking up early in the morning, and 12% reported daytime sleep greater than 2 hours. Responses to sleep questions on the basis of whether individuals reported visual impairment are compared in the table, showing greater sleep complaints for volunteers with visual impairment. Using ANOVA, volunteers were further compared using a severity index for sleep difficulty based on the five sleep questions. This analysis showed that visually impaired volunteers had a greater index of sleep disturbance \( F(1, 1110) = 35.32, p < 0.0001 \).

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>YES (45%)</th>
<th>No (55%)</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Medicine</td>
<td>13</td>
<td>5</td>
<td>23**</td>
</tr>
<tr>
<td>Fall Asleep</td>
<td>35</td>
<td>17</td>
<td>48**</td>
</tr>
<tr>
<td>Maintain Sleep</td>
<td>61</td>
<td>45</td>
<td>30**</td>
</tr>
<tr>
<td>Wake Up Early</td>
<td>39</td>
<td>20</td>
<td>45**</td>
</tr>
<tr>
<td>Daytime Sleep</td>
<td>14</td>
<td>10</td>
<td>5*</td>
</tr>
</tbody>
</table>

Table: (*p < 0.05, **p < 0.01)

**Conclusions:** Although the ethnic composition of our sample is different from the one used previously by Asplund (2000), results of both studies are consistent regarding the direct association between sleep problems and visual impairment. We note, however, that a higher proportion of elders in our study reported visual impairment. This may in part be explained by the fact that 60% of our volunteers were African-Americans. Evidence has suggested a higher prevalence of eye problems in older minority individuals compared to European Americans. Causal inferences cannot be drawn from our results, but they support the notion that visual impairment limits outdoor activities, which would provide an opportunity for bright light exposure. It has been found that healthy older adults spend only 1 hr daily in outdoor daylight receiving up to 2000 lux. Adequate exposure to the light-dark cycle is crucial in maintaining synchronization of the suprachiasmatic nuclei. We might also surmise that reduction of daytime activity itself might contribute to the disregulation of the sleep-wake pattern, leaving even more uncertain the direct effect of visual impairment on sleep. These data evidence that visual impairment has an effect on the sleep of the elderly, but causal links will have to be established by systematic, controlled studies.

**References:**

**Funding from NIGMS and NIA (SO6 GM54650) supported this work.**

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**397.H**

**A Comparison of the Epworth Sleepiness Scale and the Functional Outcomes of Sleepiness Questionnaire in the Assessment of Excessive Daytime Sleepiness in the Elderly**

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University of Pennsylvania

**Introduction:** Excessive daytime sleepiness (EDS) is a common complaint among the elderly. It can be assessed using the eight item Epworth Sleepiness Scale (ESS) which measures degree of sleepiness experienced during various activities [1]. Another useful type of assessment is a functional one, such as the Functional Outcomes of Sleepiness Questionnaire (FOSQ). It is a 30 item scale that measures how sleepiness affects a subject’s daily ability to function in five dimensions: general productivity, vigilance, social activity, activity level, and intimacy/sexual [2]. Correspondingly, these two tools measure distinct but related concepts as they were developed on different conceptual frameworks. In order to better understand the relationship of the ESS and FOSQ on a conceptual level, we have concurrently administered them to elderly subjects and compared the results.

**Methods:** A total of 184 elderly subjects, age>65, completed the protocol (72% female, 86% Caucasian). Subjects were recruited from the community-dwelling elderly and from those living in retirement communities. They were initially recruited as part of a larger study of EDS in the elderly. They were contacted by phone and then sent a packet containing the ESS, FOSQ and other survey tools.

**Results:** The response rate was high for both the ESS and FOSQ scales: 91.0% and 89.7% respectively. However, the FOSQ subscale for Intimacy/Sexual activity was completed by only 30.4% of subjects. This may be attributed to the fact that many of the elders did not engage in sexual activity or were reluctant to answer these questions. Since this leads to a strong potential for bias, the Intimacy/Sexual subscale has been omitted from the calculation of the FOSQ Global score. With this correction, the overall correlation of the ESS and the FOSQ Global score was \( r = 0.57, (p < 0.001) \). The correlation is negative because ESS values increase as one has more EDS, but with the FOSQ, the values decrease as one is less functional. The correlation [3] of the ESS with the various subscales of the FOSQ are listed below in table 1.

<table>
<thead>
<tr>
<th>Subscale</th>
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<tr>
<td>General Productivity</td>
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<td>Vigilance</td>
<td>-0.62</td>
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<td>Social Outcomes</td>
<td>-0.31</td>
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<td>Activity Level</td>
<td>-0.46</td>
<td>&lt;0.001</td>
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<td>Intimacy/Sexual</td>
<td>-0.26</td>
<td>0.057</td>
</tr>
</tbody>
</table>

**Conclusions:** The above data show that the ESS and the FOSQ have a moderate correlation with each other in elderly subjects (correlation coefficient absolute value of \( r = 0.57 \)). This is expected as the ESS looks at the symptom of EDS and the FOSQ assesses the outcomes/impact of that symptom on daily activities. However, the correlation of the ESS and the specific subscales of the FOSQ vary. This suggests that the ESS, with its conceptual focus on sleepiness, measures certain aspects of EDS in the elderly more completely than other functional aspects, such as social outcomes. There is a higher correlation between the ESS and the FOSQ Vigilance subscale because similar types of activities are assessed. These findings support the convergent validity of the FOSQ as...
an outcome measure of EDS because the FOSQ relates to the ESS as expected based on their conceptual frameworks. The use of an outcome scale such as the FOSQ contributes to our understanding of the functional effects of EDS and can complement the use of other tools such as the ESS.

References:

Research supported by HL-50051, AG-03934 and HL-60287

398.H

Slow Wave Activity In The Antero-Posterior Axis In Young And Middle-Aged Subjects

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Introduction: The most consistent age-related sleep modification during the middle years of life is a decrease in slow-wave sleep (SWS) and in slow-wave activity (SWA: spectral power between 0.75 to 4.5 Hz during N-REM sleep). We have shown recently that compared to the young, middle-aged subjects show a reduced rebound of slow-wave activity (SWA: spectral power between 0.5 Hz and 4.5 Hz in N-REM sleep) following an acute sleep deprivation, suggesting an attenuation of homeostatic drive during the middle years of life (1). It has been reported that the effects of a 40-hour sleep deprivation on spectral power density in SWA range varies along the antero-posterior axis, predominantly in frontal regions of the brain (2). The aim of this study was to evaluate age-related modifications in SWA along the antero-posterior axis during baseline sleep. We hypothesised that the difference in SWA between young and middle-aged subjects would thus be predominant in the anterior derivation of the brain.

Methods: Thirty-two subjects (Young: 25-39 y, 8W, 8M and Middle age: 40-60 y, 3 pre-menopausal W, 6 post-menopausal W, 7M) came to the sleep laboratory for three consecutive nights. The third night was used in the present analyses. Bedtime and wake time for the laboratory sleep study were based on two-week sleep diaries. EEG power Spectra from F3-C3, C3-P3 and P3-O1 bipolar derivations were computed (FFT, 4s epochs; frequency resolution 0.25 Hz). SWA was averaged for the first four N-REM periods. A three-way factorial ANOVAs with one group factor (age) and two repeated factors (derivation and N-REM period) was used to analyse SWA. P-level (alpha) was adjusted with Huynh-Feldt correction. Contrast analyses were used to decompose the interaction effects.

Results: Compared to the young, middle-aged subjects showed less SWS (Young: 32.41 min; Middle-aged: 12.49 min; p=0.006). Analysis of SWA revealed significant interactions between N-REM period and derivation (p<0.001) and between N-REM period and age group (p<0.05). Contrast analysis of the interaction between age group and N-REM period revealed that compared to the young, middle-aged subjects showed lower SWA in the first two cycles (N-REM 1: p=0.037, N-REM 2: p=0.023) but no significant difference in the last two cycles (see Figure 1). Contrast analysis of the interaction between derivation and N-REM period showed more SWA in F3-C3 than in the other derivations, however this difference is more pronounced at the beginning of the night (N-REM 1-3, p<0.000372) than at the end of the night (N-REM 4, p=0.013) (see Figure 2).

Conclusions: The present results corroborate previous observations which showed that middle-aged subjects have less SWA than the young. This age-related difference diminished across the sleep period, leading to a shallower decay rate of SWA throughout the night in the middle-aged subjects. The results also support the notion that SWA is more prominent in the anterior derivation compared to posterior derivations, especially at the beginning of the night (3). However, the difference in SWA between young and middle-aged subjects is constant across the antero-posterior axis. Further analyses on the effects of sleep deprivation in young and middle-aged subjects will allow us to determine if there are topographical differences between the groups when the homeostatic process is challenged.

References:
(2) Cajoochen C, Foy R, Dijk D: Frontal predominance of relative increase in sleep delta and theta EEG activity after sleep loss in humans. Sleep research online 1999; 3(2); 65-69

Research supported by Conseil de recherches médicales du Canada, No : Mt-14999
Circadian Changes in Hydration in Elders with OSA

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Introduction: Among seniors, obstructive sleep apnea (OSA) affects 24% in the community, 33% in acute care and 42% in nursing homes. OSA has been associated with significant derangements in fluid excretion, e.g., nocturnal polyuria (natriuresis and diuresis) that result in incontinence, enuresis and nocturia.1,2 Sleep practitioners have noted that lower extremity edema (LEE), a manifestation of altered fluid metabolism, is a frequent finding among individuals with OSA.3 Further, LEE is also common among older adults and is directly associated with chronic non-healing leg ulcers. However, like nocturia, LEE is often dismissed as age-related and considered virtually intractable despite being associated with significant and costly sequelae. The purpose of this analysis was to examine the nature of circadian intracellular-extracellular fluid shifts in older adults with and without OSA.

Methods: A sample of community-dwelling elders (n=30) was recruited based on self-reported sleep apnea symptoms and nocturia (≥2/night) as part of a multi-phase study. Both men and women (female=17; male=13) and minority subjects (African-Americans, n=18; Caucasian, n=11) participated and the mean age was 65.5 (SD 8.38; range 51-91). Subjects underwent 24-hours observation including polysomnography. Strict intake and output procedures were followed and measures of body water composition were taken using bioimpedance. Data were collected at 4-hour intervals except overnight (8 hours).

Results: Two thirds of the sample (n=19) was found to have OSA (AHI ≥ 5). Subjects with OSA were younger but had a higher BMI (mean age 64.11, mean BMI 33.5) than individuals without OSA (mean age 67.64, mean BMI 28.98). As expected, no differences were found between the ratio of extra/intracellular water between groups due to normal intra and extracellular compartment equilibration. However, subjects with OSA had greater total body water volumes (Figure 1), and extracellular - intracellular water volumes (p<.000). Controlling for BMI, these significant differences persisted across all time intervals (Figure 2).

Figure 1

Figure 2

Conclusions: These findings suggest that persons with OSA may experience systemic derangements of fluid metabolism and excretion—not just the inconvenience of nocturia or enuresis from OSA-related polyuria. These bioimpedance measures demonstrate not only the increased fluid in the interstitial spaces of the body (edema), but also elevated levels of intracellular fluid. Further study is needed regarding the effect of OSA on fluid metabolism and the impact of OSA treatment on LEE.

References:
(2) Umlauf MG, Kurtzner E, Valapail T, Burgio KL, Pillion D, Goode P. Sleep-disordered breathing as a mechanism for nocturia: Preliminary findings. Ostomy/Wound Manage 1999;45(12):52-60.

Sleep Disturbances in the Elderly: A Population Study of the Subjects over 85 Years Old

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Introduction: Sleep in elderly people shows progressive changes, because of the general aging processes. Quantitative and qualitative sleep alterations, changes of sleep/wake rhythm, modifications in duration and disruption in sleep architecture are described in the medical literature.

Methods: We studied all the 84 subjects over 85 y.o. (56 F. and 28 M., range 85-99) in a randomised group of 1000 persons over 65 y.o., stratified for sex and age, living in the Udine city area. All patients underwent a Mini Mental State Examination (MMSE) and a sleep questionnaire, particularly concerning excessive daytime sleepiness. A statistical analysis was performed: we studied sleep disorders in healthy subjects (MMSE > 24) and in patients with cognitive impairment (MMSE < 24). We treated the MMSE score as an independent variable (normal distribution of our population with the Lillieforce test).

Results: Sleep disturbances are more frequent in old-old people, and even more in old-old patients with cognitive dysfunctions. Data showed a statistically significant greater prevalence of excessive daytime sleepiness, enuresis and falling from the bed among deteriorated patients.
Conclusions: The questionnaire results revealed significant differences in sleep disorders between elderly people with and those without cognitive impairment. So this form of subjective evaluation seems to be a useful method for performing an assessment of sleep disturbances in elderly people. The prevalence of sleep disturbances in the other age groups of epidemiological sample should help to obtain normative data in different ages.

References:

Effects In Rats Of Neonatal Instrumental REM Sleep Deprivation On Adult Behavior: Depression And Mania?
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Sleep Lab, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta

Introduction: It has been reported that neonatal treatment with REM sleep (RS) suppressants produces adult depressive behavior including diminished sexual activity, decreased aggressive behavior, reduced pleasure seeking, increased locomotion and increased RS in rats. Our laboratory has systemically studied the effect of clomipramine (CLI) neonatal treatment and the findings suggest the hypothesis that RS deprivation (RSD) mediates the depressogenic behaviors of neonatally administered antidepressant drugs (1). RSD by drugs is always confounded by the other, unavoidable effects of the drugs. Therefore, we performed the following experiments with instrumental RSD (IRSD) method (2)

Methods: Five treatment groups were tested: IRSD (n=19), yoked control (YC, n=20), non-shaken and maternal-separated control (MS, n=7), CLI (n=21) and saline (SAL, n=20). At postnatal day 13 (P13), IRSD and YC rats had electrode implantation by SH method, and MS rats had only fake surgery (2). All treatments were started at P14 lasted for 7 days. For details of the methods IRSD, please see reference 3. CLI rats were injected with 20 mg/kg CLI sc. twice a day and SAL rats were injected with equivalence saline. Adult behavioral measurements, including sexual activity (6 variables, 3 tests), auto activity testing (3 tests), open field (3 tests) and sleep recording (2 days) were done consequently. After sleep recording, shock induced fighting was also tested (3 times).

Results: Four major findings were as follows: (1) Compared with YC rats, IRSD rats demonstrated diminished sexual and aggressive behavior and increased REM sleep percentage. IRSD rats had a decreased number of mounts and an increased mount latency in sexual testing, and decreased offensive and increased defensive behavior in shock induced fighting tests. IRSD rats had 17.89% more REM sleep than YC rats. (2) Sexual activity of both, IRSD and YC rats, was significantly higher than that of either MS or SAL rats. IRSD rats also had significant higher offensive behavior than SAL and CLI rats. (3) Only slight depressive signs were found in CLI rats compared with SAL rats. In sexual tests, mount latency was the only variable where CLI rats had a significant difference compared with SAL rats. Among all other behavioral tests including sleep recording, auto activity testing was the only test that produced a significant difference between CLI and SAL rats. (4) Locomotor activity of all treatment groups was measured by both auto activity testing and open field testing. Of the five groups studied, locomotor activity levels of IRSD, YC, MS and CLI was greater than that seen in SAL.

Figure 1

![Figure 1](image1)

Figure 2

![Figure 2](image2)

Conclusions: (1) Results of neonatal IRSD are consistent with previous findings in rats neonatally treated with CLI. This supports the hypothesis that RSD is the mediator of adult depressive behavior. (2) Shaking, a nonspecific stimulant occurring during the neonatal period, may contribute to the signs of manic behavior seen in IRSD and YC rats.

References:

This work was supported by NIMH grants MH 40880 and MH57904.

402.I

The Corticosterone Response of Paradoxical Sleep Deprived Animals to a Mild Stressor
Suchecki D, Tufik S
Department of Department of Psychobiology - UNIFESP

Introduction: We have recently proposed a technique to induce paradoxical sleep (PS) deprivation, the modified multiple platform method (MMPM), where animals are deprived as a socially stable group or
placed on a grid (as an environmental control), which results in augmented corticosterone (CORT) levels immediately after the deprivation period (1). This study sought to examine the time-course of corticosterone (CORT) response to a mild stressor in animals PS deprived by the Single Platform Method (2) (SPM) or the MMPM.

Methods: Wistar male rats were distributed in 5 groups: Single Platform Method (SPM): One animal placed on a single narrow platform (7.0 cm), immersed in water up to 1 cm of the platform’s surface; Control for the Single Platform Method (CSPM): One animal placed in a recipient containing one narrow platform and sawdust bedding; Modified Multiple Platform Method (MMPM): 10 animals placed onto 14 narrow platforms, in a tank containing water up to 1 cm of the platform’s surface; Grid (GR): 10 animals placed onto a grid inside the water tank; Cage-control (CTL): 10 animals remained in their home-cages. PS deprivation lasted 96 h, where rat chow and tap water were provided throughout the study, and recipients were cleaned daily. Experimental proceedings: In each condition, animals were sacrificed immediately after the end of the deprivation period for determination of basal levels. The remaining rats were injected with 0.9% saline and placed in a new cage (SAL+NOV) for 5, 20 or 60 min and then sacrificed. Statistical analysis: Two-way ANOVA, with Group (CTL, SPM, CSPM, MMPM, GR) and Time (0, 5, 20, 60 min) as main factors, followed by the Duncan Multiple Range Test (p < 0.05).

Results: There was a significant interaction between Group and Time (F(3,107) = 4.077; p < 0.0004). The Time effect showed that: CTL = [5=20 min]>[10=60 min]; CSPM = [5=20 min]>60 min; SPM = [0=5 min]>[20=60 min]; GR = 5 min>[0=60 min]; MMPM = 5 min>all time-points. The Group effects showed that: 0 min = SPM > CTL; 5 min = no difference among the groups; 20 min = [CTL=CSPM]>[SPM=MMPM] and GR>MMPM; 60 min = no difference among the groups.

Figure 1

Conclusions: CORT elevation occurred 5 min after the stimulus for all groups, and was maintained in control animals (up to 20 min), whereas PS deprived groups showed a return to basal levels already at 20 min. The suppression of CORT release, frequently observed during sleep, may be explained by the fact that sleep deprived animals were already sleeping at the 20 min time-point. It appears as though sleep deprived animals show a well-preserved regulation of the adrenocortical response to stress.

References:

Financial support: Associação Fundo de Incentivo à Psicofarmacologia (AFIP)
The importance of this phase of sleep, to relation of SWS, deprivation, occurred an initial rebound of PS, that indicate the Our results also show that after total or partial PS deprivation or partial appropriate, in respect to sleep parameters observed at the present study. Although no exclusively. The control methods utilized appear to be not deprivation period. Both techniques were efficient to suppress PS, and SP techniques in relation to paradoxical sleep deprivation, during the Conclusions

Figure 1

![SLOW WAVES SLEEP TIME](image)

**Figure 1**

**SLOW WAVES SLEEP TIME**

<table>
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**Figure 2**

![PARADOXICAL SLEEP TIME](image)

**Figure 2**

**PARADOXICAL SLEEP TIME**

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</table>

Conclusions: We conclude that there are no differences between MMP and SP techniques in relation to paradoxical sleep deprivation, during the deprivation period. Both techniques were efficient to suppress PS, although no exclusively. The control methods utilized appear to be not appropriate, in respect to sleep parameters observed at the present study. Our results also show that after total or partial PS deprivation or partial SWS deprivation, occurred an initial rebound of PS, that indicate the importance of this phase of sleep, to relation of SWS, in the homeostatic process.

References:


405.I

Paradoxical Sleep Deprivation Reduces Plasma Homocysteine Levels in Rats

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Introduction: Homocysteine is an intermediate amino acid in the methionine-cysteine metabolic pathway, as it represents a branching point in which it can be remethylated to methionine or converted to cysteine. The importance of this metabolic pathway relates to its great number of physiological functions, such as providing the methyl donor (5-Adenosyl-methionine) for virtually all methylation reactions in the organism(1) and the limiting substrate (cysteine) to the synthesis of glutathione(2). Hyperhomocysteinemia has been associated with a growing number of pathological and stressful conditions. As sleep deprivation (SD) is associated with disruption of many physiological processes we hypothesized that it would also be associated with increases in total plasma homocysteine (tHcy) levels. Further, since we had previously found evidence of oxidative stress in brain following SD, we also searched for evidence of systemic oxidative stress by measuring total glutathione (tGSH) and thiobarbituric-acid reactive substances (TBARS) levels in plasma.

Methods: Thirty-eight male Wistar rats were sleep deprived for 96 hours using the classic platform technique. Ten animals were killed just after this period and another 18 sleep-deprived animals were allowed to undergo sleep rebound (SR) for 24 or 48 hours. Ten home cage animals composed the control group. All animals were killed by decapitation and blood was collected for biochemical analysis. tHcy levels were determined by HPLC, tGSH and TBARS levels were determined by colorimetric detection.

Results: Contrary to expectation, tHcy levels were reduced by SD (4.38 ± 0.67 mM) as compared to the control group (6.86 ± 1.03 mM) and did not recover to normal levels after 24 (4.96 ± 0.84 mM) or 48 (4.87 ± 0.57 mM) hours of SR. We observed a tendency towards decreased tGSH levels and increased TBARS levels in SD rats as compared to controls.

Conclusions: The decrease in tHcy can be theoretically explained by the catabolic state related to sleep deprivation or by consumption in response to a higher demand for cysteine in order to maintain GSH status. As we observed a significantly higher TBARS/tGSH rate in SD rats, we believe sleep deprivation is associated to systemic oxidative stress, representing a situation of higher requirement for GSH and, consequently, for cysteine. In our case, the preferential use of homocysteine for cysteine synthesis may be biochemically explained by inactivation of both methionine synthase and S-adenosylmethionine synthetase and activation of cystathionine synthase by oxidation. The absence of significant differences in tGSH levels in the four groups studied may represent this metabolic effort to maintain tGSH levels and could also explain the occurrence of just a tendency to increase on TBARS levels on SD rats. If this is the case, it is still necessary to establish why tHcy levels remain
decreased yet after 48 hours of sleep rebound and which different mechanisms causes increases on homocysteine levels in other stressful conditions.

References:

Supported in part by funds from CNPq / PIBIC, FAPESP and AFIP (Brazil)

406.I

Effect of Age in Sexual Behavior of Sleep Deprived Rats After Cocaine Administration

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Introduction: It has been suggested that paradoxical sleep deprivation (PSD) could sensitize dopaminergic systems, probably by inducing supersensitivity of the post synaptic receptor (TUFIK et al., 1978). The mesolimbic dopamine (DA) system, composed of DAergic neurons in the ventral tegmental area and their projections to the nucleus accumens and other forebrain structures, has been implicated in the reinforcing and locomotor-activating properties of cocaine (HOGER et al., 1999). In 2000, ANDERSEN et al., showed that acute cocaine administration elicited sexual behavior in young PSD rats. It is known that there is a decline in sexual arousal and copulatory activity in male rats with advancing age, as well as significant changes in various sleep parameters. Thus, the objective of the present study was to examine the behaviors of penile erection and ejaculation in young and middle-age rats submitted to PSD after cocaine administration.

Methods: Young (3 months) and middle-age (18 months) male rats were PSD for 96 hours by the modified multiple platform methods or stayed in their cages (control group-CTRL). At the end of this period, the animals received an i.p. injection of cocaine (15 mg/kg) and the erections and ejaculations were assessed for 50 minutes.

Results: The cocaine-PSD study revealed a significant difference between the 3months-PSD and the three other groups with regard to sexual behavior. The young PSD rats had the greatest number of erection and ejaculation. Among the middle-age rats, the PSD group only had erection and sexual behavior was absent in the 18 months control group.* # - different from 3m-PSD animals; p<0.005 by ANOVA test.

Figure 1

Conclusions: Sexual function commonly decreases with age, but the interaction of sleep deprivation and the action of cocaine in the brain by enhanced DA transmission can facilitate and increase the sexual behavior in middle-age rats.

References:

Supported by Associação Fundo de Incentivo à Psicofarmacologia (AFIP)

407.I

Convergence Among Physiologic, Behavioural, and Subjective Estimates of Sleep Onset Latency During Prolonged Wakefulness

Davies DR, Dawson CM, Gaasbeek K, MacLean AW
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Introduction: The Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) can be considered paradigms in which basal/physiological sleep tendency is modified by alerting factors to produce manifest sleepiness. In the former case alerting factors are eliminated to permit the assessment of basal sleepiness. The dependent measure in each case is sleep onset latency measured polysomnographically. In principle, however, sleep onset latency could equally well be assessed by self-report or behaviourally. In the present study, sleep onset latencies defined physiologically, behaviourally, and subjectively were investigated under conditions of prolonged wakefulness and their sensitivity to MSLT and MWT instructions were compared.

Methods: Thirty-two healthy undergraduates (16 male, 16 female; mean age = 18.9) underwent four test sessions at 2230, 0100, 0330, and 0600 during one night of sleep loss. Each test session consisted of two 30-minute sleep latency tests - one under MSLT instructions and one under MWT instructions - separated by one hour of performance testing. The order of the MSLTs and MWTs was counterbalanced. Sixteen subjects were also monitored behaviourally during the latency tests by way of a wrist-mounted device that emitted vibratory stimuli on a random interval schedule every 30 to 60 seconds. Subjects pressed a hand-held microswitch when they detected a vibration. Non-responses were followed by another stimulus 10 seconds later. Failure to respond to this second stimulus was taken as a behavioural indication of sleep onset. In addition, all subjects were asked to give an estimate of their sleep onset latency following each test.

Results: Repeated-measures ANOVAs with time of testing and instructional set (MSLT or MWT) extracted as within subject variables were calculated for each sleep onset parameter separately. Latencies to Stage 2 decreased with prolonged wakefulness, F(3, 90) = 168.82, p < .001, were longer under the MWT condition, F(1, 30) = 28.66, p < .001, and demonstrated an interaction between time of night and instruction, F(3, 90) = 7.48, p < .001 (see Figure 1). This general pattern of main effects and interaction was replicated for Stage 1, subjective, and behavioural parameters falling short of significance (See Figure 2). Secondly, Pearson correlations calculated among all sleep onset parameters for the subjects in the behavioural monitoring condition revealed an average shared variance of 46.3% in the MSLT condition and 71.0% in the MWT condition. Finally, between-parameter comparisons revealed
that, on average, behavioural and Stage 1 sleep onset latencies did not differ significantly but were shorter than those identified by Stage 2 which were, in turn, shorter than subjective estimations.

Conclusions: Sleep onset latencies measured behaviourally and subjectively displayed a similar pattern of results to those assessed physiologically - they decreased with prolonged wakefulness and varied with test instructions. Furthermore, convergence among the parameters was quite good - particularly under MWT instructions. These results provide additional support for the use of behavioural and subjective indices of sleep onset latency as alternative, or adjunct, measures for assessing sleepiness.

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408.I

Sleep Rebounds From Total and Paradoxical Sleep Selective Deprivation in Rats

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Introduction: The effects of total sleep deprivation (TSD) as well as paradoxical sleep deprivation (PSD) on subsequent sleep-wakefulness cycle (SWC) and the general state of the rats are controversial. A special interest draw results of chronic TSD or selective PSD obtained by means of the Disk-Over-Water method which suggest that in all the deprivation types a huge rebound of the PS and modest increase of the slow wave sleep (SWS) does occur. Because TSD per se, even “non-stressful” method for its elicitation would be used, results in a conflict between an increased need for sleep and impossibility of its satisfaction, it must be accompanied by stress processes. The question is rising: do different data result from different method or length of deprivation procedure? One way to ascertain this question, taken in the present study, would be to investigate short lasting TSD and PSD effects, elicited by least stressful method and to determine whether both type of deprivation produce rebounds similar to each other and to those of other methods.

Methods: Adult male rats (n=8), chronically implanted with stimulating (AHL) and recording electrodes (EEG, EMG, EOG), were maintained under constant light and baselines of 24h SWC recorded. TSD as well as PSD, lasted 8-12h, were performed by an abrupt awakening through AHL electrical stimulation. Subjects were monitored continuously and whenever there appeared the signs of SWS in case of TSD, and PS in case of PSD, animals were awakened by threshold stimulation for behavioral arousal. Sleep phases onset was recognized visually. Recovery periods lasted 12-16h. Behaviors such as grooming, rising, ambulation and sniffing were recorded digitally. The animals’ body weight, volume of consumed food and the number of bolus were monitored daily. The data were processed statistically by the Student’s t-test.

Results: The definite regularities in the process of both type of deprivation were revealed. Significant increase in the frequency of SWS attempt during TSD and PS - during PSD occurred. Intensification of stimulation parameters was required. The longer was a deprivation procedure, the harder was its accomplishment. After 6-8h TSD, the need for sleep was so pressing that the animal managed to “smuggle” the SWS EEG fragments. In post TSD period the SWS volume as well as delta power increased significantly. There was no compensatory increase of the PS - neither quantitatively nor qualitatively. Only insignificant increase of PS amount was occurred after 12h TSD. As regards to post PSD period, the selective PS rebound was observed: PS onset frequency, its total duration, hippocampal theta power and the frequency of eye movements were increased. Animals’ behavioral parameters were not changed considerably neither in the deprivation-, nor in the post deprivation periods.

Conclusions: The idea that PS rebound compensates for specific loss of both SWS and PS was not supported in present study. However, the longer was the TSD, the longer was the time of the “smuggled” sleep. Consequently, the long lasting TSD enables us to speak about specific compensatory process caused by sleep total loss. Therefore, it could be suggested that homeostatic compensation of lost sleep occurs if sleep restriction is performed during short time by least stressful method when the stress effects and the volume of “smuggled” sleep do not reach significant values and precise evaluation of TSD effects could be achieved.

409.I

The Effects of Selective Sleep Deprivation on the Memory for a Declarative Learning Task

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Introduction: Declarative memory has not been as consistently linked to sleep as procedural memory, but there have been hints that a relationship exists. REM augmentation studies have found that some sleep parameters change after tasks with a declarative learning component [e.g., REM density(1), and percent REM sleep(2)]. We hypothesized that memory for a purely declarative non-verbal learning task would be adversely affected by REM sleep deprivation.

Methods: 20 undergraduate Trent University students, who were screened for any sleep abnormalities, participated in the study. The Declarative Memory Task: fifteen diagrams of the human brain were presented on the computer, each highlighting a different area in the brain. A 60-item multiple-choice exam was given after learning; if a score of 80% was not achieved, a second version of the task was given. Procedure: Participants spent an acclimatization night in the sleep laboratory. On the second day, participants were taught the declarative task in the afternoon and were tested immediately for retention. Participants
were told prior to learning the material that a score of 80% or more would earn them an extra twenty dollars (to create the motivation to learn). That night, participants were subjected to one of the following sleep conditions: REM deprived, Stage 2 interrupted, in-lab control, or home control.

**Results:** An ANCOVA was conducted to examine the effects of the sleep deprivation condition on re-test scores; the score on test one was the covariate. The groups did not differ in terms of their score on the re-test \([F(3,11) = 1.064, p = 0.404, \text{MSE} = 157.350, \text{Eta2} = 0.0967]\). The REM deprived group spent significantly less time in REM sleep than did the controls or the Stage 2 interrupted groups \([F(2,9) = 21.730, p = 0.000]\). The REM deprived group also spent significantly less time asleep than either the Stage 2 interrupted or the controls \([F(2,9) = 4.503, p = 0.044]\).

**Conclusions:** The data from this study did not support the hypothesis that REM sleep is necessary for the effective consolidation of non-verbal declarative material. Neither REM deprivation nor Stage 2 interruption had a detrimental effect on memory for the declarative learning task. These findings differ from other studies that have found signs of a relationship between declarative learning and sleep. However, many of these previous studies actually required a procedural component for retrieval; participants were often directed to apply their knowledge, rather than using a rote recall method. Since procedural memory has been found to require REM sleep for efficient learning, it is not surprising that they found significant results. When both the learning and the recall methods are declarative, it appears that sleep deprivation does not negatively affect memory.

**References:**

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**410.I**

**Telemetered EEG Data Collected from Sleep-deprived Aviators**

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**Introduction:** Sleep deprivation is a well recognized cause of degradation in aviator performance, which leads to concerns for the safety of pilots and their crew, as well as for the success of the mission. Nonintrusive, objective measurement of fatigue during flight is required for in order to proactively identify, and potentially rectify, situations which are potentially dangerous. Two issues must be addressed: identification of both a useful parameter to measure fatigue in flight, and a system by which such a measurement can be taken. Electroencephalographic (EEG) data would appear to be a promising parameter, as past research has shown that increases in slow-wave EEG activity tend to be closely associated with fatigue in laboratory situations, both at rest and during aviation simulation tasks (Caldwell et al., 2000; Lorenzo et al., 1995). As for the measurement system, the U.S. Army Aeromedical Research Laboratory (USARML) maintains a specially designed airborne EEG collection device, capable of monitoring real-time EEG data from an aviator during flight. The present study sought to determine whether EEG data collected in this manner, from sleep-deprived aviators during actual flight maneuvers, would demonstrate the fatigue-related changes in slow-wave activity that have been demonstrated under laboratory conditions.

**Methods:** EEG data from 10 U.S. Army aviators were collected, both in the laboratory and during actual flight maneuvers. The participants remained awake for approximately 26 hours and data collection occurred during the 13th through 26th hours of continuous wakefulness. This enabled both baseline (alert) and sleep-deprivation measurements. In the laboratory, the pilots also periodically completed self-ratings of mood and wakefulness throughout the deprivation period using the Profile of Mood States (POMS) questionnaire.

**Results:** EEG theta activity increased as a function of sleep deprivation both in the aircraft and in the laboratory (see Figures 1 and 2, respectively). Delta activity followed a similar pattern. EEG alpha activity also changed as a function of deprivation; however, this activity decreased over time in the laboratory, and increased over time in the aircraft. Four of the six POMS subscales, specifically tension, vigor, fatigue and confusion, showed deprivation related changes over the testing period.

**Figure 1**

Absolute Theta Power Collected In Flight

**Figure 2**

Absolute Theta Power Collected In Flight

**Conclusions:** The findings indicate that it is practicable to measure EEG data in aviators in the actual flight environment, and thereby monitor their alertness levels in a minimally intrusive way. Slow-wave EEG activity collected in flight is shown to follow a pattern comparable to that of data collected in the laboratory, over a period of sleep deprivation. The fact that these increases in EEG theta and delta activity are indicative of sleep deprivation were supported by robust fatigue-related mood alterations in the laboratory.

**References:**
(1) Caldwell JA, Smythe NK, LeDuc PA, Caldwell JL. Efficacy of dextroamphetamine for the maintenance of aviator performance during 64 hours of sustained wakefulness. Aviation, space and environmental medicine 2000;71:7-18.

411.1

Comparative Analysis of Sleep Regulation in Good and Poor Sleeper Mammals

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Introduction: It is known that mammals are divided into “good” and “poor” sleepers, which have quite contrast sleep-wakefulness cycle (SWC) organization. In order to investigate whether sleep regulation mechanisms of these different groups are similar, the effects of total sleep deprivation (TSD) were studied in guinea pig, a representative of “poor” sleepers, and in the rat, a “good” sleeper. The results are shown in the present study.

Methods: TSD (8, 10 hours) was performed in chronic adult male rats (n=8) and guinea pigs (n=8). Prior to the experiments the animals were placed in the experimental cage (1m\(^2\)), where optimal conditions for regular SWC were maintained. Implantation of EEG and electromyogram electrodes was performed under deep nembutal anesthesia. Baseline SWC was recorded for 5-6 days. For the purpose of sleep restriction the rats were awakened by the stimulation of the lateral hypothalamus, while guinea pig -by gentle handling. Throughout the procedure and after its termination the electrophysiological variables and behavioral reactions were recorded. At standard time of the SWC the frequency of the onset, total duration and ratio of different phases were determined. In addition, the amplitude-frequency analysis of the delta and theta waves were made. The results were processed statistically by the Student’s t-test.

Results: The TSD in the rats and guinea pigs resulted in significant changes of the animals’ SWC structure. In a course of the procedure there occurred sharp increase in the number of sleep attempts. Besides, there started to manifest itself the dissociation of the wakefulness EEG and behavioral indices. The pressure of sleep increased step by step, there appeared the “smuggled” sleep and eventually, after 10-12 h of TSD, the maintenance of uninterrupted wakefulness became nearly impossible. In the post-deprivation period the development of compensatory processes was evident in both species. In comparison to control conditions, the volume of slow-wave sleep (SWS) increased significantly, especially deep SWS. The EEG delta power increased as well. Behavioral delta-sleep deepened also: the tone of the neck muscles decreased and paradoxical sleep (PS) occurred on the background of an already developed atony. In the post-deprivation SWC of both species there was no significant compensatory increase of PS. In guinea pigs total PS duration was increased but the intensity of PS and SWS/PS ratio in total sleep was not considerably changed against the control.

Conclusions: Comparative analysis of the results has shown that the TSD in the rats and guinea pigs induced similar effects: it caused in the body of the animals formation and gradual accumulation of internal need for delta-sleep. The acute deficit of the sleep was compensated in the post-deprivation period by its sharp rebound. So, it can be said that sleep regulation mechanisms of “good” and “poor” sleepers are similar.

412.1

Response Surface Modeling of the Effects of Chronic Sleep Restriction With and Without Diurnal Naps

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Introduction: Research has shown that the physiological sleepiness and performance deficits engendered by sleep debt can progressively worsen (i.e., accumulate) over consecutive days of sleep restriction, and that sleep limited to levels commonly experienced by astronauts (i.e., 4-6 hr per 24 hr) for as little as 1 week, can result in increased lapses of attention, degradation of response times, deficits in complex problem solving, mood disturbance, etc. An experiment was performed to determine how to best prevent such cumulative deficits from sleep restriction. A response surface experimental paradigm was used to identify the most effective ways to obtain sleep in order to maintain cognitive performance when time available for sleep per 24 hr is chronically restricted.

Methods: N = 91 healthy men and women (43% female, mean age=29.5yr) underwent a 14-day laboratory protocol involving random assignment to one of 18 sleep-ratio cells, each involving the same sleep ratio for 10 consecutive days. The sleep-ratio assignments involved 4 chronic anchor sleep durations (4.2, 5.2, 6.2, 8.2 hr) and 6 chronic nap sleep durations (0.4, 0.8, 1.2, 1.6, 2.0, 2.4 hr). These were crossed to yield a total of 4 anchor-sleep-only conditions and 14 anchor + nap sleep conditions spanning a dynamic range of cumulative sleep debts from 0 to 40 hr in a 10-day period. Every 2 hr throughout all waking periods during the 14 experimental days, subjects underwent a number of performance tests and continuous monitoring of PSG, waking EEG/EOG, and core body temperature. Statistical methods utilized two-stage random effects regression analysis. Least squares estimates of slopes representing average daily changes were obtained for each subject under three different models that reflected constant, accelerating, or decelerating change across days—these slopes served as inputs to second stage response surface modeling. The objective was to identify high yield (i.e., efficient) anchor + nap sleep combinations that tended to minimize functional degradation over time while controlling for baseline performance, age, and gender.

Figure 1

Results: A typical response surface map (RSM) for lapses per trial on the psychomotor vigilance test (PVT) is illustrated in Figure 1. This model included indicator variables for an anchor sleep factor, linear and quadratic terms for nap duration and age, gender, and a term for baseline performance (F[9,81]=3.99, p<0.001, R\(^2\)=30.7%, R\(^2\)(adj.)=23.0%). Results
demonstrated that naps were effective in reducing performance degradation over time, but that no combination achieved the negligible degradation seen in the 8.2 hr anchor sleep condition. Figure 2 illustrates a similar RSM based on a first-stage model for changes from baseline in Karolinska Sleepiness Scale (KSS) scores.

**Figure 2**

![Response Surface Map: Karolinska Sleepiness Scale Changes from Baseline](image)

**Conclusions:** Response surface modeling revealed that shorter restricted nocturnal anchor sleeps combined with longer diurnal naps could limit accumulating sleepiness and performance deficits similar to longer-duration nocturnal anchor sleeps alone. However, total sleep time per 24 hr remained a potent dose-response determinant of how subjects felt and performed. Response surface modeling offers an efficient way to evaluate the effects of a large number of sleep-wake schedules in search of an optimal sleep duration and timing relative to operational demands.

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**413.I**

**Electroencephalographic Indices Predict Future Vulnerability to Fatigue Induced by Sleep Deprivation**

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**Introduction:** Electroencephalographic (EEG) parameters are sensitive indicators of drowsiness and have been proven to correlate with performance on a second-by-second basis (Makeig, 1995). This study applies the B-Alert system, a discriminant function analysis (DFA) model designed to classify one-second epochs of EEG on a continuum from highly vigilant to sleep onset to quantify the effects of partial sleep deprivation. The system was designed to provide real-time detection of drowsiness and recommend the optimal time to take a short nap to extend vigilance.

**Methods:** Forty-nine healthy subjects (males = 32, females = 17; age range 25–68) participated in a 12-hour overnight study 14 hours after awakening from partial sleep deprivation. Continuous EEG and EOG recordings were acquired from the subjects during fully-rested baseline and overnight sessions. Two-choice Psychomotor Vigilance Tests (PVT-ABM) were administered at baseline and 15, 19, 23, and 25 hours after waking from partial sleep deprivation (Maximum reaction time cut-off = 1.5 seconds). EEG classifications, reaction times and percentage correct responses were averaged across each of the PVT-ABM sessions. Differential recordings for CzPz and CzOz were obtained with disposable Ag/AgCl electrodes. EEG and EOG were acquired with Teledyne amplifiers, low pass filter at 75 Hz and high pass filter at 0.5 Hz, fixed gains at 10,000 and 2,000, respectively. EEG classification results were collapsed into high vigilance and drowsy categories. This study was not designed to assess the effects of napping as a countermeasure. In an effort to ensure all subjects completed the study, however, 35 subjects were allowed a short nap approximately 20.5 hours after awakening from partial sleep deprivation based on technician observations of fatigue. The remaining 14 subjects did not exhibit sufficient fatigue at the scheduled napping time and completed the protocols without a nap.

**Results:** Repeated measures ANOVA revealed a significant decrease in high vigilance classifications, a significant increase in drowsy classifications, and a significant interaction between the two as a function of time elapsed after awakening from partial sleep deprivation. The percentage of correct PVT-ABM responses decreased significantly and the PVT-ABM reaction time increased significantly as a function of time. EEG classifications for subjects requiring naps (“Nappers”) showed a distinctive pattern when compared to “No-Nappers”. The Nappers evidenced a rapid increase in drowsy epochs with a steep decline in high vigilance epochs (Fig. 1.a.). The No-Nappers showed similar but less pronounced trends; the drowsy and high vigilant epochs were less affected even at the 25-hour time point (Fig. 1.b.). Percentage correct responses (Fig. 2.a.) and PVT-ABM reaction times (Fig. 2.b.) closely paralleled the B-Alert classifications.

**Figure 1**

![B-Alert Classifications](image)

Percent epochs classified as high vigilance vs. drowsy during 20-min PVT-ABM at fully-rested baseline and time-points subsequent to awakening from partial sleep deprivation for a. Nappers and b. No-Nappers.

**Figure 2**

![PVT Performance](image)

a. Mean percentage of correct responses for Nappers vs. No-Nappers. b. Mean reaction time for Nappers vs. No-Nappers.

**Conclusions:** These results demonstrate the sensitivity of the B-Alert
classification and performance measures to identify groups who differ in their vulnerability to the effects of sleep deprivation. These results support the B-Alert system’s sensitivity to fatigue and suggest that the system could be applied in real-time to recommend the optimal time for a strategic nap.

References:
(1) Makeig S, Jung T: Changes in alertness are a principal component of variance in the EEG spectrum. NeuroReport, 7,213-216, 1995

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414.I

Modafinil and Caffeine Improve Alertness During Sleep Deprivation

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Introduction: Performance and alertness decline with sleep deprivation. Previously we showed that modafinil and caffeine significantly improved performance during total sleep deprivation (TSD).1,2 In the present abstract, we report the effects of modafinil and caffeine on objective alertness as measured by a modified maintenance of wakefulness test (MWT). We addressed the following questions: (1) Do modafinil and caffeine improve alertness during total sleep deprivation? (2) Is modafinil comparable to an active control dose of caffeine 600 mg? (3) Is modafinil’s effects dose-dependent?

Methods: 50 healthy young adult males and females participated after giving informed consent. Following 7 hours of undisturbed nocturnal sleep (2330-0630), subjects remained awake for the next 54.5 hours (0630 Day 1 - 1300 Day 3) with continuous polysomnographic (PSG) recordings obtained throughout. Every 2 hours from 0800 Day 1 until 2200 Day 2 subjects performed a modified maintenance of wakefulness test (MWT). At 2355 Day 2 (after 41.5 hours awake), subjects ingested double-blind one of 5 drug doses as follows: placebo*, modafinil* 100 mg, 200 mg, or 400 mg, or caffeine 600 mg. The modified MWT was then administered every hour from 0000 through 1200 Day 3. Modifications to the MWT consisted of off-line PSG scoring and decreasing the standard 20-minute test to 15 minutes. Subjects lay in bed with lights off and were instructed to stay awake. Sleep latency to stage 2 was scored blind to drug group. Statistical analyses of post-drug data were conducted using analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests. All values were Greenhouse-Geisser adjusted.

Results: Due to equipment failure, only 27 subjects’ data were included in the present analysis. Both modafinil and caffeine increased sleep latency relative to placebo (see figure-drug main effect, F [4, 22] = 12.47, p = 0.00). The session effect also was significant, F [6, 128] = 3.27, p = 0.0056. The Session X Drug interaction was not significant, p > 0.05. Post-hoc analyses revealed that sleep latency for modafinil 200 mg, 400 mg and caffeine 600 mg were significantly longer than placebo, but not from each other. Modafinil 100 mg was not significantly different from placebo.

Conclusions: The results confirm that modafinil and caffeine improve alertness during TSD in normals, and that the effectiveness is dose-dependent. Modafinil at the 200 mg and 400 mg dose levels improved alertness (relative to placebo) as did caffeine 600 mg. These results indicate that sleep deprivation effects in alertness can be temporarily countered through the use of modafinil or caffeine in normals.

References:

*Modafinil and placebo kindly provided by Cephalon, Inc., West Chester PA, USA

415.I

Modafinil and Caffeine Reverse Sleep Deprivation/Fatigue Effects on Performance

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Introduction: Previously we showed that during total sleep deprivation (TSD), both caffeine and modafinil improve speed on a psychomotor vigilance task (PVT) across test sessions (Wesensten et al., 2000). In this abstract, we describe the effects of caffeine and modafinil on PVT speed within a 10-minute test session during TSD, i.e., the efficacy of modafinil and caffeine for combating the combined effects of TSD and “fatigue,” the latter operationally defined as time on task (Balkin et al., 2000).

Methods: 50 healthy young adult men and women participated after giving informed consent. Following 7 hours of undisturbed nocturnal sleep (2330-0630), subjects remained awake for the next 54.5 hours (0630 Day 1 - 1300 Day 3) with continuous polysomnographic (PSG) recordings obtained throughout. Every 2 hours from 0800 Day 1 until 2200 Day 2 subjects performed a computer test battery immediately followed by a modified maintenance of wakefulness test (MWT). At 2355 Day 2 (after 41.5 hours awake), subjects ingested double-blind one of 5 drug doses as follows (n=10 per group): placebo (PLA); modafinil 100 mg (M100), 200 mg (M200), 400 mg (M400); or caffeine 600 mg (C600). The computerized test battery and modified MWT were then administered every hour from 0000 through 1200 Day 3. Data reported here are for PVT post-drug sessions only. MWT results are reported in a companion abstract (Reichardt et al., this volume). PVT - Subjects pressed a response key whenever a time display began to increment. The interval between the subject’s response and the next time display increment was
Results: Effects of drug, session, block, Drug x Session and Session x Block on PVT speed were significant (p < .05) and were presented elsewhere [JSR, 9(S1), #414]. A significant Drug x Block interaction was found, F[36,396] = 1.98, p = 0.0173 (see figure-means collapsed across all 13 post-drug sessions; Drug x Block x Session interaction NS, p > .05). M200, M400 and C600 maintained speed across the 10-min task compared to PLA (p < .05). M100 and PLA were not significantly different (p > .05).

Figure 1

Conclusions: TSD and time on task or “fatigue” synergistically impair performance. Furthermore, fatigue effects are evident even across a relatively short (10-min) task. Results of this study show that both modafinil (at appropriate doses) and caffeine 600 mg effectively reverse the interactive effects of sleep deprivation and fatigue on performance, a finding that suggests that performance improvement can result from at least two distinct neurobiological mechanisms.

References:

Modafinil and placebo provided by Cephalon, Inc., West Chester PA, USA

416.I

Statistical Modeling of the Waking Neurobehavioral Response to Chronic Partial Sleep Deprivation

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Introduction: Chronic sleep loss causes cumulative waking neurobehavioral performance deficits. Three different models were compared for describing the day-to-day changes in neurobehavioral performance across 14 days of partial sleep deprivation, with sleep restricted to 4h, 6h or 8h per night. These models were (1) a linear model, which would fit the data if the response to chronic sleep loss continued at a constant rate; (2) a decelerating model, which would fit the data if the response was substantial first but continued at more marginal rates later; and (3) an accelerating model, which would fit the data if the response was subtle first but escalated later.

Methods: Thirty-five subjects spent 20 days inside a laboratory. After 3 baseline days with 8h time-in-bed (TIB), they underwent sleep restriction for 14 days. Thirteen subjects received 4h TIB (03:30-07:30); thirteen subjects received 6h TIB (01:30-07:30); and nine subjects received 8h TIB (23:30-07:30). Neurobehavioral performance was tested every 2h during wakefulness, and included a psychomotor vigilance test (PVT), a probbed-recall memory task (PRM), a digit-symbol substitution task (DSST), a serial addition-subtraction test (SAST), the Karolinska Sleepiness Scale (KSS) and the Stanford Sleepiness Scale (SSS). Daily averages (09:30-23:30) were computed for PVT lapses; PRM, DSST and SAST number correct; and KSS and SSS score. The three models were cast in equations involving time t (in days), waking performance y (as difference from baseline), and parameter a. The equations were: for the linear model (1) \[ y = at \]; for the decelerating model (2) \[ y = a + \frac{\beta}{t} \]; and for the accelerating model (3) \[ y = at^2 \]. These models were fit to the data for each subject, and ranked by goodness-of-fit (mean square error). For each condition, differences in average ranks were evaluated with a \( \chi^2 \) statistic (2 d.f.). Over the three conditions, a composite \( \chi^2 \) statistic (6 d.f.) was computed to determine if overall, the three models differed in goodness-of-fit. Also, pairwise comparisons involving composite \( \chi^2 \) statistics (3 d.f.) were performed to identify the best model. This procedure provided a robust model selection criterion.

Results: The Table shows the \( P \) values for the differences between the models’ goodness-of-fit, for the six neurobehavioral variables. For the KSS and SSS, the decelerating model (2) was superior. For the objective performance measures, the accelerating model (3) generally did not fit the data well, but there was no clear superiority of either the linear or the decelerating model. Parsimoniously, the linear model (1) was selected as the best fitting model for these variables.

Table 1

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<th>Variable</th>
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<th>2 vs 3</th>
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</table>

Conclusions: The accelerating model did not provide the best fit for any of the neurobehavioral variables. For the objective performance measures, neither the linear nor the decelerating model was clearly superior. For subjective sleepiness, however, the decelerating model consistently fit best. This inconsistency between objective and subjective measures of wakefulness may reflect a systematic aspect of the way subjects filled out the KSS and SSS. Since these scales were not used across their full range in this experiment, precluding a ceiling effect, we hypothesize that a response bias developed over days of sleep restriction.

Research supported by NIH grants NR04281 and RR00040, NASA grant NAG9-1161, and IEPRF
The Effects of Sleep Deprivation on NREM Sleep Event-Related Potentials

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Introduction: There are a number of differences between the event-related potentials (ERPs) seen during wakefulness and those seen during sleep. While much research has examined the functional and especially the cognitive significance of ERP components obtained from awake subjects, much less has been done regarding the waveforms of the NREM sleep ERP. The purpose of this research is to examine the effects of sleep deprivation on the NREM ERP. Previously reported findings showed larger N350 amplitudes following sleep deprivation compared to baseline measures (Peszka & Harsh, 2000). The present report focuses on waveforms identified as P220 and P450 and on the N550-P900 complex (often associated with the K-complex). It has been hypothesized that the NREM ERP may not reflect a cognitive process, but rather a noncognitive process such as sleep-related inhibition of incoming sensory information, which may be modulated by cognitive processing (Hull & Harsh, in press). Sleep deprivation should serve to increase sleep pressure and consequently build greater inhibition. If NREM ERPs reflect sleep-related inhibition, then sleep deprivation should produce larger waveforms.

Methods: At their normal bedtime, ten subjects took a 20-min nap followed by a 20-min break and a second 20-min nap. The process was repeated 24 hours later following total sleep deprivation. Three tones (60, 75, and 90 dB) were presented during naps with 5-s interstimulus intervals. Wake/sleep state was determined using 10-s prestimulus EEG activity and categorized as one of six states: Wake/Alpha, Wake/Mixed, Wake/Theta, Stage 1, Stage 2 with no resultant K-complex, and Stage 2 with a resultant K-complex. ERPs recorded at Fz, Cz, and Pz were averaged across trials (maximum: 20; minimum: 5) for each subject in the wake/sleep stages.

Results: Differences in mean ERP amplitude (in microvolts) between pre and postdeprivation were compared for each tone intensity, stage, and lead. For the positivities, there were no consistent significant differences between pre and postdeprivation, although a clear effect for tone intensity was seen for P220 (Figure 1, CZ) and P900. For N550, beyond a tone intensity effect, postdeprivation amplitude was significantly larger than predeprivation for all tones during Wake/Alpha, for the loudest tone in Wake/Theta, Stage 1 and Stage 2 no K, and for the middle tone for Stage 1 (Figure 2, FZ).

Figure 1

Conclusions: Although sleep deprivation did not systematically affect the amplitude of the positive NREM ERP waveforms; N550 amplitude did significantly increase following sleep deprivation as was previously reported for the N350. The negative waveforms of the NREM ERP may reflect inhibition of incoming sensory information while the positivities may be more sensory in nature reflecting more the physical characteristics of the evoking stimulus rather than any cognitive process.

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(1) Hull J, Harsh J. P300 and sleep-related positive waveforms (P220, P450, and P900) have different determinants. Journal of Sleep Research, In Press.

Subjective, Objective and Physiological Measures of Alertness During 32 Hours of Continuous Wakefulness

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Introduction: This study was designed to obtain and compare subjective, objective and physiological measures of alertness in subjects maintained continuously awake for 32 hours.

Methods: Eight healthy normal male subjects were studied on a regimen of continuous bed rest with enforced wakefulness and constant caloric intake under the form of an intravenous glucose infusion. Tasks and questionnaires were given to the volunteers every hour to estimate cognitive performance and subjective alertness. The computerized tasks consisted of two tasks of the Harvard Cognitive Performance Battery, the perceptual cueing task and the vigilance task, from which reaction times and lapses were calculated. The questionnaires consisted of the Stanford Sleepiness Scale (SSS) and of a set of Visual Analogue Scales (VAS) from which we derived a measure of Global Vigor. Eyelid movements, a putative physiological marker of alertness, were measured every minute with the Nightcap, a headband with a sensor detecting both active movements of the eyelid and passive movements of the underlying eyeball. In addition, recordings of the EEGs were performed every two hours. For 2 minutes, subjects closed their eyes and relaxed. A spectral analysis was then performed on the central EEG (Cz) on 1-minute
periods, after removing artefacts.

**Results:** Subjective alertness, as assessed by the Global Vigor and its mirror image, the SSS scores, showed progressive deterioration as the time the subjects were awake increased, with a minimum/maximum in the morning hours (8h15 ± 49 min and 8h19 ± 38 min, respectively). Subjective alertness then improved even though the subjects remained sleep deprived. Cognitive performance deteriorated to reach a trough more than an hour after the maximum of subjective sleepiness (9h30 ± 52 min for the reaction time and 9h24 ± 36 min for the lapses). Similar to subjective measures of alertness, cognitive performance subsequently improved although the subjects remained awake. Eyelid movement counts decreased continuously throughout the daytime, starting well before any deterioration of alertness or performance, and reached a minimum during the early part of the usual sleep period (2h22 ± 56 min). Eyelid movements counts then increased abruptly and peaked at the time when performance was at its minimum. Analyses of the EEG recordings showed an increase in power in the theta and delta ranges paralleling the profile of SWS, with a peak in the early morning hours and, conversely, a decrease in power in the alpha range, paralleling the profile of subjective alertness.

**Conclusions:** Dissociations between subjective alertness, measures of cognitive performance, EEG changes and eyelid movements observed in the present study suggest that the impact of sleep loss needs to be characterized by multiple markers.

**419.I**

**Sleep Duration at Home in a Sample of Commercial Drivers**

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**Introduction:** Estimates of the duration of sleep habitually obtained by truck drivers have varied considerably in recent reports [1,2]. As part of a study of prevalence of sleep apnea in commercial drivers we assessed sleep duration at home, using actigraphy, in those drivers having in-depth laboratory assessment of sleep and alertness.

**Methods:** The sample, on which this study was based, was a random sample of holders of commercial drivers licenses (CDL) in the state of Pennsylvania within 50 miles of our sleep center. From this sample we selected, for laboratory testing, 249 individuals who had, based on their multivariable apnea prediction (Maislin et al, Sleep 18:158, 1995), a higher risk of sleep apnea and 159 individuals with a lower risk. We obtained actigraphy data for 7 days from 208 higher risk individuals and across risk groups. The higher risk group slept less than the lower risk group (358.5±84.4 minutes (mean±SD) versus 395.2±74.1 minutes, p<0.0001). Important determinants of sleep duration were time of awakening and the presence of sleep apnea. 12.3% of groups, respectively; p<0.0001.) Important determinants of sleep duration had also more variable durations from night-to-night. (Spearman rank correlations were -0.34 and -0.43 in the higher and lower risk groups, respectively; p<0.0001.) Important determinants of sleep duration were time of awakening and the presence of sleep apnea. 12.3% of subjects awoke before 5:00 AM while 35.6% awoke before 6:00 AM. Subjects with severe sleep apnea (RDI ≥ 30 episodes/hour) had significantly shorter sleep durations (p=0.0002) than those without apnea (RDI <5 episodes/hour). The difference in sleep duration was on average 73.8 minutes.

**Conclusions:** Thus, cumulative partial sleep deprivation was common among this cohort of short-haul and long-haul CDL holders, which was a considerably larger sample than reported in previous studies [1,2]. Sleep apnea was associated with shorter sleep durations, and this will likely compound the effects of sleep apnea on daytime performance.

**References:**


**Research supported by Trucking Research Institute contract DTFH61-93-R-00088 and NIH grants HL-60287 and RR-00040.**

**420.I**

**Dynamics of Slow-Wave Activity during Chronically Restricted Sleep**

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**Introduction:** Slow-wave activity (SWA) and its time-integrated equivalent slow-wave energy (SWE) are quantitative measures of the slow waves in the electroencephalogram (EEG) of non-rapid-eye-movement (NREM) sleep. These measures may serve as markers of the homeostatic drive for sleep in contemporary models of sleep regulation (1). We investigated the temporal dynamics of the homeostatic drive for sleep, as reflected in SWA and SWE, under conditions of chronic sleep restriction.

**Methods:** As part of a larger study, n=16 subjects spent 20 days inside a laboratory, undergoing a strict schedule of performance tasks during the day and sleeping during the night. After 3 baseline days with 8h time-in-bed (TIB), nine subjects underwent a 14-day restricted condition of 4h TIB (03:30-07:30), while seven control subjects remained on the baseline schedule (23:30-07:30). Polysomnography was recorded on the baseline nights and on ten nights during the 14-day restriction period, and the records were visually scored using conventional criteria. SWA and SWE were determined from the C3 derivation of the EEG using power spectral analysis, and expressed as percentage of baseline. For SWA and SWE values, acute changes in the first night of restriction (offset) as well as daily changes across nights of sleep restriction (slope) were described using linear regression analysis. Differences between conditions were tested with analysis of variance (ANOVA).

**Results:** The offset and slope values are given in the Table (statistically significant differences are marked with an asterisk; P<0.05). For both SWA and SWE, only the offset values exhibited a significant difference between conditions (P<0.005). In the restricted condition, SWA intensified acutely on the first night of sleep restriction while the total amount of SWE significantly decreased. Remarkably, both SWA and SWE remained stable on the subsequent nights of sleep restriction.

**Table 1**

<table>
<thead>
<tr>
<th>TIB</th>
<th>SWA (mean ± s.d.)</th>
<th>SWE (mean ± s.d.)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>offset (%)</td>
<td>slope (%/day)</td>
</tr>
<tr>
<td>4h TIB</td>
<td>+0.6 ± 4.0*</td>
<td>+0.1 ± 0.3</td>
</tr>
<tr>
<td>8h TIB</td>
<td>-0.3 ± 2.8</td>
<td>0.0 ± 0.4</td>
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**Conclusions:** While the acute intensification of SWA in the restricted
condition was expected, the observed intensification was not sufficient to maintain baseline SWE. This net loss of SWE may have resulted from the reduced time available for NREM sleep, and because the 4h TIB period was displaced to a circadian phase more favorable for REM sleep. Thus, an incomplete dissipation of the homeostatic drive for sleep may have led to a cumulative “sleep debt.” This could explain the increasing neurobehavioral deficits observed during the restriction period, as reported previously (2). In the face of these increasing deficits, a further intensification of SWA across days of sleep restriction would have been expected, but was not observed. This seems to be incompatible with interpreting SWA as a marker of the homeostatic drive for sleep, unless one also posits that SWA expression rapidly reaches a “ceiling” when sleep is restricted. To investigate this issue further, analyses are underway involving detailed investigation of the dynamics of SWA and SWE between sleep cycles during sleep restriction.

References:

Research supported by NIH grants NR04281 and RR00040, NASA cooperative agreement NCC 9-58 with NSBRI, and NASA grant NAG9-1161

421.I

Effect of Paradoxical Sleep Deprivation During Pregnancy on Cognitive Performance in Offspring: A Pilot Study

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Introduction: One of the early functions of Paradoxical Sleep (PS) is to contribute to brain maturation. The first 10 days of pregnancy in the rat are known as the synaptogenesis period. In the present study we used chronic partial PS deprivation (PSD) during the synaptogenesis period of pregnancy in order to verify its effect in learning performance of the offspring.

Methods: Twenty-three rats born from three mothers were studied. Fourteen rats (7 males, 7 females) were born from two mothers deprived of PS using the flower pot technique. Eight rats (4 males, 4 females) were born from a control mother submitted to an equally stressful procedure but without the severe deprivation effects on PS (large platform). Mothers were exposed to their respective platform for four hours a day, starting at the beginning of the light period (8h00), after which they were returned to their individual home cage. Half the offspring was tested from postnatal day 21 to day 24 in either one of two versions of a water maze(1). In the standard (“Morris-type”) allocentric version, rats had to rely on external cues to find the hidden platform while departing from a different quadrant of the pool on every trial. In the alternation version, the hidden platform alternated between two quadrants while rats always started from the same quadrant. The rats had 6 trials of 60 seconds each to locate the platform where they remained for 30 seconds. If they did not succeed in time, they were placed on the platform by the experimenter where they stayed for 30 seconds. Time latency and number of quadrants entered before finding the platform were measured for each trial; results on postnatal day 24 were compared using Mann-Whitney U-tests.

Results: Rats from PSD mothers crossed more quadrants than controls to reach the platform (30.8 ± 1.9 vs 23.7 ± 1.8, p<.05). The time spent finding the platform was similar in the two groups (141.0 sec. ± 9.5 and 143.3 sec. ± 7.9, respectively). There were no differences between the two groups in the allocentric water maze (19.0 ± 3.2 vs 16.5 ± 3.6 quadrants and 90.2 ± 11.9 vs 91.5 ± 24.3 sec., respectively).

Conclusions: The learning deficit showed in the present study by offspring of PSD pregnant females is comparable to what was described following acute short-term PSD in adult rats (1). Since the alternation water maze task used in both studies was shown to rely on the integrity of the prefrontal cortex(2), we propose that repeated interference of PS during the synaptogenesis period of pregnancy is associated with learning difficulties in task that require an intact prefrontal cortex network. The accumulation in the pregnant mother of a PS deficit upon chronic partial PSD may be the a determining factor(3).

References:
(2) Ethier K, Beaulieu I, Le Marec N, Rompré PP, Godbout R. Effects of a medial prefrontal cortex lesion on a PS deprivation-sensitive version of the Morris Water Maze in the rat. Sleep, 2000; 23 (Suppl. 2): A76.

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422.I

Changes in Plasma Growth Hormone Levels Following Chronic Sleep Restriction

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Introduction: Secretion of human growth hormone (hGH) is primarily modulated by sleep-wake activity, with the majority of the secretion occurring during the initial part of the sleep period. Consequently, during acute total sleep deprivation, hGH secretion is suppressed (1, 2). The effects of chronic partial sleep deprivation on hGH secretion, however, have not been fully characterized. The goal of this study was to investigate the effects that chronically reduced nocturnal sleep time has on plasma hGH profiles.

Methods: A total of N=10 subjects (6m; 4f; mean age 30.1 ± 4.4) attended the sleep laboratory for a 14-day (13-night) protocol. Following 2 nights of baseline sleep (8.2h between 2154h-0606h) subjects were ran-
domly assigned to a sleep restriction condition that was maintained for 10 consecutive days, followed by 1 recovery day (14h sleep). In the control condition (N=5) subjects were allowed 8.2h time in bed (TIB) between 2154h-0606h; in the restricted condition (N=5) subjects were allowed 4.2h TIB between 2354h-0406h. On the first baseline day and the tenth final condition day, starting at 1630h, subjects were maintained in a quasi-constant routine paradigm for twenty-five hours. During this time subjects were near-supine in bed, and allowed to sleep at the allocated times. Blood samples (2cc) were collected at 15-minute intervals via an indwelling non-thrombogenic venous catheter. From these samples plasma hGH concentrations were determined, using an RIA (Diagnostic Systems Laboratories, Inc., TX). The hGH profiles were analyzed using within-subject repeated-measures ANOVAs comparing baseline day 1 with condition day 10 separately within the control and restricted conditions.

Results: For both conditions there was a significant time of day variation in hGH levels (p<0.001). As expected, in condition A (8.2 hr TIB on both baseline day 1 and condition day 10) there were no significant differences in hGH profiles between days. In sleep-restriction condition B (8.2h TIB on baseline days 1 and 2 and 4.2h TIB on condition days 1 through 10) there was no significant difference in the amount under the curve of hGH in plasma between baseline day 1 and condition day 10. However, the secretion of hGH was delayed, corresponding to the delayed timing of the sleep period.

Conclusions: The findings from the present study suggest that some sort of compensatory mechanism exists, such that over 10 days of sleep restriction, hGH secretion levels equilibrate to baseline levels, even if sleep is restricted by 4h, as well as delayed by 2h. Polysomnographic data from the study are currently being analyzed in order to investigate the relationship between sleep architecture and hGH profiles. This data will be utilized to investigate the effect of chronically reduced nocturnal sleep on hGH levels and the possible relationship with slow wave sleep intensity (3).

References:
(3) Van Cauter E, Leprout R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000; 284: 861-868.

Research supported by NASA cooperative agreement NCC-958 with NSBRI, and NIH grants NR04281, M01-RR00040 and K23-AG-00867-03

423.1

Digit-Symbol Substitution Task: Learning and Sleep

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Introduction: Performance on a digit-symbol substitution task (DSST) typically exhibits a learning curve. Animal studies suggest that learning may be associated with REM sleep (1). We investigated in humans whether learning on a DSST was affected by sleep deprivation, and whether any effects could be attributed to REM sleep loss in particular.

Methods: Data was obtained in studies involving five different sleep conditions, conducted under analogous laboratory circumstances. Each condition began with three baseline days of 8h time in bed (21:30-07:30). Subsequently, subjects were restricted to either no sleep or a predetermined amount of time for sleep every 24h: 13 subjects were totally sleep deprived for 3 days; 13 subjects were restricted to two 2h naps per day (02:45-04:45 and 14:45-16:45); 9 subjects received a 4h sleep opportunity each day (03:30-07:30); 8 subjects received a 6h sleep opportunity each day (01:30-07:30); and 7 subjects received an 8h sleep opportunity each day (23:30-07:30). Data from 3 condition days of each sleep condition were used. Across the 3 condition days, cumulative total sleep time (TST), rapid-eye movement (REM) sleep, and slow-wave sleep (SWS) were determined from polysomnographic records scored using conventional criteria. The mean number of correct responses on a DSST (seven test bouts per day) was used to compute the slope of performance changes, relative to baseline, across the 3 condition days. This measure of learning (positive slope) or impairment (negative slope) was correlated with the cumulative TST, REM and SWS values, controlling for condition.

Results: The Table shows cumulative TST, REM and SWS over the 3 condition days (means ± s.d.) and the slope of changes in DSST performance (mean ± s.d.; positive values indicate performance improvement), for each condition. One-way ANOVA revealed that all four variables differed significantly among conditions (F[4,45]>11.3; P<0.001). Within conditions there was large inter-individual variability in the DSST slopes, which probably reflected aptitude differences. Overall, learning was evident in the 4h, 6h and 8h sleep conditions, while the other two conditions yielded performance impairment. Partial correlations, controlling for condition, revealed significant positive associations of DSST slope with cumulative TST (r=0.32, P=0.013) and SWS (r=0.30, P=0.018). No significant correlation between DSST slope and cumulative REM was found when controlling for condition (r=0.01, P=0.47).

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cumulative time (hours)</th>
<th>DSST slope</th>
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<tbody>
<tr>
<td>no sleep</td>
<td>0.0 ± 0.0</td>
<td>-15.8 ± 10.7</td>
</tr>
<tr>
<td>naps</td>
<td>11.4 ± 1.9</td>
<td>-1.4 ± 9.7</td>
</tr>
<tr>
<td>4h sleep</td>
<td>11.4 ± 0.1</td>
<td>+1.8 ± 4.5</td>
</tr>
<tr>
<td>6h sleep</td>
<td>16.2 ± 0.8</td>
<td>+1.8 ± 3.8</td>
</tr>
<tr>
<td>8h sleep</td>
<td>19.7 ± 1.7</td>
<td>+5.1 ± 6.0</td>
</tr>
</tbody>
</table>

Conclusions: Analyses on the basis of individual subjects indicated that REM sleep is not a determining factor for learning on the DSST. Instead, TST and/or SWS may be involved in learning and impaired performance on the DSST. It remains to be assessed, however, whether the learning curve is merely masked by sleep loss, or whether the performance impairment due to sleep loss constitutes an actual loss of learning. Analysis of DSST performance after one and two nights of recovery sleep is underway to address this issue.

References:

Research supported by NIH grants NR04281 and RR00040, AFSOR grant F49620-95-1-0388, and NASA grant NAG9-1161
Long Term Total Sleep Deprivation Results in Altered Cu/Zn-SOD Activity

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Introduction: Prolonged sleep deprivation in animals results in increased eating, altered thermoregulation and eventually death (1). It has been proposed that reactive oxygen species (ROS), which accumulate during waking may be responsible for some of these effects. A variety of antioxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) help to regulate the level of ROS. Reduced glutathione (GSH) is also a potent scavenger of ROS. Glutathione reductase (GR), though not an antioxidative enzyme, is involved in the GPx/GSH pathway. In this study we investigated the changes in the activities of SOD, GPx and GR as well as GSH levels in the cortex of sleep deprived rats (DRAT), yoked controls (CRAT) and home cage controls (HC).

Methods: Male Sprague Dawley rats (350-450 g) were subjected to total sleep deprivation by the disk-over-water method. The rats were placed in constant light and given food and water ad libitum. After surgery, the rats were allowed to recover for at least 5 days before being placed in the disk-over-water apparatus for 4 days of adaptation. The experiment was initiated with 3 days of baseline recording where the animals were subjected to a timed stimulus (disk rotation once every hour for 6s). This was followed by 5-13 days of total sleep deprivation. Five sets of animals were sacrificed in groups of three (HC, CRAT, DRAT). The animals were killed by decapitation and brain regions were dissected and stored at -80 °C prior to performing biochemical assays. The cortex was homogenized and the mitochondrial fraction was used for the analysis of Mn-SOD activity while the cytosolic fraction was used for measuring the activities of Cu/Zn-SOD, GPx and GR as well as GSH levels.

Results: The activity of Cu/Zn-SOD was significantly reduced in DRATs compared to CRATs (81% of CRAT; t=3.4, df=5, p=0.03). Also, both CRATs and DRATs showed significantly lower Cu/Zn-SOD activity compared to HC (84% of HC; t=6.9, df=5, p=0.003 respectively). No significant change in Mn-SOD activity while the cytosolic fraction was used for measuring the activities of Cu/Zn-SOD, GPx and GR as well as GSH levels. The paired student’s t-test was used to determine statistical significance.

Conclusions: This study shows that prolonged sleep deprivation results in decreased Cu/Zn-SOD activity. It has been reported that decreased activity of this enzyme is correlated with neuronal death. Therefore, decreased Cu/Zn-SOD activity may be responsible for the cortical tissue damage observed in sleep deprived rats (2).

References:

REM Sleep Deprivation and Nicotine: Effects on Alcohol Intake in an Animal Model of Depression

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Introduction: Comorbidity of depression and alcoholism has been reported. Also, both selective REM sleep deprivation (RSD) and nicotine seem to improve depression(1,2). We believe these antidepressant treatments may also decrease or prevent alcohol intake.

Methods: We used neonatal male Long-Evans rats which received CLI (30 mg/kg/day, sc) or saline from p8 to p21. Three months later, rats were tested on locomotor activity and aggressive behavior to detect depressed rats. After these tests, both control (n=24) and CLI (n=24) rats were divided into 3 groups: one group was treated with RSD (flowerpot method, 22h/day); the second group was implanted with osmotic minipumps to receive nicotine (0.25, 1.5 mg/kg/day) and one last group remained intact. One week after the treatment, rats were tested on locomotor activity and aggressive behavior. Using new control (n=18) and CLI (n=18) rats, we formed 2 groups: one group was treated with RSD as aforementioned, for 2 weeks. The other group remained intact. Simultaneously all groups of animals were exposed to alcohol (10% v/v) during 7 days. After this period, rats had the option to ingest fresh water and/or alcohol for the following 4 weeks. A last group of control (n=18) and CLI (n=17) rats was implanted with osmotic minipumps to receive nicotine (0.25, 1.5 mg/kg/day) for a period of 4 weeks. Immediately after the implantation of the minipump, all groups of animals were exposed to alcohol schedule as aforementioned. Fluid intake was scored daily at 10:00 A.M. and the amount of alcohol (g/kg) determined. Body weight was evaluated weekly. Statistical significance of the data was obtained by using the Student t-test (single comparisons) or the one-way ANOVA and posthoc tests (multiple comparisons).

Results: Both RSD and nicotine produced a significant decrease in locomotor activity and an increase in the aggressive behavior in the CLI group. CLI rats ingested more alcohol both when alcohol was their only choice (11.35±0.2 vs. 8.62±0.35; p<0.05) and when they also could choose water (4.73±0.25 vs. 2.82±0.28; p<0.01). However, CLI rats under RSD had a significantly lower alcohol intake during the first week (11.35±0.2 vs. 4.77±0.63; p<0.05). One week after the RSD, alcohol intake decreases significantly in CLI rats (4.8±0.47 vs. 2.9±0.50; p<0.05). CLI group treated with both concentrations of nicotine had a significant decrease in alcohol intake during the first week (11.35±0.2 vs. 8.19±0.65, 7.9±0.59; p<0.05). During weeks 2-5, alcohol consumption in CLI rats was significantly lower (only high dose of nicotine, 4.73±0.25 vs. 1.58±0.24; p<0.01). With the low nicotine dose there was a trend to decrease the alcohol consumption, which became significant at the 5th week (5.18±0.73 vs. 2.79±0.59; p<0.05).

Conclusions: CLI treatment during a neonatal period prompts the adult rats (depressed) to ingest a larger amount of alcohol. Both RSD and nicotine revert depression signs and reduce alcohol consumption in CLI rats.

References:
Mitochondrial Respiratory Enzyme Function After Long Term Sleep Deprivation

Gulyani S, Ramanathan L, Nienhuis R, Siegel JM
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Introduction: The consequences of sleep deprivation at the cellular level are largely unknown. Total sleep deprivation in rats results in a syndrome of physiological changes leading ultimately to death. Mitochondria are the major site of energy metabolism. Recent studies have shown that mitochondrial genes have higher levels of expression after short term sleep deprivation (1). In the current study we investigated the effect of long term sleep deprivation on mitochondrial respiratory chain enzyme activities with the hypothesis that sleep deprivation may affect mitochondrial function. Mitochondrial Complex I (NADH :Coenzyme Q reductase), Complex II/III (Succinate: Cytochrome C oxidoreductase) and Complex IV (Cytochrome C oxidase) enzymatic activities were measured in brains of sleep deprived, yoked control and home cage rats.

Methods: Four to 6 months old Sprague Dawley rats (350-450gms) served as subjects. The disk over water method (2) was used to achieve total sleep deprivation. Pairs of rats were placed in the experimental apparatus for 4 days of adaptation. Three days of baseline were recorded during which the disk moved once every hour. This was followed by deprivation. During deprivation rats were awakened with a stimulus (disk rotation) whenever sleep was detected in a 30 second epoch. Polygraphic records were scored manually. The animals were sacrificed, in groups of 3 (deprived, disk control and home cage control), after 5-13 days of sleep deprivation. The animals were killed by decapitation and brain regions were dissected. The mitochondrial enzyme activities were measured in cortical homogenates using spectrophotometric methods. Complex I activity was estimated as nmoles NADH oxidized/min/mg protein. Complex II/III activity was estimated as micromoles of succinate oxidized /min/mg protein. Complex IV activity was estimated as nmoles cytochrome C oxidized/min/mg protein. A paired t-test was used for statistical analysis

Results: Total sleep loss of 56-85 % was achieved in deprived rats whereas control rats lost 6-53 % of total sleep (n=5pairs). Mitochondrial complex I ,II/III and IV activities were estimated in the cortex. No significant difference was seen in respiratory chain enzyme activities among the three groups (yoked, deprived and home cage controls). Complex I activity, however, showed a tendency to decrease with deprivation (yoked control =81.5 ± 13.9 %of home cage value and sleep deprived = 66.5 ± 27 % of home cage value, df=3, t=-.137) but this change was not statistically significant. Sets with higher ratio of sleep loss between yoke control and sleep deprived rats did not show increased differences in their enzyme activities. This decreased activity shown by both sleep deprived and control rats might have been due to the movement stress, as mitochondrial enzymes are very sensitive to stress.

Conclusions: This study shows that long term sleep deprivation does not affect cortical mitochondrial electron transport chain enzyme activity.

References:
(1) Cirelli C, Tononi G. Differences in gene expression between sleep and waking as revealed by m RNA differential display. Mol.Brain Res. 1998; 56; 293-305.

Research supported by NS 14160, MH 4151,NS59594,MH18825 and the VA Medical Research Service

Effects of Prolonged Sleep Deprivation on Cortisol Secretion in Humans

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Introduction: The 24-hour cortisol profile is known to be primarily driven by the endogenous circadian pacemaker. However, cortisol is not entirely independent from sleep influences since earlier studies have described an inhibitory effect of sleep on its release, and an intimate relationship between cortisol secretory rates and delta wave activity during sleep has been recently described (1). Effects of sleep deprivation on cortisol secretion have been investigated, but remain controversial. Indeed, studies have reported either no effect, or a decrease, or more recently, an increase in cortisol levels after acute (2) or chronic (3) sleep deprivation. This study aims to examine the effects of a prolonged sleep-deprivation on cortisol secretion.

Methods: 16 healthy young subjects (mean age ± SD: 26.1±5.2 yr.) underwent a 10-day protocol in an environment free of time cues. Following 3 adaptation days, subjects underwent a 40-h constant routine followed by a light exposure session. On days 6-9 of the study, after an 8-h sleep episode, subjects were scheduled to a 64-h sleep deprivation episode (~2.7 days) under constant routine conditions. Constant semi-recumbent posture, isocaloric meals every hour, dim light (<1.5 lux at angle of gaze) and constant wakefulness were insured at all times. Blood samples were obtained at 20-min intervals, cortisol was assayed by RIA method, and secretory rates were estimated using a deconvolution procedure. ANOVAs for repeated measures were used comparisons of cortisol values across time. Data are expressed as mean ± SE.

Results: The successive nadirs (p<0.02) and acrophases (p<0.01) of cortisol increased significantly over the sleep-deprivation. The number of secretory pulses and their amplitude showed a trend, although not statistically significant, toward an increase over the sleep deprivation. Consistent with this observation, the amount of cortisol secreted per 24-hours increased significantly from day 1 to day 2 of sleep deprivation (56.5±2.1 mg vs. 59.6±2.7 mg, p<0.03). An analysis of cortisol secretion per 8-h bins revealed an increase (not significant) in the amount of cortisol secreted when comparing each 8-hour bin to the corresponding bin at the same circadian phase (Figure 2).

Figure 1
Conclusions: The results demonstrate that a prolonged sleep deprivation is associated with an increase in the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Whether sleep-deprivation alters the feedback mechanisms of the corticotrophic axis (2), or that the sleep-deprivation procedure itself stimulates the HPA axis as a stressor cannot be inferred from these results. We will be investigating whether this increase in cortisol secretion is associated with a change in heart rate variability which is used as an estimator of the sympathovagal balance.

References:

Research supported by NASA Grant NAG 5-3952.

428.I

Cannabinoid Receptor 1 (CB1) Expression Is Modified By Sleep Rebound.

Martinez-Vargas M,1 Murillo-Rodríguez E,1 Landa A,2 González-Rivera R,1 Prospéro-García O,1 Navarro L1

Introduction: Cannabinoids are the psychoactive substances extracted from marihuana (Cannabis sativa). The most active molecule, delta-9-tetrahydrocannabinol (delta-9-THC), binds to two types of cannabinoid receptors: CB1 and CB2. CB1 receptor has a preferential distribution in the brain and mediates many of the actions of marihuana. Among marihuana effects is impairment of memory, motor coordination, distortion of self perception, increase in subjective sleepiness as well as graphically defined alpha waves and an increase in slow wave sleep (SWS). Anandamide (ANA), a recently described endogenous lipid that binds to CB1 receptors, mimics the effects of delta-9-THC. We have previously reported that ANA administration increases SWS2 and Rapid Eye Movement Sleep (REMS), and decreases Wakefulness (W) and SWS1 (1). In this study we decided to investigate if the CB1 receptor expression varies in relation to sleep-waking cycle, by determining the immunoreactive CB1 receptor concentration at different hours of the day, in rat hippocampus and pons, and by evaluating CB1 receptor concentration in rats with total sleep deprivation (TSD) and rats with TSD + two hour of sleep rebound.

Methods: Thirty Wistar male rats (250-300 g) were sacrificed at different hours: 9:00, 13:00, 17:00, 21:00, 01:00 and 5:00, five rats by point. Hippocampus and pons were extracted. We prepared the tissues with aprotinin and PMSF and used electrophoresis (SDS-PAGE) for protein separation. Finally we determined CB1 receptor expression by using antiCB1 (western blot). In the order to determine if the CB1 receptor expression was altered by TSD or rebound, ten Wistar male rats (250-300 g) were TSD by gentle manipulation for twelve hours (9:00-21:00 hrs), with food and water ad libitum. Five of them were allowed to rebound for two hours (19:00-21.00 hrs). They were sacrificed at 21:00 hrs and the tissues were manipulated as was described above.

Results: Changes in the CB1 receptor expression were detected in the pons and in the hippocampus, with maximum values in the light period; although they were not statistically significant. In addition TSD did not modified CB1 receptor expression but it highly increased by sleep rebound in pons.

Conclusions: We conclude that CB1 receptor expression exhibits a variation across the 24 hour, being higher during the light phase of the cycle in both hippocampus and pons. In addition sleep rebound is accompanied by an increase in CB1 receptor expression in the pons.

References:

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429.I

Changes in Brain Glucose Uptake Following Acute REM Sleep Deprivation

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Introduction: Both total sleep deprivation and rapid-eye movement sleep deprivation (REMD) affect a number of physiological processes and ultimately result in death. Little is known about the effects of sleep deprivation on the brain at the cellular level, and most studies have focused on total sleep deprivation. Everson et al. demonstrated decreased C14-deoxyglucose uptake in the hypothalamus, thalamus and limbic system, but no changes in average brain glucose utilization in rats with prolonged sleep deprivation. In this study, we sought to determine whether changes in brain glucose utilization could be detected following short-term REMD.

Methods: Two pairs of male F344 rats (120-150) days old underwent REMD for 28 hours using a modified flowerpot technique. Rats were placed in an enclosure containing three platforms surrounded by water 3-5 cm below the level of the platform. The platforms were 6.5 cm in diameter for the REMD group and 12 cm in diameter for the apparatus control animals. Following 26 hours of REMD, the animals were given iv injections of [F18] -fluorodeoxyglucose (FDG), after which they were returned to the apparatus for 1 hour to allow for FDG uptake. The animals were then sacrificed, the brains were removed, and total radioactivity within each brain was measured. Whole body mass, brain mass and blood glucose were also measured at the time of sacrifice. Radioactivity measurements were corrected for differences in decay time. The brains were frozen, sectioned at 50 mm and thaw-mounted on superfrost slides. Slides were exposed to Phosphor screens overnight and scanned with a PhosphorImager at 50 mm resolution. Signal analysis was performed with ImageQuant 5.0 software (Molecular Dynamics).
Results: Whole brain FDG uptake in the REMD animals was decreased by 25% and 49% compared to their apparatus controls. Autoradiographic analysis of specific brain regions is in progress, and suggests regional differences in changes in FDG uptake.

Conclusions: We found that short-term REMD resulted in decreased whole brain FDG uptake, in contrast to the earlier study of prolonged total sleep deprivation that did not find global decreases. Regional effects were noted and may be related to functional consequences of sleep deprivation. These preliminary results suggest that short-term REMD may result in changes in brain metabolic rate. Alternatively, the differences observed could be related to changes in glucose metabolism by other organs in response to REMD. An advantage of the FDG technique employed is that it allows for more precise quantitation of whole organ glucose uptake. It may also be combined with the C14-FDG method to compare two behavioral states (e.g., sleep and wakefulness).

References:

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Acute Effects of Lighting Changes on Human Performance

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Introduction: Bright light has immediate alerting and activating effects in humans in addition to its ability to phase shift circadian rhythms (1). Apart from its effects on visual acuity, little is known about the effects of light on performance. The purpose of this study was to determine whether people show shifts in performance levels following lighting changes. Immediate application of such findings could be made to people who work under varying artificial lighting conditions.

Methods: Subjects were trained on a test (Wombat-CS, Aero Innovations, Saint Laurent, QC) used to evaluate commercial pilot candidates. Sleep and light exposure was monitored for 5 d prior to testing. Subjects remained awake for the first half of their normal sleep period the night before testing. Four testing batteries (two in the morning and two after lunch) were administered. Each battery consisted of PANAS mood scales, a sentence completion task and the Wombat-CS. The batteries were presented in alternating condition of bright (1000 lux) and dim (10 lux) light. Seven males (ages 20-45) and 14 females (ages 18-41) completed this demanding protocol; 12 were tested in bright light first, the remaining nine began with dim light. We are presenting the results of two of the subscales of the Wombat-CS: tracking (number of lapses at following a moving figure), and quadrant location which requires the subject to locate, in order, the numbers 1-32 which are scattered across the four quadrants of the screen. Score is number of these sequences successfully completed. Both tracking and quadrant tasks are use light figures on a dark monitor. Within subject z scores were used for comparison.

Results: As can be seen from the figures performance on the quadrant task was significantly better in the bright conditions than in dim conditions, whereas performance on the tracking task tended to be worse in the bright than in the dim.

Conclusions: These results suggest that changes in lighting conditions can produce task-specific changes in performance, at least in partially sleep-deprived individuals during the subjective day. Such changes in lighting conditions normally occur as people move from home to work, and among various sites at a workplace. A better understanding of the acute effects of light on humans may suggest interventions that can maximize performance in critical settings; for example, performance may be enhanced if individuals are acutely exposed to brighter lighting conditions.

References:

Supported in part by a seed grant from the Center for Human Performance in Complex Systems of the University of Wisconsin - Madison.

Changes in Brain-Derived Neurotrophic Factor (BDNF) mRNA and Protein Levels Following Acute REM Sleep Deprivation.

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Introduction: Brain derived neurotrophic factor (BDNF) is broadly distributed in the brain and has been found to be an important modulator of plasticity and development. BDNF may also play an important role in sleep regulation since ICV injections of BDNF increase NREM sleep in rats (1). Further, BDNF mRNA has been shown to increase in the cortex and thalamus following total sleep deprivation in the rat (2). The purpose of the present study was to determine whether short term REM sleep
deprivation (REMD) alone can effect the expression of BDNF in specific forebrain regions.

**Methods:** Male Fisher F344c rats (120-150 days old) underwent acute REMD for 11-12 hours using a modified flowerpot technique. REMD animals were placed on small flowerpots (6.5 cm diameter) and apparatus control (AC) animals were placed on large flowerpots (12 cm) set in water. Home-cage control (HCC) animals were left in their control cages for the duration of the experiment. In situ hybridization was conducted with an antisense probe recognizing BDNF exon V. Slides were exposed for 72 hours and were statistically analyzed. BDNF peptide levels in the cortex, hippocampus and thalamus in six REMD and apparatus control rats were assayed using a QuantiKine BDNF ELISA kit. Differences were tested using Student-t tests.

**Results:** BDNF protein levels were reduced in hippocampus, but increased in cortex and thalamus following 12 hours of REM sleep deprivation (Figure). To determine the specific cellular regions undergoing changes in BDNF expression, in situ hybridization to BDNF mRNA was performed. In cortex, REMD and AC animals both had significantly higher BDNF mRNA levels compared to HCC in the auditory cortex, with marginally significant increases in the visual cortex. Decreases in BDNF in the hippocampus resulted from selective decreases in BDNF mRNA expression in the dentate gyrus of REMD animals. Similarly, specific increases in BDNF mRNA levels were found in the paraventricular nucleus (PVT) of the thalamus.

**Conclusions:** We found that acute REMD has distinct regional specific effects on BDNF expression. Most prominent was an increase in BDNF protein levels in the thalamus that resulted from a selective increase in BDNF expression in the PVN. REMD also caused a decrease in BDNF expression in the hippocampus that was confined to the dentate gyrus. Changes in BDNF in the cortex may have resulted from the experimental paradigm rather than from REM sleep deprivation specifically. These results suggest that short term REMD causes region-specific changes in BDNF expression and provide further evidence for an involvement of BDNF in sleep processes.

**References:**

Supported by NIH grant MH52226 to RMB and an NSF predoctoral fellowship to MJP.
A Case Series in Upper Airway Resistance Syndrome Masquerading As Periodic Limb Movements of Sleep

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Introduction: We present two cases of periodic limb movements of sleep (PLMS) originally diagnosed by conventional polysomnography (PSG). Both cases had a total arousal index of at least 15.2 and an Epworth Sleepiness Scale (ESS) of at least 6. Subsequent repeat PSG using a GaelTec (Hackensack, New Jersey) multiport esophageal catheter revealed upper airway resistance syndrome (UARS) in both cases. Evidence of PLMS resulting from UARS appeared in both cases.

Methods: First PSG: 12 channel PSG including EOG, EEG, chin EMG, snore lead, airflow (thermocouple), chest and abdominal excursion, EKG, leg EMG, oxygen saturation. Second PSG: Identical to first PSG but four-channel GaelTec multiport esophageal catheter used for esophageal pressure monitoring. Esophageal pressures required <-12 cm H2O fluctuation to be abnormal and all UARS related arousals coincided with significant preceding shifts in esophageal pressure.

Results: See Table

Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Snore</th>
<th>Ht</th>
<th>Wt</th>
<th>BMI</th>
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<th>PLMSAI</th>
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<td>166</td>
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</tr>
<tr>
<td>#2</td>
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<td>Y</td>
<td>68</td>
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<td>17</td>
<td>15.5</td>
<td>-26.5</td>
<td>18.7*</td>
<td>4.4**</td>
</tr>
</tbody>
</table>

Conclusions: PLMS may be subtle markers for UARS. Both patients snored. Failure to quantify arousals and investigate snoring and significant arousal indices further with esophageal manometry may miss an underlying diagnosis of UARS. Mistaking UARS for PLMS resulted in an ineffective treatment plan and fail to correct the causative sleep disorder breathing.

References:
(3) Chervin RD, Aldrich MS. Effects of esophageal pressure monitoring on sleep architecture. AJRCCM 1997;881-885.
as measurements of sleep quality. Dipping was evaluated using the change in systolic BP, diastolic blood pressure (DBP) and mean arterial pressure (MAP). Patients were classified as dippers and non-dippers based on a nocturnal drop in MAP > 10%. Differences between groups were evaluated by independent sample t-tests. Pearson correlation and linear regression were used to evaluate the association of sleep quality and BP dipping.

**Results:** There were no differences between dippers and non-dippers in body mass index, age, or respiratory disturbance index. Eighty-four percent were non-dippers. No difference was found between dippers and non-dippers in sleep quality. None of the sleep quality measures correlated with the measurements of dipping. In multiple regression analyses %SWS and arousal index each independently predicted only a small percent of the variance (about 10%) of nocturnal DBP dipping (t[37]=2.175 for %SWS and t[37]=2.516 for arousal index; p < 0.05).

**Conclusions:** The prevalence of non-dipping was very high in a population of untreated patients with mild to severe OSA. Nonetheless, sleep quality was unrelated to nocturnal BP dipping.

**References:**
(2) Leary AC, Donnan PT, MacDonald TM, Murphy MB: Physical activity is an independent predictor of the diurnal variation in blood pressure. J Hypertens 2000; 18:405-410.

Research supported by NIH grants HL44915, AG02711, AG08415, RR00827, HL36005 and K23 HL04056-01

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**Compliance of Obstructive Sleep Apnea (OSA) Patients (PTS) in a Randomized, Double-blind Trial: Continuous Positive Airway Pressure (CPAP) vs. Proportional Positive Airway Pressure (PPAP).**

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**Introduction:** Despite proven efficacy, many OSA pts have difficulty with acceptance of CPAP. PPAP is a unique mode whereby different gains can be set for inspiration and expiration causing airflow change within each breathing cycle in proportion to pt effort. See fig. 1. The primary aim of this study was to obtain compliance and pt response data. We hypothesized that PPAP would show a better compliance rate and reveal a similar pt reported clinical improvement (functional outcome sleep questionnaire and Epworth sleepiness scale).

**Methods:** Adult subjects with suspected OSA were excluded if they had previously known OSA, severe COPD, heart failure, or sleep disorders other than OSAS. All subjects underwent standard split-night polysomnography ( PSG) study and if the apnea/hypopnea index (AHI) was >10 and <100, subjects were first titrated with CPAP and then were optimized to the PPAP. They received instructions and were provided with equipment double blindly set to either PPAP or CPAP mode set according to the titration from the previous night PSG. After 30 days, pts returned with objective compliance data and repeat questionnaires.

**Results:** A total of 40 pts signed consent and all 27 (22 males) meeting criteria after the PSG returned. There were no significant (p>0.05) group differences at baseline with mean ±SD age (yr.) = 44 ± 11; body mass index (kg/m2) = 35 ± 5; sleep efficiency (%) = 75.4 ± 15.5; AHI (pre) = 44.2 ± 23.9; AHI (on CPAP) = 7.6 ± 11.9; or CPAP pressure (cmH2O) = 9 ± 1.3. Pts showed similar improvement by questionnaire scores. There were also no significant group differences for CPAP vs. PPAP in % days use = 91.8 ± 20.1 vs. 95.2 ± 6.1; % nts > 4 hrs use = 77.6 ± 24.8 vs. 80.5 ± 24; or hrs/nt = 5.6 ± 1.7 vs. 5.6 ± 1.4. Patients appeared to establish and maintain their compliance patterns by the first week of therapy. See fig. 2.

**Conclusions:** We conclude that PPAP therapy is as efficacious as CPAP but offers no distinct advantages in first time users. Pts in this trial showed a very high rate of compliance over 30 days and established their pattern after 1 week of use. A possible role for PPAP in OSAS pts who fail to tolerate CPAP is being explored.

**References:**

**Supported by Respironics Inc. Murrysville, PA.**

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Is the MSLT a Valid Measure of Sleepiness in All Apnea Patients?

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Introduction: Our research focuses on patients with obstructive sleep apnea with a complaint of daytime sleepiness but with an MSLT score well within the range of normal alertness. We attempt to identify factors which may contribute to this paradox of subjective sleepiness in the absence of objective sleepiness as measured by the MSLT. Several questions are addressed. Is this the sleep of this subgroup of patients more solidified? Do they have fewer apnea/hypopnea episodes? Awakenings? Arousals? etc. To answer these questions a “control” group of patients from the same population was selected who also complained of sleepiness at admission but, in contrast, had MSLT scores less than 10 Min. Thus we compared polysomnographic records of a subgroup of patients complaining of sleepiness but having an alert MSLT profile with another group of patients complaining of sleepiness and having a sleepiness MSLT profile.

Methods: The records of 68 patients (22 women) with mean MSLT latencies greater than 10 Min (“not sleepy”) were recovered from archival files (1997 through 1999) for patients with a complaint of EDS at admission and with a final diagnosis of obstructive sleep apnea. Records of 78 Control patients (22 women) were then selected with a similar RDI (>10) but with a mean MSLT <10 Min (“sleepy”). Insomnia was not a chief complaint of any patient. The age range varied from 22 years to 70 years (analysis of age indicated no significant difference but the short latency group was significantly heavier by 20 pounds).

Results: Comparisons of nighttime polysomnograph records between the two groups revealed several counterintuitive findings. As shown in Table 1, the sleep of the long sleep latency patients (LL) was significantly shorter (p<0.05) and also more disturbed than the short sleep latency patients (SL) on most of the measures. Yet their MSLT suggests that they are well within the normal alertness level of patients without sleep disorders.

Table 1

<table>
<thead>
<tr>
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<th>Short Latency</th>
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<tr>
<td>MSLT</td>
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</tr>
<tr>
<td>Total Sleep</td>
<td>335*</td>
<td>382</td>
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<tr>
<td>Sleep Eff</td>
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<td>%Awake</td>
<td>28*</td>
<td>18</td>
</tr>
<tr>
<td>%Stage 1</td>
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<td>23.3</td>
</tr>
<tr>
<td>%Stage 2</td>
<td>38</td>
<td>42</td>
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<tr>
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<tr>
<td>RDI</td>
<td>69.2</td>
<td>58.9</td>
</tr>
<tr>
<td>Awakening Index</td>
<td>10.5*</td>
<td>9.1</td>
</tr>
<tr>
<td>PLMS</td>
<td>13.5*</td>
<td>3.9</td>
</tr>
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</table>

*p < 0.05

Conclusions: These results are difficult to explain. One possibility is that this LL subgroup may be more sensitive to arousal inducing events. This may make it more difficult for these patients to meet the sleep criterion (16s?) required on the MSLT. Even though achieving the sleep onset criterion during the transition may be interrupted in all patients by an arousal, thus extending the sleep onset latency, the frequency of interruption may be greater in a subgroup of sensitive patients. Perhaps the use of a shorter sleep latency criterion would reveal greater similarities in sleepiness between the two groups. Due to existing scoring criteria, the MSLT, in some cases, may fail to detect daytime sleepiness.

The Relationship of Sleep Apnea Syndrome and Hypertension

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Introduction: Several epidemiological studies have shown that the prevalence of arterial hypertension is elevated in patients with Sleep Apnea Syndrome. Since the association between hypertension and OSA is well known, a direct relationship between SAS and hypertension has been questioned. The patients with SAS are often overweight, a condition that is also known to be associated with arterial hypertension. This study aimed to detect the influence of OSA on 24-h BP profile independently of age, obesity.

Methods: We used 24-hour ABPM and PSG simultaneously, and analyzed 56 patients who received no antihypertensive medicine or discontinuation treatment 14 days prior to the visit. The subjects were classified into normal (AHI<5 n=17), mild SAS (25>AHI>5 n=20) and moderate to severe SAS (AHI>25 n=19). We analysis the relationship between SAS and hypertension using correlation and covariant analysis.

Results: Correlation analysis showed that AHI was related to systolic/diastolic daytime BP (r=0.41, p<0.05/r=0.48, p<0.01), nighttime BP (r=0.61, p<0.01/r=0.60, p<0.01) and BP day-night/day ratios (r=0.49, p<0.01/r=0.39, p<0.05). Age was related to systolic/diastolic daytime (r=0.36, p<0.05/r=0.30, p<0.05) and systolic nighttime BP (r=0.30, p<0.05). BMI was related to diastolic daytime BP (r=0.27, p<0.05), systolic/diastolic nighttime BP (r=0.35, p<0.01/r=0.38, p<0.05) and BP day-night/day ratios (r=0.28, p<0.05/r=0.30, p<0.05). ANOVA analysis showed that AHI was independently related to systolic or diastolic daytime BP, nighttime BP and systolic or diastolic BP day-night/day ratio. When subjects were grouped according to AHI, daytime BP increased as AHI increases, SBP 127±6mmHg and DBP 83.7±9mmHg in normal, SBP 132.3±6mmHg and DBP 88.4±9mmHg in mild SAS, SBP 140.7±11mmHg and DBP 92.2±8mmHg in moderate to severe SAS. Compared to subjects with mild SAS or normal, BP night-day/day ratios were greater in patients with moderate to severe SAS (p<0.05).

Conclusions: SAS is associated with hypertension independent of the confounding factors of age and obesity. Nondipper is related to apnea severity. These alterations might contribute to the increased mortality in patients with severe SAS.

References:
439.J

Periodic Leg Movements and Sleepiness in Patients Evaluated for Sleep-Disordered Breathing

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Introduction: Most polysomnograms are performed because sleep-disordered breathing (SDB) is suspected, but periodic leg movements during sleep (PLMS) are frequent incidental findings, and their significance is not well understood. In a large clinical series, we tested for an association between the rate of PLMS per hour of sleep (PLMI) and one important outcome, the severity of daytime sleepiness.

Methods: We conducted a retrospective analysis of polysomnographic and Multiple Sleep Latency Test data from 1,124 adult, referred patients with suspected or confirmed SDB. Some data were also available on polysomnographic arousals (n = 321 subjects) [1], self-rated problem sleepiness (n = 873) [2], and subjective sleep propensity (Epworth Sleepiness Scale, n = 201) [3].

Results: Subjects’ mean age was 46 ± 12 (s.d.) years and 70% were male. The mean apnea and hypopnea index (number per hour of sleep, AHI) was 31 ± 33, the mean PLMI was 3.5 ± 6.4, and the mean sleep latency (MSL) was 7.3 ± 4.6 minutes. Increased PLMI was weakly associated with decreased sleepiness (higher MSL) (linear regression with outcome as square-root transform of MSL, \( R^2 = 0.004, p = 0.03 \)). Among 270 subjects with AHI > 45, PLMI was more strongly associated with reduced sleepiness (\( R^2 = 0.038, p = 0.001 \); Figure 1), whereas in remaining subjects no association was identified (\( R^2 = 0.000; p = 0.941 \); Figure 2). Among subjects for whom arousals were scored, rates of PLM-arousal complexes predicted less sleepiness (\( R^2 = 0.022, p = 0.008 \)); rates of PLMS without arousals did not (\( R^2 = 0.000, p = 0.808 \)). The PLMI showed no association with subjective problem sleepiness (logistic regression, odds ratio = 0.998, \( p = 0.878 \)) or sleep propensity (linear regression, \( R^2 = 0.009; p = 0.170 \)). Rates of PLM-arousal complexes and rates of PLMS without arousals both failed to show associations with problem sleepiness (n = 220 subjects with these measures available) and Epworth scores (n = 88) (all \( p > 0.10 \)).

Figure 1

Figure 2

Conclusions: Incidental PLMS in patients suspected or confirmed to have sleep-disordered breathing show no positive association with daytime sleepiness, and therefore appear unlikely to contribute to this problem. The association between PLMS and increased MSL among patients with more severe SDB is difficult to explain, but one speculation is that PLMS may destabilize breathing at the beginning of nap attempts and thereby prolong sleep onset. Our data also raise the possibility that increased sleepiness may reduce the likelihood of arousals when PLMS occur.

References:

440.J

Poor Sleep Quality is Associated with Hypercoagulability in Apneic and Non-apneic Subjects.

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Introduction: The prevalence of coronary artery disease is increased in obstructive sleep apnea (OSA)(1). Hemostatic disturbances in coagulant, anticoagulant, fibrinolytic and platelet activities play a pivotal role in the growth of artherosclerotic plaques. Previous investigations in our lab have suggested that increased coagulation activity in apneics as measured by increased levels of hypercoagulability markers is mediated by comorbid hypertension (2). The regulation of hemostatic factors may be affected by the autonomic system, which in OSA is highly disrupted. Using sleep architecture measures of poor sleep quality as indirect indicators of autonomic dysregulation, we speculated that disrupted sleep would be associated with higher levels of procoagulant molecules in the blood of apnea and non-apnea patients.

Methods: Ninety subjects (see Table 1 for demographics) were recorded all-night in the sleep laboratory. Blood samples were drawn into EDTA containing tubes the following morning at 8 am, centrifuged at
3000 g at 4°C for 10 min and frozen immediately at -70°C until analysis. Three molecular markers of a hypercoagulable state in plasma were measured with commercially available ELISA assays: thrombin-antithrombin III complex (TAT), fibrin D-dimer (DD), and von Willebrand factor antigen (vWF:ag). Standard correlations were performed between these values and selected polysomnographic measures of interest (sleep latency, minutes Stage 3 sleep, minutes Stage 4, and SWS minutes).

Results: Table 2 shows r statistics (p values in parentheses). Briefly, for all subjects, SWS was negatively correlated with vWF:ag; that is, this coagulation marker increased as SWS decreased. The negative association between stage 3 minutes and vWF:ag in apneics (RDI > 15/hr) likely contributed to that finding. Sleep latency showed a direct association with DD across all subjects that was apparently driven by the effects in apneic individuals. There were no significant correlations between TAT and either sleep measure.

Table 1
Subject demographic and clinical information

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<tr>
<th></th>
<th>All (n=90)</th>
<th>Apneic (n=51)</th>
<th>Non-apneic (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) [years]</td>
<td>47.8 ± 12.8</td>
<td>48.8 ± 15.4</td>
<td>45.8 ± 9.9</td>
</tr>
<tr>
<td>Body mass index [kg/m^2]</td>
<td>30.6 ± 5.4</td>
<td>30.6 ± 5.4</td>
<td>30.5 ± 5.4</td>
</tr>
<tr>
<td>Respiratory disturbance index (mean ± SD)</td>
<td>86.3 ± 35.7</td>
<td>52.5 ± 35.7</td>
<td>65.4 ± 35.7</td>
</tr>
<tr>
<td>Hypertensive [DBP&gt;100mmHg and/or DBP&lt;90 mmHg]</td>
<td>60/30</td>
<td>39/19</td>
<td>21/11</td>
</tr>
<tr>
<td>Smoker [yes/no]</td>
<td>27/63</td>
<td>18/35</td>
<td>9/28</td>
</tr>
<tr>
<td>TAT (median, inter-quartile range) [ng/ml]</td>
<td>8.8 (5.2-15.6)</td>
<td>7.8 (5.2-14.4)</td>
<td>10.3 (6.8-15.6)</td>
</tr>
<tr>
<td>DD (median, inter-quartile range) [ng/ml]</td>
<td>341 (223-536)</td>
<td>331 (195-473)</td>
<td>454 (278-648)</td>
</tr>
</tbody>
</table>

Conclusions: As hypothesized, the two procoagulant molecules vWF:ag and DD were positively related to sleep measures of increased sympathetic nerve activity: sleep stages and sleep onset latency. Of interest, these associations were driven mainly by the apneic subjects. It is well known that arousal and adrenergic infusions may increase vWF:ag, D-dimer, and a variety of other hemostatic molecules. In addition, vWF:ag and DD are predictive for coronary events in apparently healthy individuals as well as patients with coronary artery disease. Along these lines, our results suggest that the sympathetic burden and general hypercoagulability may disrupt sleep in apneic individuals. There were no significant correlations between these values and selected polysomnographic measures of interest (sleep latency, minutes Stage 3 sleep, minutes Stage 4, and SWS minutes).

References:


Research supported by CA23100, HL36005, HL44915, RR00827

441.J

Homocysteine Total Plasma Levels in Obstructive Sleep Apnea

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Institute of Neurology "C. Mondino". Pavia

Introduction: Increased plasma levels of homocysteine(Hcy) represent an independent risk factor for thrombotic vascular diseases(1). Hyperhomocysteinemia can also be associated with a wide range of neurological and/or psychiatric manifestations,including cognitive dysfunction, personality and mood disorders. Vascular diseases and such manifestations are frequently encountered in patients suffering from Obstructive Sleep Apnea (OSA). Patients with OSA may be at risk of hyperhomocysteinemia for various reasons.In particular, the impaired production of nitric oxide(2) and deficient vitamin B12 and folate status resulting from an unbalanced diet- might interfere with the metabolism of Hcy. Previous studies(3) indicate that OSA patients with cardiovascular morbidity have higher plasma levels of Hcy than OSA patients without cardiovascular morbidity or healthy controls. The present study is a prospective survey aimed at investigating the plasma levels of Hcy in OSA patients and controls, selected so as to minimize the coexistence of confounding factors for hyperhomocysteinemia.

Methods: Patients and controls were selected from the subjects referring for sleep disorders, to the Sleep Unit of the Institute of Neurology “C. Mondino” of Pavia. In each subject, OSA was diagnosed or ruled out on the basis of clinical and full-night polygraphic findings. Thirty-five subjects (30 M and 5 F: mean age 50.3 years, sd 10) received a definite diagnosis of OSA and were enrolled. Twenty subjects (18 M, 2 F: mean age 51 years, sd 8.9), for whom OSA was ruled out, served as controls. Patients and controls were similar in terms of body mass index and daily habits, such as alcohol consumption and smoking, which both were of moderate degree. Subjects with cardiovascular vascular diseases, severe hypertension, diabetes mellitus, hyperthyroidism, renal insufficiency, alcohol abuse or subjects who were on diet or who were assuming medications were excluded. After giving informed consent, all participants underwent a venous blood sampling, performed between 8 and 9 a.m. after an overnight fast. Plasma Hcy levels were measured using high-performance liquid chromatography (HPLC) with fluorometric detection. We also measured the serum concentrations of folic acid, vitamin B12 and creatinine. In addition, subjects with Hcy concentrations above the upper normal limit of 15 micromol/L underwent genetic testing, including that for the detection of known mutations in the gene encoding for the enzyme 5,10-methylene tetrahydrofolate reductase (MTHFR). whose deficiency causes hyperhomocysteinemia. The Mann Whitney U-test was used to evaluate differences in the mean values of Homocysteine, folate and Vit B12 plasma levels, daily alcohol consumption of the patients and controls.

Results: OSA patients showed a slight, non-significant increase in the mean values of plasma Hcy, compared to controls(11.6 micromol/L, sd 8 versus 9 micromol/L, sd 3). Analogously, no significant differences were found in the mean serum levels of folate and vitamin B12 (5.4 ng/ml, sd 2.1 versus 4.2 ng/ml, sd 1 and 459.8 ng/ml, sd 159 versus 432.5 ng/ml, sd 175 respectively). However, 6 OSA patients (18%) showed Hcy levels above 15 micromol/L (mean 24.8 micromol/L, range 16-55), while no control subject exceeded such limit. These patients were slightly older than the others OSA patients (58 years, sd 10 versus 50 years, sd 8), respectively. The difference was not statistically significant. They did not differ significantly from the other OSA patients in terms of nocturnal oxygen desaturation indexes (ODI 42 vs 39; Proportion of Total Sleep Time with HbSaO2 below 90%: 34.7% versus 26.4%), mean plasma levels of folate and vitamin B12 (4.1 ng/ml, sd 2 versus 5.6 ng/ml, sd 2; 430.8 pgr/ml, sd 200 versus 455 pgr/ml, sd 153, respectively), alcohol consumption, smoking habit and body mass index. None of these 6 OSA
patients had mutations in the MTHFR gene.

Conclusions: Our data show a prevalence of 18% of hyperhomocysteinemia in OSA patients without cardiocerebrovascular morbidity or other conditions known to correlate with high levels of plasma Hcy. The hyperhomocysteinemia observed in a sub-group of OSA patients is not ascribable to deficient folate or vitamin B12 or to the derangement of Hcy metabolism resulting from mutations in the MTHFR gene. This sub-group of patients does not show a pattern of nocturnal HbSaO2 desaturation significantly more severe than that of the others OSA patients. Thus, our data support the hypothesis of an association between OSA and mild hyperhomocysteinemia, although the mechanisms underlying such association remain obscure. Cross-sectional and longitudinal investigations, as well as further biochemical and genetic investigations, will be needed to clarify the real prevalence, significance and causative mechanisms of hyperhomocysteinemia in the OSA syndrome.

References:

442.J

Digital Recording and Analysis of Esophageal Pressure for Obstructive Sleep Apnea/Hypopnea

(1) Department of Otolaryngology, Tohoku University School of Medicine, (2) Department of Orthodontics, Tohoku University School of Dentistry

Introduction: Esophageal pressure (Pes) was recommended as having good to excellent agreement with the reference standard for methods of measurement (grade A) and for quality of evidence (level 1) in adult sleep related breathing disorders by the report of the AASM task force in 1999. However, standard digital polysomnography usually does not include detailed Pes analysis. Analogue analysis of the Pes is usually so complicated that only a few sleep laboratories are doing Pes recording for night sleep studies. Using a Power Lab system, we digitally recorded the Pes in obstructive sleep apnea/hypopnea patients in non-REM sleep.

Methods: Pes was recorded all night with a micro-tip type pressure transducer (MPC500: Millar, Houston, TX, USA) which was inserted 35 cm from the nostrils. Signals from the transducer were amplified by a signal-conditioner and converted by a 4-channel A/D converter (Power Lab 4k: Power Lab, Gladstone, Australia). Simultaneously, all patients had polysomnography (Alice 3: HealDyne Technologies, Marietta GA, USA) with a standard technique. Analysis of Pes parameters was performed using Chart software and statistical Excel software.

Results: Sixty obstructive sleep apnea/hypopnea patients including 4 patients with upper airway resistance syndrome were evaluated in this study. The patients’ ages ranged from 25 to 70 years, with a mean of 48.8 years. The mean body mass index was 26.9 kg/m2. The patients’ apnea/hypopnea index (AHI) ranged from 2.9 to 71.8/hour, and the mean AHI was 36.2/hour. The mean nadir end-apneic Pes swing (Nadir Pes) ranged from -10 to -115 cmH2O, with a mean of -48.6 cmH2O. Pes parameters, such as the Nadir Pes, the mean ratio of maximal Pes swing to apnea duration (RPes) (Krieger 1997), the mean area of the Pes (Pes Area), and the percentage of < -15 cmH2O (%15Pes) were digitally analyzed. These four indexes were closely correlated with each other. These Pes parameters and their correlation data with sleep parameters were elucidated.

Conclusions: Digital recording of the Pes with a PowerLab system is easy to perform for clinical sleep centers, and it provides a detailed Pes analysis in obstructive sleep apnea/hypopnea patients.

References:

443.J

Modafinil Improves Alertness and Driving Simulator Performance in Sleep-Deprived Mild Obstructive Sleep Apnoea (OSA) Patients

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Introduction: Mild OSA is a very common form of sleep disordered breathing, affecting 10–20% of the population, which leads to excessive daytime sleepiness and impaired function. Patients with OSA are at a higher risk of involvement in motor vehicle accidents and perform worse on driving simulator tasks than controls. Mild OSA commonly remains untreated due to the relatively inconvenient nature of current treatments. Modafinil is a novel wakefulness-promoting drug with few side effects which improves subjective alertness and performance on simple vigilance tasks. This single dose study assessed the use of modafinil for the relief of the daytime symptoms of mild OSA when combined with partial sleep deprivation conditions often experienced by professional drivers.

Methods: Eight patients with mild OSA (RDI = 5–15) took part in a randomised, double-blind, crossover, placebo-controlled protocol. Testing consisted of the 30 minute Neurobehavioural Assessment Battery (in Dinges, U. Penn, USA) followed by a 30 minute simulated night-time, rural drive (AUS Ed Simulator). Waking electroencephalography (EEG) was recorded concurrently with driving simulator runs. Baseline performance was recorded at 2100 and subjects were put to bed at 2300. Sleep was restricted to 4 hours time in bed. Subjects were woken at 0300 and either 200 mg modafinil or a placebo was administered. Further testing took place at 0500 and 0900. Subjects returned after a one week washout period for the crossover night.

Results: Modafinil significantly counteracted increases in both subjective and objective measures of sleepiness due to sleep deprivation. Subjects on modafinil had a 26% lower effort to Stay Awake Survey score than subjects on placebo at 0500 and 0900 (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05). In addition, modafinil decreased frontal EEG power in the alpha band (p < 0.05) and beta band (p < 0.05).
0.05). However, these effects had diminished by 0900, 6 hours after drug ingestion. Interestingly, modafinil appeared to impair advanced mathematical calculations at 0500, with improvements on the Serial Addition / Subtraction Task in placebo subjects not seen after modafinil administration.

Conclusions: The results of this trial suggest that peak plasma concentrations of modafinil, as achieved around its tmax of 2 hours, are required to counteract the combined effects of mild OSA and partial sleep deprivation on vigilance. Thus, repeated doses of modafinil may be necessary to maintain improvements in daytime performance in this population. Further studies are required to investigate possible modafinil-induced deteriorations in advanced cognitive performance and to test prolonged use of modafinil in OSA patients.

Partial support provided by the Motor Vehicle Accidents Authority of New South Wales

444.J

Modafinil X Placebo Effects on Residual Excessive Diurnal Sleepiness (EDS) in Obstructive Sleep Apnea Syndrome (OSAS) Patients Treated With Nasal CPAP

Bittencourt LA,1 Rueda AD,2 Palombini LO,2 Guilleminault C,2 Tufik S1 (1) Sleep Institute - Department of Psychobiology - UNIFESP - Sao Paulo, Brazil, (2) Sleep Clinic - Stanford University - Palo Alto, USA

Introduction: Excessive diurnal somnolence (EDS) in OSAS patients is one of the main factors responsible for traffic accidents and cognitive deficits (1-2). Some OSAS patients treated with nasal CPAP still show EDS, despite exclusion of other conditions (inadequate CPAP pressure, other diseases-induced EDS, sleep deprivation, use of alcohol and hypnotics) (3). Modafinil, a new drug, has been used for its action as a vigilance enhancer, with minor side effects. The goal of this study was to run a double blind placebo controlled study of the activity of Modafinil on residual sleepiness in OSAS patients treated with nasal CPAP.

Methods: Twenty patients, mean age 52 ± 6 years, BMI 32.9 ± 5.8 kg/m2 were involved in the following protocol: 1) Investigation of abnormal breathing during sleep - patients underwent clinical interview and examination, responded to Epworth Sleepiness Scale (ESS) and Visual Analogic Scale (VAS) (daytime sleepiness). Then, subjects underwent nocturnal polysomnography, Maintenance of Wakefulness Test (MWT). 2) Patients were titrated with nasal CPAP during polysomnography. 3) Follow up (at last 1 month) included clinical interview (ESS), polysomnography to confirm OSAS treatment (RDI < 5) and persistence of excessive sleepiness despite regular use of CPAP (pressure at the mask) 4) a) 7 days single blind placebo intake; and b) double blind placebo/ Modafinil (300 mg) intake for 21 days. 5) Clinical evaluation, ESS, VAS, nocturnal polysomnography and MWT at the end of the first week and on day 28. Analyses were performed (Student t test) comparing clinical subjective reports, ESS, VAS, nocturnal polysomnography and MWT between baseline and placebo/Modafinil values and between placebo and Modafinil patients.

Results: Side effects: no patient dropped out of the study. During 7-day single blind placebo period, 6 patients reported headache, irritability, anxiety and epigastralgia. During the double placebo/ Modafinil period, 6 patients reported headache, irritability, drowsiness and nausea. Positive effects: Comparison between basal and Modafinil values showed reduction of ESS (p=0.017), improvement on VAS (p=0.017) and increased sleep latency on MWT (p=0.048). The latter effect was obtained in the comparison between placebo and Modafinil (p=0.04).

Conclusions: There was a subjective and objective improvement of daytime sleepiness in Modafinil patients compared to baseline values and to placebo patients.

References:

Supported by a Grant from L. Lafon Laboratory and AFIP 445.J

Evaluation of Obstructive Sleep Apnea (OSA) Patients With CPAP Prescription Submitted to an Educational Program in the CPAP Clinic

Rueda AD, Bittencourt LA, Takemoto K, Tufik S Sleep Institute - Department of Psychobiology - UNIFESP- Sao Paulo, Brazil

Introduction: CPAP is the treatment of choice for OSA and its side effects are generally of low intensity and severe complications are rare (1). However, patients who complain of these effects will probably use less the apparatus (2). A training program for CPAP use increases the hours of use and, as a consequence, improves OSA symptoms, mood and cognitive function (3). The purpose of the present study was to evaluate patients who were submitted to an educational program to use the device.

Methods: One hundred and one patients who began to use CPAP, were involved in an educational program in the CPAP clinic between November of 1997 and August of 2000. The protocol was followed on days 7, 15, 30, 60 and 90, and from then on, every 6 months: 1) Clinical interview and examination, when a trained nurse explained how to use the CPAP, 2) Epworth Sleepiness Scale (ESS); 3) CPAP Clinic Questionnaire (Stanford University); 4) Reports of side effect complaints; 5) CPAP time use check-up (by pressure at mask). Analyses (Student t test) were performed comparing regular users (timer showing ≥ 5 hours/night) with irregular users (timer showing < 5 hour/night).

Results: The mean age was 52.1 ± 11.7 years, BMI 32.0 ± 5.9 kg/m2, 85% of men and 15% of women. On day 90, 24% dropped from CPAP treatment and/or from the clinical follow-up. Of the 77 patients who continued in the program, 62% presented improvement of the OSA symptoms. The ESS was decreased from 19.6 ± 19.0 to 7.4 ± 4.3. All patients complained of mask-related side effects at some time during the study. No correlation (Pearson’s Correlation) between the objective and subjective hours of use was obtained (r=0.28). Comparison between regular (n=31) and irregular (n=46) users did not reveal differences of age (p=0.74), BMI (p=0.44), basal AHI (p=0.72), CPAP pressure (p=0.60) and pre-CPAP ESS (p=0.43). Only post-CPAP ESS differed between regular (7 ± 5) and irregular users (10 ± 6) (p=0.04).

Conclusions: Despite CPAP efficacy, only 76% of the patients remained under treatment after 90 days, of which 40% presented a good compliance. The objective evaluation about the length of CPAP use did not correlate with the subjective one. Improvement of Excessive Daytime Somnolence (EDS) after CPAP was greater in regular users.
Decreased Nocturnal Testosterone Secretion in Patients with Obstructive Sleep Apnea (OSA)

(1) Endocrine Institute, Haemek Medical Center, Afula, Israel., (2) Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 32000, Israel.

Introduction: Recently we have demonstrated that in normal young adult men, the sleep-related rise in serum testosterone levels is associated with the appearance of the first REM sleep episode(1). Fragmented sleep disrupted the testosterone rhythm with considerable attenuation of the nocturnal testosterone rise. We have also shown that patients with severe OSA had decreased libido and sexual activity (unpublished data). The aim of the present study was to evaluate the diurnal testosterone rhythm in patients with severe OSA who also suffer from fragmented sleep.

Methods: Ten patients (aged 46.1±6.7 yrs) and eight controls (aged 46.3±7.9 yrs) were included in the study. Serum testosterone levels were determined every 20 min between 19:00-07:00h with simultaneous sleep recordings between 22:00-07:00h.

Results: Patients had a mean±SD RDI of 52.6±16.5/h (vs. 7.0±0.8 in controls), Sa02 of 83.0±6.4 (vs. 89.3±2.4) and BMI of 30.5±4.7 kg/m2 vs. 26.0±2.1. Mean nocturnal testosterone levels and the area under the curve (AUC) were significantly higher in controls vs. OSA (see Table). The mean testosterone levels in 6/10 OSA patients were below the lower normal adult male range of 10.0 nmol/L.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline level (nmol/L)</th>
<th>Baseline level (mmol/L)</th>
<th>Mean nocturnal level (nmol/L)</th>
<th>AUC (mmol x h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>10.1±3.0</td>
<td>24.2±1.3</td>
<td>7.5±3.5</td>
<td>9.4±2.8</td>
</tr>
<tr>
<td>CONTROL</td>
<td>17.9±4.4</td>
<td>43.0±5.2</td>
<td>14.7±4.0</td>
<td>16.3±3.9</td>
</tr>
</tbody>
</table>

Conclusions: Our results show that the nocturnal increase in testosterone secretion is blunted in OSA patients. Hypoxia, sleep disruption, or both, may be the cause of decreased testosterone concentrations in these patients. Further studies are needed to clarify whether correction of sleep apnea will normalize testosterone secretion in OSA patients.

References:
(2) Buena F et al. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. Fertil Steril 1993, 59:1118-1123.

CPAP (Continuous Positive Airway Pressure) Follow-Up Polysomnography

Schutte SL, Menig K, Breuninger W
Jefferson Medical College of Thomas Jefferson University Hospital, Philadelphia, Pennsylvania

Introduction: Follow-up polysomnography (PSG) is indicated for the assessment of sleep apnea treatment efficacy after: (1) substantial weight change (2) surgical (ENT) treatment (3) oral appliance treatment (4) symptoms persist despite treatment with CPAP. The American Sleep Disorders Association’s Practice Parameters for the Indications for Polysomnography and Related Procedures (Sleep, vol. 20(6), 1997, page 409) states that “follow-up polysomnography or a cardiorespiratory study is not routinely indicated in patients with CPAP whose symptoms continue to be resolved with CPAP treatment.”

Objective: To assess treatment changes when: (1) routine CPAP PSG was performed (2) CPAP PSG was performed because of clinical changes (including substantial weight loss or gain, ENT surgery or dental appliance treatments, or any sleep-related complaints)

Methods: PSG data between 1990 and 1996 from 261 patients (185 males and 76 females) were retrospectively analyzed. These 261 patients had baseline and follow-up (f/up) data (range 2 to 9 f/up studies). The mean time between the initial titration and the first f/up was ½ year, and the mean time between other studies was 1.5 years. Data were analyzed to determine treatment changes (change of CPAP/BIPAP, oxygen, or other treatments) on patients undergoing routine or indicated studies. Study type (routine or indicated) was determined by review of clinical charts. Indicated studies included the presence of any sleep-related complaint (any CPAP complaint, any nocturnal symptoms such as awakenings, persistent sleepiness, any change of medical conditions), change of weight < or >20 lbs., or ENT or dental treatments.

Results: Of 577 total f/up PSGs (Table 1), 52% (298) were routine and 48% (279) were indicated f/up PSGs. Of patients undergoing routine f/up studies, 37% required a treatment change. Of patients undergoing indicated f/up, 59% required a treatment change. Increased CPAP/BIPAP was the most common treatment change for both groups (Table 2). For patients requiring increased CPAP, the mean CPAP increase was 2.5 cm/H2O for the routine group and 2.6 for the indicated group (p=ns). For patients undergoing decreased CPAP, the mean CPAP decrease was -2.0 for the routine group and -4.8 for the indicated group (p=0.001).

Table 1

<table>
<thead>
<tr>
<th>F/up PSGs</th>
<th>Routine f/up PSG</th>
<th>Indicated f/up PSG</th>
<th>Number of f/up studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment Change</td>
<td>181 (63%)</td>
<td>115 (41%)</td>
<td>303</td>
</tr>
<tr>
<td>Treatment Change</td>
<td>111 (37%)</td>
<td>164 (59%)</td>
<td>271</td>
</tr>
<tr>
<td>(p&lt;0.001)</td>
<td>291 (100%)</td>
<td>279 (100%)</td>
<td>577</td>
</tr>
</tbody>
</table>
Conclusions: Over 1/3 of patients undergoing routine follow-up studies required treatment changes, which otherwise would have been missed. These patients had no subjective symptoms. Like other chronic medical disorders, the course of sleep apnea may be fluctuating or progressive, requiring follow-up studies on asymptomatic and asymptomatic patients. Routine follow-up PSG may be medically necessary.

448.J
Evaluation of the Cyclic Alternating Pattern Behavior in Patients with a Slightly Augmented Apnea-Hypopnea Index.
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Sleep Institute - Department of Psychobiology - UNIFESP, Sao Paulo, Brazil

Introduction: The Cyclic Alternating Pattern (CAP) described by Terzano et al. consists of a periodic activity found during NREM sleep with two distinct electronecephalographic patterns: phase A, related to a higher activation and susceptibility to awakenings, and phase B, period of smaller reactivity. These two patterns are organized in a biphasic manner. The CAP is associated to physiological fluctuations on the awakening level and modulation, being accompanied by autonomic effects. Few studies describe CAP behavior in OSAHS, especially in patients who present a slight increase in the index of respiratory disorders and none of them did correlate it to snoring and to the Epworth Sleepiness Scale. Our objective was to identify and quantitatively evaluate CAP in patients with AHI ≤ 15/hour and to correlate the index with snoring and Epworth Scale.

Methods: Twelve patients were retrospectively studied, of which 11 were men and 1, woman, submitted to a nocturnal polysomnography in 1997. The visual analysis was performed by the observer, counting the total CAP time and the respective length of each phase, calculating the total percentage in regard to sleep time and to each one of the stages, within the average values reported in the literature.

Results: Statistical analysis allowed the inference of positive correlation between total and stage 2 CAP percentage and AHI, snoring and the Epworth Sleepiness Scale. Our objective was to identify and quantitatively evaluate CAP in patients with AHI ≤ 15/hour and to correlate the index with snoring and Epworth Scale.

Conclusions: We concluded that: 1. Total CAP percentage is placed within the average values reported in the literature. 2. There is a positive correlation between total and stage 2 CAP percentage and the number of micro-arousals, leading to the question about the existence of common controlling mechanisms of arousal threshold; 3. Further studies are necessary to better grade a positive correlation between CAP and the other variables.

References:

449.J
Comparison of PSG and PAP (Positive Airway Pressure) Compliance Characteristics Among Patients From an Urban Public vs. Academic Hospital
Herdegen JJ, Clark LJ
Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Introduction: The sleep apnea syndrome (SAS) affects approximately 2-4% of the general U.S. population. However, the prevalence and severity of this condition shows variability. Indigent populations served by public and county hospitals often present with more advanced disease processes and appear to represent a group at high risk for SAS. This report provides the first known comparative study of two populations, one from a public and one from an academic institution, referred for SAS evaluation and studied in the same laboratory.

Methods: Clinical data from two urban hospitals located within one block of each other, Cook County Hospital and Rush Medical Center, was reviewed. Only data from patients referred to a specialty sleep disorder clinic, identified to have significant SAS, and prescribed PAP treatment were included in this review. Both groups underwent an identical sleep history with polysomnography performed at a single site using standardized scoring criteria to minimize variation of sleep study characteristics. Patients were provided identical PAP equipment and instruction by the same medical equipment vendors (utilizing downloadable compliance machines). Follow-up at regular intervals was provided at both institutions. Comparative statistics utilized a two-tailed t-test for independent samples or chi squared analysis.

Results: The comparative demographic, sleep study, and PAP usage data are presented in the table below:

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Academic (n=246)</th>
<th>Public (n=154)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.2 yrs</td>
<td>45.8 yrs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>39.8</td>
<td>47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>63% male</td>
<td>59% male</td>
<td>NS</td>
</tr>
<tr>
<td>Married</td>
<td>51% married</td>
<td>24% married</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epworth</td>
<td>13.3</td>
<td>15.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>47.8</td>
<td>74.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Sat (Sao)</td>
<td>74%</td>
<td>56%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Best PAP</td>
<td>10.5 cm H2O</td>
<td>12.9 cm H2O</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAP use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>4.8 hrs/day</td>
<td>3.8 hrs/day</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAP use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>4.8 hrs/day</td>
<td>4.1 hrs/day</td>
<td>NS</td>
</tr>
<tr>
<td>PAP use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td>5.0 hrs/day</td>
<td>5.0 hrs/day</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusions: Patients seen in an urban, public hospital display a much greater severity of SAS compared to an urban, academic hospital. Initial PAP use was lower in the public hospital patients but improved over time, possibly due to the intensiveness of follow-up and support. This unique comparative study indicates that a greater level of awareness and education in diagnosing and treating sleep-disordered breathing is required for patients seen at public hospitals. The degree of disease severity warrants increasing efforts to target this high-risk population for SAS screening which may lead to improved health care in this under-

Research supported by ResMed Corporation, Respironics

**450.J**

Comparison of Peripheral Arterial Tonometry and Invasive Blood Pressure in Obstructive Sleep Apnea

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**Introduction:** A new sensor was recently introduced which reflects peripheral circulatory responses to respiratory breathing (1). This peripheral arterial tonometry (PAT) sensor selectively measures the arterial component of finger volume changes accompanying the pulse wave. These changes are an integral part of the hemodynamic response to obstructive sleep apnea related arousal. In order to directly relate these changes to hemodynamic changes we compared PAT and invasive blood pressure.

**Methods:** 20 patients with obstructive sleep apnea (AHI>20) and arterial hypertension according to WHO criteria (> 140 / 90 mmHg) were recruited for the comparative study. After an initial sleep study used to confirm the diagnosis of sleep apnea a second sleep study was performed with the additional recording of invasive arterial blood pressure and the PAT signal. Attenuations in the amplitude of PAT signal by 50% were counted visually. Attenuations were classified as isolated, or synchronized with a drop in oxygen saturation, or with an increase in heart rate. Evaluation of blood pressure was done beat by beat and systolic, diastolic and mean values were derived.

**Results:** Patients’ age was 56.6 ± 9.2 years. BMI was 33.7 ± 5.7. Evaluation of polysomnography resulted in an AHI of 27 ± 18 events per hour. This corresponded to 212 ± 148 respiratory events per night. The total number of attenuations in the PAT signal summed up to 260 ± 113 events. 205 ± 112 attenuations in the PAT signal were accompanied by oxygen desaturation and heart rate increases. Invasive blood pressure swings reflected apnea and hypopnea events (fig. 1). Small blood pressure swings at a short time scale also reflected snoring. The PAT signal did follow apnea related blood pressure changes in a complex way. The initial decrease in blood pressure at the beginning of an apnea was reflected as an increase in the PAT signal. The increase in blood pressure during an apnea often had no, or minor effects of the PAT signal. The final large increase of blood pressure during hyperventilation was consistently well mirrored by a distinct drop in the PAT signal.

**Conclusions:** The PAT signal is a good marker for arousal with concomitant cardiovascular changes. The correlation between AHI and attenuations in the PAT signal did not confirm a uniform relation between apneas, hypopneas and cardiovascular arousals. The direct comparison with blood pressure indicates that the PAT signal reflects changes in sympathetic tone and stroke volume. Local vascular tone changes also influence the signal, so a direct relation between PAT and stroke volume cannot be expected. The fractions of these contributions remain unclear and may vary with time, also dependent on sleep stage. The PAT signal with the current conditioning cannot be used to predict changes in blood pressure in patients with sleep apnea.

**References:**

**451.J**

Intermittent Hypoxia Elicits Differential Responses in the CAI and CA3 Regions of the Rat Hippocampus: A Proteomic Analysis

Gozal E, Klein JB, Pierce WM, Scherzer JA, Sachleben LR, Cai J, Gozal D
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**Introduction:** Obstructive sleep apnea is characterized by intermittent hypoxia (IH) during sleep, and leads to significant neurobehavioral deficits and apoptosis within the CAI region, but not the CA3 region of adult rats. We hypothesized that IH will elicit differential changes in a subset of proteins within the 2 hippocampal regions.

**Methods:** To identify proteins showing major IH-induced expression changes, proteomic analysis was performed in CAI and CA3 tissue punches of Sprague-Dawley young male rats exposed to either room air (RA) or 6 hours IH (1146). Tissue lysates corresponding to 4 animals/group were resolved by 2-D high resolution gels, and proteins identified after in-gel trypic digestion and peptide mass fingerprinting by MALDI mass spectrometric analysis. Digital densitometric analyses of identified proteins was performed followed by statistical comparisons.

**Results:** Sixty different proteins have thus far been identified by peptide mass fingerprinting. Three major groups of proteins displayed differential changes in expression in CAI and CA3. The expression of anti-oxidant proteins, metabolic enzymes and cytoskeletal proteins was altered by IH.

**Conclusions:** Proteomic analysis of the hippocampus reveals that IH exerts disparate effects on proteins involved in regulation of cellular metabolism, anti-oxidant pathways, the cytoskeleton and cell survival in the CAI (vulnerable) and CA3 (tolerant) regions.

**Research supported by National Institutes of Health HL-66358, HL-65270, HL-63912, P20 RR-15576, and the American Heart Association AHA- 005442N.**
Expression of Monocarboxylate Transporters in Rat Heart and Brain During Chronic Intermittent and Sustained Hypoxia

Gozal E,1,2 Bedford AM,2 Bonen A,3 Sachleben LR,1,2 Schurr A,2 Gozal D1,2
(1) Kosair Children’s Hospital Research Institute, (2) Departments of Pediatrics, Pharmacology and Toxicology, and Anesthesiology, University of Louisville, (3) Department of Kinesiology, University of Waterloo

Introduction: A higher prevalence of sleep-disordered breathing (SDB) is found among patients with stroke, hypertension and myocardial infarction, suggesting that the characteristic pattern of intermittent hypoxia in SDB may contribute to such morbidities (1). In established hypoxic ischemic models of neural and cardiac tissue, lactate is critical for recovery of cellular function upon reoxygenation (2). During hypoxia, lactate is released and taken up by cells via monocarboxylate transporters (MCTs) and used as the major energy substrate (lactate shuttle) (3).

Methods: To assess how hypoxia affects MCTs expression in neural and cardiac tissue, rats were exposed to 1, 3 or 7 days of intermittent (IH) or continuous hypoxia (CH). IH consisted of alternating room air and 10% O₂ either every 90 sec, while in CH, 10% O₂ was sustained throughout the duration of the exposure. Cardiac (left ventricle) and brain cortical tissues were harvested and snap frozen in liquid nitrogen. Tissues were then processed for assessment of either protein expression by western blot using well characterized antibodies against MCT-1, MCT-2, and MCT-4, or for mRNA expression using northern blots.

Results: Exposure to CH enhanced MCT-1 and MCT-2 in rat brain, contrasting with a reduced expression following IH. Similarly, MCT-1 was up-regulated by CH but not by IH in cardiac tissue, whereas MCT-4 expression was unchanged. In a preliminary experiment, Northern blots revealed increased MCT-1 mRNA in both CH and IH (n= 1).

Conclusions: Taken together, these preliminary data suggest that failure to up-regulate MCTs in response to intermittent hypoxia may lead to an inefficient lactate shuttle, and could therefore increase the susceptibility of SDB patients to stroke and cardiovascular disease.

References:

Research supported by National Institutes of Health HL-65270, HL-63912, HL-66358, P20 RR-15576, and the American Heart Association AHA-0050442N.

Sleep Disorders in a Military Population

Kryger MH,1 Pouliot Z, Peters M,2 Neufeld H,3 Delaive KE
(1) University of Manitoba, Section of Respiratory Diseases, (2) Sleep Disorders Center, St. Boniface General Hospital

Introduction: Military personnel are presumed to be physically fit and therefore less prone to obesity and sleep disorders. Because of the proximity of a military base to our sleep disorders center, we have received referrals and wondered what sleep problems lead to referral and consultation from the military.

Methods: We reviewed the records of 50 Canadian military personnel on active duty referred by physicians employed by the Department of National Defense to the Sleep Disorders Centre over a three year period. All personnel underwent comprehensive overnight polysomnography and physician interview.

Results: The group consisted of 43 males and 7 females, mean age 40.7 ± 7.4(SD) years, mean Body Mass Index (BMI) (kg/m²) 30.1 ± 5.7, and mean Epworth score 11.2 ± 4.6. Thirty-five of the 50 patients reviewed (70%) were referred to rule out a sleep breathing disorder. Eleven of the 50 (22%) were referred to rule out a movement disorder. Four of the 50 (8%) were referred because of excessive daytime sleepiness or insomnia. Of the group referred to rule out a sleep breathing disorder, 71% were diagnosed with obstructive sleep apnea (OSA), 23% were diagnosed with OSA and restless legs syndrome/periodic leg movements in sleep (RLS/PLMS), and 6% were diagnosed with PLMS. Demographics for the group found to have OSA are as follows: mean age 40.9 ± 7.1, mean BMI 31.5 ± 6.2, mean Epworth score 11.1 ± 4.2, mean apnea index (AI) 21.9 ± 22.4. Of the group referred to rule out a movement disorder, 8/11 were diagnosed with RLS/PLMS, 2/11 were diagnosed with RLS and OSA, and 1/11 was diagnosed with alpha-delta sleep. Of the group referred for excessive daytime sleepiness (EDS) or insomnia, 2/4 had RLS/PLMS, 1/4 had upper airway resistance syndrome (UARS), and 1/4 had idiopathic hypersomnolence.

Conclusions: The military personnel we evaluated who had OSA were obese. They were substantially younger (mean age = 40.9 ± 7.1 years) than the typical civilian patient first referred to our center (mean age about 50 years). The neurocognitive impairment associated with these undiagnosed and untreated sleep disorders has the potential to impact highly on the ability of these active military personnel to safely and accurately perform their jobs in the infantry and air force. The patients included aircraft technicians, officers in the air force and infantry, flight engineers, fire fighters and medics. Sleep disorders in military personnel has been reported anecdotally (1,2). Review of the medical history for sleep disorders in this population is important, especially in the overweight.

References:
Efficacy of an Oral Interface for the Delivery of CPAP Therapy in the Treatment of OSA.

Pedler H, Whyte K, Smith NC, Ofa M, Searle E
(1) Sleep disordered breathing unit, Green Lane Hospital, Auckland, New Zealand, (2) Fisher & Paykel Healthcare, Auckland, New Zealand

Introduction: Nasal continuous positive airway pressure (CPAP) is the treatment of choice for obstructive sleep apnoea (OSA). Compliance rates are sub-optimal and in some patients this is because nasal CPAP is intolerable. Delivering CPAP through the mouth could avoid some of the problems associated with nasal CPAP therapy and potentially improve overall compliance rates. In addition, as oral CPAP delivers the pressure directly to the oropharynx, theoretically lower positive pressure may be required using this route. Aim: To compare the delivery of CPAP through a standard nasal mask to delivery of CPAP through a new oral interface in CPAP naïve subjects on the first night of a diagnostic/CPAP titration (i.e. split night) polysomnography (PSG) study.

Methods: 19 patients referred for diagnostic sleep study on the diagnostic portion of a split night sleep study were randomly assigned to receive CPAP either from a standard nasal mask (11 patients) or the ORACLE™ oral interface (8 patients). Patients underwent full PSG and if after a minimum of two hours OSA was diagnosed (AHI >20/hr) then they were assigned to one treatment limb. CPAP was applied and the pressure titrated until all evidence of upper airway obstruction was eliminated. Both the diagnostic study and the entire treatment study was analysed, including the period of CPAP titration, the variables analysed were severity of disease and sleep quality. The two treatment groups including the patient demographics were compared by student’s t test.

Results: One subject was excluded because of dominant central apnoeas though he also had some obstructive events. There were no significant demographic differences between groups and the severity of OSA (Table 1). While receiving CPAP therapy there was no significant difference between the oral and nasal groups with respect to sleep variables and sleep quality though there was a trend for a shorter sleep latency in the nasal group (11.9cmH2O+1.8; mean+SD) compared to the oral group (10.6cmH2O+1.9) but this was not significant (p=0.23). Between the oral and nasal groups with respect to sleep variables and sleep quality though there was a trend for a shorter sleep latency in the nasal group (11.9cmH2O+1.8; mean+SD) compared to the oral group (10.6cmH2O+1.9) but this was not significant (p=0.23).

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Nasal</th>
<th>Oral</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency (minutes)</td>
<td>14.2 (15.2)</td>
<td>6.6 (8.0)</td>
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<td>Total Sleep time (minutes)</td>
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<td>125 (47)</td>
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<td>59.1 (24.6)</td>
<td>60.7 (21.4)</td>
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<td>Total RDI (events per hour)</td>
<td>86.0 (30.0)</td>
<td>85.4 (25.7)</td>
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<tr>
<td>Mean SaO₂ desaturation (%)</td>
<td>11.2 (4.7)</td>
<td>9.6 (4.3)</td>
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</table>

#### Diagnostic study summary.
- Values are the means (standard deviation)

### Table 2

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<th>Oral</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>Sleep Latency (minutes)</td>
<td>18.5 (20.1)</td>
<td>4.9 (3.1)</td>
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<tr>
<td>Total Sleep time (minutes)</td>
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<td>265 (34)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>80.6 (15.0)</td>
<td>91.3 (4.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>REM Sleep (% of total sleep)</td>
<td>26.4 (10.9)</td>
<td>24.5 (6.3)</td>
<td>0.67</td>
</tr>
<tr>
<td>AHI (events per hour)</td>
<td>0.37 (1.1)</td>
<td>0.19 (0.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Total RDI (events per hour)</td>
<td>0.61 (1.8)</td>
<td>0.51 (1.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean SaO₂ desaturation (%)</td>
<td>1.3 (2.8)</td>
<td>1.4 (2.3)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

#### Titrator study summary.
- Values are the means (standard deviation)

Conclusions: Sleep quality and OSA severity was similar in the two groups. From the data obtained in the treatment studies CPAP delivered via an oral interface is at least as effective as CPAP therapy delivered via a standard nasal mask. There is a trend for a lower sleep latency in patients who commence CPAP via this oral interface. This is possibly due to less patient disturbance at the initiation of the titration study with the oral interface as it is simpler to fit than a nasal mask and headgear.

Research supported by Fisher & Paykel Healthcare

Prognostic Indicators for Successful Uvulopalatopharyngoplasty

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Introduction: Uvulopalatopharyngoplasty (UPPP) remains the most common surgical procedure performed for sleep-disordered breathing. Although reported success rates vary considerably, meta-analysis of the data indicates a success rate of only 40%. Most surgical treatments with a 60% failure rate would be considered unacceptable for benign disease. The purpose of this study is to identify prognostic indicators that will lead to stratification of patients likely to have successful surgery versus those destined to fail.

Methods: We retrospectively reviewed 130 patients to correlate palate position and tonsil size to the success of the UPPP as based on postoperative polysomnography. Similar to our previously published data on the Friedman Score as a predictor of the presence and severity of obstructive sleep apnea, the palate position was determined on physical examination of the oral cavity. This is based on a modification of the Mallampati classification used by anesthesiologists to predict a difficult airway.

Results: The Mallampati grade was inversely related to the likelihood of successful surgery, as opposed to the tonsil size, which correlated directly with successful surgery. Mallampati grade I or II with tonsil size 3 and 4 resulted in successful surgery 80% of the time. Patients with a Mallampati IV and tonsil size less than 2 were most likely to fail after the UPPP.

Conclusions: Mallampati classification and tonsil size should be incorporated in surgical planning for obstructive sleep apnea. This will change the surgical procedure success rate from 40% to 80% through appropriate and accurate preoperative assessment and selection of patients.

References:
(2) Friedman M et al: Quantifiable physical findings in obstructive sleep apnea. Poster presentation at the 1999 annual meeting of the American Academy of Otolaryngology - Head and Neck Surgery.

Subclassification of Japanese Patients with Obstructive Sleep Apnea Syndrome by Cephalometric Measurements and Its Significance

Sakakibara H, Tong M, Sasaki F, Matsui K, Hirata M, Konishi Y
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Introduction: The present work was undertaken mainly to: (1) introduce a new approach to the evaluation of cephalometrics in Japanese patients
with obstructive sleep apnea syndrome (OSAS), and (2) subclassify OSAS patients into certain types according to their cephalometric abnormalities.

**Methods**: The study was carried out in 115 consecutive male OSAS patients and 40 healthy men diagnosed by one night polysomnography. A lateral cephalogram was obtained in each subject through a computed radiography system and analyzed using the NIH Image program. Twenty-six variables (14 variables on craniofacial bony structures, eight variables on upper airway soft tissues and four variables on hyoid bone positions) were measured and first standardized into SD values using the following formula, the SD value = (X-Cmean)/Csd: X, measurement; Cmean and Csd, mean value and standard deviation of the measurements in normal controls. The upper or lower normal limit of each variable was set as maximum or minimum SD value = 1.96 or -1.96.

**Results**: Among the 115 OSAS patients, 55 patients (47.8%) had abnormalities only in soft tissue, 12 patients (10.4%) had abnormalities only in bony structure, whereas 37 patients (32.2%) had abnormalities in both soft tissue and bony structure. Only 11 patients (9.6%) exhibited no obvious cephalometric abnormality.

**Conclusions**: Most of the Japanese OSAS patients (90.4%) had certain degrees of cephalometric abnormalities, and upper airway soft tissue aberrations were more frequently seen than craniofacial bony structure defects and contributed more to apneic activity. By examining the SD values case by case, it is possible to define the specific cephalometric abnormalities for each OSAS patient, which may provide a rationale for the selection of an individualized treatment modality for each patient.

**References**:


457.J

**Do Women Experience Similar Impairment as Men Despite a Lower Apnea-Hypopnea Index?**

Lutley-Borland KM, Freeland A, Busby K, McKendry J, Dales RE

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**Introduction**: For many illnesses, the presentation and course differs between men and women (Schwab, 1999). The purpose of this study was to assess gender differences surrounding obstructive sleep apnea.

**Methods**: We administered the Functional Outcomes of Sleep Questionnaire (FOSQ; Weaver et al., 1997) and Epworth Sleepiness Scale (ESS; Johns, 1991) to consecutive, consenting patients presenting to a large sleep laboratory serving a community of 350,000 people. Fifty-three women and 130 men, mean age 47.7(SE=0.81) years, completed the questionnaires and underwent overnight polysomnography.

**Results**: The apnea-hypopnea index (AHI) was half as great in women as in men, 11.4 (SE=3.0) vs. 24 (SE=2.8; p=.008) respectively. Despite this, quality-of-life was significantly worse in women than men after controlling for AHI; respective ESS scores were 13.9(SE=0.5) vs. 15.8(SE=0.3; p=.000). Daytime sleepiness was similar between women and men: respective ESS were 10.2(SE=0.8) and 10.7(SE=0.5), and FOSQ-vigilance score means were 2.7(SE=0.1) for women and 2.9(SE=0.1) for men. There were no gender differences in age, body mass index, and the number of periodic limb movements. To obtain further evidence that the reported impairment was related to sleep apnea, we followed up an unslected subgroup of 28 subjects (6 females, 22 males) who were prescribed continuous positive airway pressure (CPAP). Combining genders, significant improvements with CPAP occurred in ESS: preCPAP 11.8(SE=1.3), postCPAP 7.1(SE=1.1); p=.003. FOSQ measures also improved: preCPAP 15.5(SE=0.5), postCPAP 18.3(SE=0.4); p=.000. There were no significant sex differences on the ESS or FOSQ following CPAP treatment.

**Conclusions**: Women may be more impaired for a given severity of sleep apnea, as measured by the apnea-hypopnea index. Despite a lower AHI, women appear to achieve as much benefit from CPAP as men. These findings suggest that the clinical significance of a relatively low AHI may be greater in women than men, and may warrant a lower threshold for treatment in the presence of symptoms.

**References**:


458.J

**Effectiveness of the Prone Position in the Treatment of Obstructive Sleep Apnea**

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**Introduction**: The supine position has long been observed to facilitate snoring and obstructive sleep apnea in susceptible individuals. Compared to supine, sleep in the side position has been shown to decrease AHI by greater than 50% in over 50% of patients with OSA.(1) It is postulated that sleep in the true prone (face down) position would further promote upper airway patency as gravity would act to pull the tongue and soft palate anteriorly decreasing the likelihood of collapse against the posterior pharyngeal wall. This study was undertaken to evaluate the effectiveness of the true prone sleep position in reducing AHI in patients with OSA.

**Methods**: Prospective, open-labeled study of 10 patients with moderately severe OSA. These patients were intolerant to, or initially refused nCPAP and expressed confidence that they could sleep in the true prone position. Split-night polysomnography was performed using routine clinical methodology with baseline measurements of sleep obtained during the first part of the night in both the supine and side positions. During the second half of the night, patients were placed in an Oakworks Face Support system that allowed them to sleep in the true prone (face down) position.

**Results**: Eight patients were able to complete the study (5M,3F). Two patients were unable to sleep in the prone position due to orthopedic discomfort. Mean age was 45±14.4, BMI 32±4.1kg/m2. Mean time in bed at baseline was 244±24.1 min during which they spent 75±21% of the time sleeping on their sides. Time in bed prone was significantly reduced at 166 ± 44.1 min (p<0.013). No significant differences were observed between baseline and prone sleep, as measured by the apnea-hypopnea index. Initial sleep latency, percent time spent in NREM stages 1, 2, 3/4 and REM sleep, arousal index, or lowest SpO2, see table. Although only a trend toward significance was noted in total AHI (baseline vs prone), highly significant differences in AHI were noted for supine vs side (p<0.002) and supine vs prone (p<0.001), see figure. There was no difference in AHI side vs prone. All patients complained of significant back and/or neck pain by the end of the study.
Conclusions: Prone positioning results in a significant decrease in AHI compared to sleeping supine. However, the decrease in AHI was no better than sleeping on the side. Both prone and side sleep improved but did not revert AHI to normal. Sleeping exclusively in the true prone position produced musculoskeletal discomfort in all patients. Although prone positioning using a face support is effective for decreasing AHI, intolerance to this position for extended periods would limit its application in the treatment of OSA.

References:

Spectral Waking EEG Activity in Patients with Obstructive Sleep Apnea: Relationship with Daytime Sleepiness

Sforza E, Grandin S, Joupy C, Rochat T, Ibanez V
(1) Sleep laboratory, Hôpital Belle Idée, Departmet nt of Psychiatry, (2) Division of Pneumology, University of Geneva

Introduction: The Obstructive Sleep Apnea syndrome (OSA) results from the repeated occlusion of the upper airway during sleep, inducing nocturnal hypoxemia, sleep fragmentation, sleep loss, and reduced alertness. Although sleep loss and sleep fragmentation play a key role in the regulation of daytime performances and alertness, neither total sleep time, nor apnea recurrence and concomitant sleep fragmentation significantly contributed to the degree of diurnal impairment in OSA. We know that some components of the EEG recorded during wakefulness are sensitive to changes in alertness and in diurnal performance (1), alpha power with open-eyes increasing when alertness decreases and theta power enhancing when sleepiness becomes manifest (2). The current study was undertaken to determine whether waking EEG activity had greater sensitivity compared to other measures of sleepiness to assess reduced alertness and waking impairment in OSA patients.

Methods: The polygraphic recordings of 24 patients aged 47.8±2.5 yr. with a mean BMI of 31±1.3 kg/m2 and an average AHI of 48.1±6 were examined. Diurnal sleepiness was assessed by the administration of the Epworth Sleepiness Scale (ESS) and the maintenance wakefulness test (MWT). Before each MWT session, the patients rated their subjective daytime sleepiness by administration of the Stanford Sleepiness Scale (SSS) and the Visual Analogic Scale (VAS). Prior to lights-out for each MWT nap, an alpha attenuation test (AAT) was administered. The alpha attenuation coefficient (AAC) was calculated within the alpha frequency range to obtain ratio of mean eyes-closed to mean eyes-open. The EEG signals during each AAT trial were subjected to spectral analysis with a Fast Fourier Transform (FFT) on the PZ-O2 lead using a 2-sec Hanning window. The absolute power values (mV2/Hz) of four EEG components known to be sensitive to drowsiness (theta 4.5-7.5 Hz), slow alpha (8-10 Hz), fast alpha (10.5-12.5 Hz), and total alpha (8-12.5 Hz power) were computed during eyes-closed and eyes-open sessions.

Results: Over-time analysis of the mean sleep latency, alpha attenuation test coefficient (AAC) and EEG spectra power demonstrated that all measures tended to vary throughout the day. Regarding the mean sleep latency at the MWT there was a decline in alertness during the morning with a progressive fall from the initial value of 19.2 min at 9:00 AM to the final value of 17.4 min at 13.00 PM. Thereafter, objective daytime sleepiness increased progressively. The AAC rose from the initial value of 4.35 to the value of 4.67 peaking at 13.00 PM. Thereafter, while mean sleep latency rose, an opposite downward trend for AAC was present. Spectral EEG analysis at eyes-closed and eyes-open conditions showed that there was no relationship between variation in alpha and theta power and sleep latency. Any of waking EEG measures showed significant differences between sleepy and non-sleepy patients.

Conclusions: Our results suggest that: 1) the waking EEG activity did not reflect the subjective tiredness and the lesser ability to stay awake of OSA patients; 2) EEG density did not differentiate patients having daytime sleepiness, suggesting that the waking EEG could not reliably identify and predict reduced alertness; 3) the diurnal impairment in OSA patients is related to factors other than those implicated in sleep deprivation and sleep fragmentation conditions.

References:
(2) Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. Intern J Neuroscience 1990 ; 52:29-37

Coping Style is Associated with Depressive Symptoms in Obstructive Sleep Apnea (OSA)

Bardwell WA,1,2 Ancoli-Israel S,1,2 Dimsdale JE1
(1) University of California, San Diego, Psychiatry, (2) Veterans Affairs San Diego Healthcare System

Introduction: The sleep literature is mixed regarding the role psychological factors play in OSA. Some researchers have reported that clinical depression or increased depressive symptoms are common in OSA. Others have found that OSA patients do not show depressive symptoms in excess of those reported by a general population or patients with other chronic illnesses. (1) Previously, we have reported that many psychological symptoms of OSA can be explained in part by other OSA comorbidities (e.g., age, hypertension, body mass). We wondered if personality might also play a role in determining the extent of depressive

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Prone</th>
<th>P Value</th>
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<tr>
<td>TIB(min)</td>
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<tr>
<td>TST(min)</td>
<td>165.9±40.8</td>
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<td>Sleep eff(%)</td>
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<td>TLL(min)</td>
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<td>Annual Index(#/hr)</td>
<td>49.5±21.6</td>
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Figure 1

![Graph showing effect of prone sleep on AHI](image-url)
symptoms experienced by OSA patients. The depression literature shows that people who use more passive and less active coping techniques show higher levels of depressive symptoms. (2) We examined relationships between coping styles and depressive symptoms in OSA patients, while controlling for OSA severity and fatigue to ensure that coping style wasn’t simply a matter of illness severity or lack of energy.

Methods: 64 OSA patients were studied with polysomnography to verify presence of OSA, which was defined as a respiratory disturbance index (RDI) >= 15 (range = 15-142; mean = 51 ± 3.4). Subjects completed the Ways of Coping (WC), Profile of Mood States (POMS), and the Center for Epidemiological Studies-Depression (CESD) Scales. WC was consolidated into Approach and Avoidance factors. These factors can be thought of as representing active and passive coping styles, respectively. Both factors were dichotomized into Hi/Lo groups using median splits. Data were analyzed using analysis of covariance (with RDI and POMS Fatigue as covariates).

Results: No significant main effects emerged for either WC Approach or Avoidance. However, the WC Approach X WC Avoidance interaction was significant (p=.01) (see Figure): Hi Avoidance/Low Approach subjects reported more depressive symptoms (CESD = 18.1 ± 2.1) than all other groups (CESD = 9.2 to 13.6).

Figure 1

Conclusions: After controlling for illness severity and fatigue, OSA patients who reported the most passive and the least active coping techniques reported the highest levels of depressive symptoms. The extent of depression experienced by OSA patients may not be due solely to the effects of the illness itself. Rather, premorbid personality may play a role in determining which OSA patients will experience higher levels of depressive symptoms.

References:
(1) Bardwell WA, Berry CC, Ancoli-Israel S, Dimsdale JE. Psychologi-

Research supported by NIH Grants HL44915, AG02711, RR00827

461J

Obstructive Sleep Apnea in Chronic Renal Failure: a risk fac for Systemic Hypertension

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Introduction: Background: Obstructive Sleep Apnea (OSA) is common in individuals with Chronic Renal Failure (CRF). Although no broad population-based survey of sleep apnea in patients with CRF have been performed, limited data suggest 53% to 89% of individuals in this population have OSA. It is well recognized the role of OSA as a risk factor for Systemic Hypertension. So, patients with the association of CRF and OSA could present a higher risk to develop systemic hypertension compared to those without OSA.Aim: To study the prevalence of OSA in our patients with CRF. To determine in these patients the impact of this sleep disorder for development of systemic hypertension. Subjects: 37 patients with CRF, in dialysis program, were consecutively selected from the Renal Transplante Ambulatory of the Kidney Hospital - Universidade Federal de Sao Paulo.

Methods: All patients underwent: 1.Clinical and laboratoril evaluation including: Hemoglobin, Hematocrit, BUN, Creatinine, Alkaline Phosphate, Paratormonio and KTV.2.Polysomnograph containing 12 channels ( Polysmith system) including: 3 for EEG, 2 for EOG, 2 for EMG, 1 for oro-nasal termistor, 1 for toracic pletsmograph and other for abdominal pletsmograph, 1 for pulse oximetry and 1 for EKG.

Results: 25 (67.5%) of 37 patients had Apnea + Hypopnea (AHI) < 5 per hour (GI) and 12 (32.4%) had AHI > 5/h (GII). No differences were detected between groups considering age (mean of GI:35,9 ± 9,7 years and GII: 39,3 ± 13,1years) and Body Mass Index ( mean of GI: 22,43 ± 4,07 kg/m2 and GII:21,8 ± 4,1kg/m2). Higher blood pressure was detected in GII compared to GI (mean of systolic pressure of 168 ± 23,7 mmHg versus 148,2 ± 19,9 mmHg; p<0.05).Mean of systolic pressure 108 ± 16,33 mmHg versus 96,1 ± 13,4 mmHg; p<0.05)No differences were detected in laboratory evaluation between groups. creatinine (mean of GI: 11,2 ± 2,74 mg/dl and GII: 11,3 ± 1,66 mg/dl). A poiste correlation between Apnea Index and dystolic blood pressure was detected.

Conclusions: The studied population with Chronic Renal Failure presented high prevalence of Obstructive Sleep Apnea.Obstructive Sleep Apnea was a risk factor for Systemic Hypertension.

References:

Supported by Associated Fundo de Incentivo a Psicofarmacologia (AFIP)
Eight-year Progression of Sleep-disordered Breathing in the Wisconsin Sleep Cohort

Peppard PE, Young T
University of Wisconsin Medical School, Department of Preventive Medicine

Introduction: Sleep-disordered breathing (SDB) is common in the United States general population, and its prevalence might be expected to increase as the population ages and grows more ponderous. Because SDB has been linked to harmful outcomes including cardiovascular and behavioral morbidity, there will likely be serious public health ramifications of increasing prevalence. Few data exist on the progression of SDB or on the relation of progression to risk factors of SDB such as middle age, male gender and obesity. This report examines progression of SDB over eight-years in the Wisconsin Sleep Cohort Study, an ongoing longitudinal study of the natural history of SDB.

Methods: Baseline and eight-year follow-up overnight in-laboratory polysomnography data were available from 249 Cohort participants. Additional data included health history, demographics and body habitus. SDB was characterized by the apnea-hypopnea index (AHI, apnea plus hypopnea events per hour of sleep). Eight-year change in mean AHI and change in the prevalence of AHI >5 and AHI >15 events/hr were calculated. Sex, baseline age (30-44 years vs. 45-60 years), obesity (BMI, <30 vs. >30 kg/m^2), and self-reported snoring (frequent or always vs. infrequent or never) were examined as predictors of change in mean AHI and prevalence of elevated AHI. Multiple linear regression modeling was performed to assess independent associations of sex, baseline age, BMI and snoring with 8-year change in the AHI.

Results: The mean AHI of the cohort participants increased significantly from baseline to 8-year follow-up (Table 1). Overall mean AHI increased 2.9 events/hr, from 2.5 at baseline to 5.4 at follow-up. There were significant increases in mean AHI among all examined sex, obesity, age and snoring subgroups. Mean AHI increase was not significantly greater in men compared to women (p=0.2). Mean AHI increase was greater in obese compared with non-obese (p<0.001), older compared to younger (p=0.02), and snorers compared to non-snorers (p<0.001). Overall prevalence of AHI >5 and AHI >15 events/hr increased significantly over 8 years of follow-up (Table 2). All subgroups had significant increases in prevalence of AHI >5 events/hr. All subgroups also experienced increased prevalence of AHI >15 events/hr. However, the increases of prevalence of AHI >15 events/hr were not significant (p>0.05) in women, non-obese participants, younger participants, and non-snorers. In linear regression modeling baseline older age (p=0.06), greater BMI (p=0.01) and snoring (p=0.002), but not sex, were independently associated with 8-year increase in mean AHI.

Conclusions: In a general population cohort, prevalence of SDB is increasing rapidly. SDB is, on average, increasing in severity in both men and women, obese and non-obese persons, younger and older adults, and snorers and non-snorers. These increases likely reflect aging and weight gain in the cohort and, possibly, other factors. Because the United States general population is aging and growing more obese, it is reasonable to expect an increase in prevalence and severity of SDB beyond the high levels already seen.

Research supported by NIH grants R01HL62252, RR03186, and AG14124-05

Hostile Personality Traits in Sleep Apnea are Associated with Plasma von Willebrand Factor Levels

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Introduction: There is a hypercoagulable state in obstructive sleep apnea (OSA) thought to underly atherosclerosis (1). Psychological factors such as hostility may exert an adverse impact on vessel health by promoting procoagulant disturbances (2) as evidenced by increased platelet activity (3). The von Willebrand factor (vWF) is crucial in mediating platelet-endothelium adhesion and platelet aggregation. Elevated levels of plasma vWF are a marker of endothelial dysfunction and atherosclerosis. Even within a normal range, the vWF has predictive value for coronary events. We wondered whether hostility would be associated with plasma vWF levels in apneic and/or hypertensive subjects.

Methods: Table 1 shows demographics of 108 (84 male, 24 female) community-dwelling volunteers (mean age±SD, 48±8 years) with symptoms suggestive of OSA who underwent standard polysomnography and screening blood pressure (BP) recordings. Seventy-one subjects had OSA (respiratory disturbance index at least 15/hr), 42 had hypertension (systolic and/or diastolic BP at least 140 and/or 90 mmHg), 27 had OSA and hypertension, 22 had neither OSA nor hypertension and were thus study controls. Aside from OSA and hypertension, subjects were free of any major illness. They took no drugs interfering with hemostasis; anti-hypertensives were tapered at least 3 weeks prior to the study. Plasma vWF antigen levels were measured by ELISA. The subscales “Hostility”, “Cynicism”, “Paranoia”, and “Stress”, from the Cook-Medley (CM) Hostility Scale, and “Expression” (physical assaultiveness, verbal expression, indirect hostility) and “Experience” (resentments, suspiciousness) of hostility from the Buss-Durkee Hostility Inventory were used for analysis.

Results: Across the different subscales, the vWF correlated significantly with hostility in the apneic, the hypertensive, and the apneic hyper-
tensive groups but not in controls (Table 2). In a stepwise multiple regression analysis, CM Paranoia alone entered the model for apneics (R²=0.151, F(1,66)=11.8, p=.001), and CM Stress entered the model for hypertensives (R²=0.121, F(1,37)=5.1, p=.030). CM Paranoia and CM Stress together entered the model in the apneic hypertensives (R²=0.442, F(2,22)=0.002). After controlling for demographics, CM Stress did not significantly add to the variance in vWF in hypertensives any more (p=.13; controlled for body mass index (BMI) and diastolic BP), though CM Paranoia when controlled for gender (R² change=0.144, F(1,65)=11.9, p=.001), and CM Stress when controlled for BMI (R² change=0.263, F(2,22)=.48, p=.019) still did so in apneics and apneic hypertensives, respectively.

### Table 1

<table>
<thead>
<tr>
<th>vWF</th>
<th>RDI</th>
<th>SBP</th>
<th>DBP</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTR (n=22)</td>
<td>102 (49)</td>
<td>5 (4)</td>
<td>120 (10)</td>
<td>76 (7)</td>
</tr>
<tr>
<td>AP (n=71)</td>
<td>95 (51)</td>
<td>53 (31)</td>
<td>132 (17)</td>
<td>83 (10)</td>
</tr>
<tr>
<td>HTN (n=42)</td>
<td>87 (53)</td>
<td>42 (39)</td>
<td>148 (9)</td>
<td>94 (5)</td>
</tr>
<tr>
<td>AP/HTN (n=27)</td>
<td>99 (60)</td>
<td>61 (36)</td>
<td>148 (10)</td>
<td>92 (5)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Buss-Durkee</th>
<th>Cook-Medley</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES</td>
<td>EN</td>
</tr>
<tr>
<td>CTR (n=22)</td>
<td></td>
</tr>
<tr>
<td>AP (n=71)</td>
<td>.261</td>
</tr>
<tr>
<td>p</td>
<td>.030</td>
</tr>
<tr>
<td>HTN (n=42)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>.348</td>
</tr>
<tr>
<td>AP/HTN (n=27)</td>
<td>.503</td>
</tr>
<tr>
<td>p</td>
<td>.010</td>
</tr>
</tbody>
</table>

### Conclusions:

Compared to non-apneic controls, hostility features are positively associated with the plasma vWF concentration in apneic subjects. Depending on the presence of co-morbid hypertension, hostility predicted an additional either 14 or 26% of the variance in vWF after demographic variables were accounted for. The finding suggests a psychobiological mechanism that could contribute to the increased cardiovascular morbidity in OSA.

### References:


Research supported by NIH grant HL4915, fellowship 81BE-56155 from the Swiss National Science Foundation, unrestricted educational grant from Novartis Foundation, Switzerland.

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**465.J**

**Obstructive Sleep Apnea in Epilepsy Patients: Further Validation of the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) in a Disease-specific Population.**

**Weatherwax KJ, Krantz SB, Malow BA**

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**Introduction:** Up to one-third of epilepsy patients who do not respond to medication have co-existing obstructive sleep apnea (OSA). The Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ), a 12-item validated measure of sleep-related breathing disorders, has seen limited use to screen medically refractory epilepsy patients for OSA. Previously suggested cutoff points for OSA for the SA-SDQ are 32 for women and 36 for men. The authors’ purpose was to investigate the validity of the SA-SDQ in epilepsy patients who underwent polysomnography (PSG) and to determine if previously set cut-off points for OSA are applicable to an epilepsy population.

**Methods:** Seventy subjects with medically refractory epilepsy without a history of OSA completed a survey about their sleep, including the 12-item SA-SDQ scale. All subjects also underwent routine PSG as part of their involvement in one of three research protocols at the University of Michigan (examining the relationship of interictal epileptiform discharge to sleep stage (n=45), determining the effects of vagus nerve stimulation on sleep patterns (n=17), and examining the effects of OSA treatment on seizure frequency and daytime sleepiness (n=8)). Major predictor variables between subjects with OSA and those without were compared using two-tailed independent sample t-tests, with a p value of < 0.05 considered significant.

**Results:** Twenty-four of the 70 subjects (34%) had respiratory disturbance indexes (RDI; apneas and hypopneas per hour) greater than 5, indicating obstructive sleep apnea. The mean SA-SDQ score for men with OSA was 28.2 ± 7.9 and the mean score for women with OSA was 31.2 ± 11.4. The table below shows the differences between the two groups.

### Table 1

<table>
<thead>
<tr>
<th>Value</th>
<th>Age (years ± S.D.)</th>
<th>Body Mass Index (mean ± S.D.)</th>
<th>SA-SDQ score (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA n=24</td>
<td>40.3 ± 10.7</td>
<td>29.9 ± 7.5</td>
<td>29.5 ± 10</td>
</tr>
<tr>
<td>No OSA n=46</td>
<td>33 ± 10</td>
<td>26 ± 5.7</td>
<td>23.3 ± 6</td>
</tr>
</tbody>
</table>

**p Value**

.008

.040

.016

**Conclusions:** In our sample of 70 subjects studied to date, PSG results indicate that the SA-SDQ continues to be a useful screening instrument for OSA in a medically refractory epilepsy population. Variables predictive of OSA in our sample included age, body mass index, and SA-SDQ score. Our results also indicate that the previously suggested cut off points for OSA of 32 for women and 36 for men may be too high for this specific population. Further studies will determine adequate SA-SDQ cut off points for OSA in this population.

**References:**

Upper Airway Responsiveness to Hypercapnea, Hypoxemia and Resistive Loading during NREM sleep

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Introduction: Previous studies have suggested that during NREM sleep, neither large short-duration resistive loads nor sustained normoxic hypercapnea alone lead to increased genioglossus (GG) muscle activity. However, in normal individuals during stable NREM sleep GG activity rises above baseline as PaCO2 rises and airway resistance increases. This suggests that combined chemical and mechanoreceptor stimuli can activate the muscle during sleep. We therefore hypothesized that combinations of normoxic hypercapnea (5-10mm Hg above eupnea), hypoxic eucapnea (SaO2 80-85%) and inspiratory resistive loading (IRL) (at –10cm H2O/L/s) during NREM sleep would lead to increased peak phasic GG muscle activity (% of maximum).

Methods: We studied 7 normal subjects (5 males/2 females), (BMI< 25), during stable NREM sleep, measuring GG EMG (intramuscular electrode), epiglottic/choanal pressure (Millar catheters) and airflow/volume (pneumotachograph) under 4 conditions: (1) baseline, (2) IRL, (3) increased EtCO2 (5-10mm Hg above baseline) and (4) combined IRL and increased CO2. Five subjects were studied under two additional conditions: (1) hypoxia (SaO2 80-85%) and (2) combined hypoxia/IRL.

Results: Table 1 shows all NREM sleep data. Under the combined condition of hypercapnea and resistive loading, GG activity trended upward from baseline (p=0.07). Hypoxia during NREM sleep combined with resistive loading had no significant effect on GG activity compared to baseline.

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>[Baseline]</th>
<th>[IRL]</th>
<th>[CO2]</th>
<th>[CO2/IRL]</th>
<th>[Hypoxia]</th>
<th>[Hypoxia/IRL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtCO2 (mm Hg)</td>
<td>48±2/3</td>
<td>48±2/3</td>
<td>48±2/3</td>
<td>45±2/2</td>
<td>43±2/4</td>
<td>44±2/4</td>
</tr>
<tr>
<td>SaO2 (percent)</td>
<td>95±1/1</td>
<td>95±1/1</td>
<td>95±1/1</td>
<td>95±1/1</td>
<td>95±1/1</td>
<td>95±1/1</td>
</tr>
<tr>
<td>Epiglottic/Choanal (cm H2O/L/s)</td>
<td>6.8+/-4.7</td>
<td>6.6+/-4.6</td>
<td>6.6+/-4.7</td>
<td>6.8+/-4.6</td>
<td>6.8+/-4.3</td>
<td>7.5+/-4.5</td>
</tr>
<tr>
<td>Nasal (cm/L/s)</td>
<td>1.33+/-.85</td>
<td>1.6+/-1.5</td>
<td>2.6+/-1.7</td>
<td>2.4+/-2.8</td>
<td>2.2+/-2.1</td>
<td>2.3+/-1.9</td>
</tr>
<tr>
<td>GG peak (% max)</td>
<td>4.4+/-3.3</td>
<td>4.4+/-3.6</td>
<td>5.3+/-2.3</td>
<td>3.5+/-3.6</td>
<td>2.3+/-1.5</td>
<td>4.8+/-3.2</td>
</tr>
</tbody>
</table>

* p < 0.05 different from baseline  ** p = 0.07 different from baseline

Conclusions: These data suggest that the genioglossus muscle is not responsive to either chemical stimuli (hypercapnea, hypoxia) or inspiratory resistive loading alone during NREM sleep. However, when a chemical stimulus (CO2) is combined with increased intrapharyngeal negative pressure (during resistive loading) the muscle does respond. This combined stimulus may be what drives the genioglossus activity during NREM sleep in normal subjects and muscle activity in apnea patients over the course of an apnea.

Research supported by NIH NHLBI HL48531/ HL60292 / HL07633

Heart Rate Variability and PTT During Sleep-disordered Breathings in UARS and Mild OSAS Subjects

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Stanford University, Sleep Disorders Center

Introduction: We evaluated autonomic activation and arousal responses during abnormal breathing events in UARS and mild OSAS patients. Autonomic activation was investigated by analysis of Pulse Transit Time (PTT), heart rate frequency, and determination of its low and high frequency components. EEG arousals were scored visually, and were considered as greater than 1.5 sec.

Methods: 10 UARS mean age=39.7 ± 8.6, and 10 mild OSAS mean age= 46.5 ± 10.0, with BMI < 35 kg/m2 were studied with polysomnography. Respiratory was monitored by nasal cannula with the flow measured on a pressure transducer; mouth thermocouple; inductive plethysmography; esophageal pressure (Pes), calibrated on supine position; and pulse oximetry. PTT events were defined as a fall in PTT curve greater than15 msec. Period Amplitude Analysis and power spectrum analysis were performed to ECG signal to assess the RR Interval and heart rate variability, respectively, on 148 respiratory events randomly selected in NREM and REM sleep. The events were defined according to presence/absence of visual EEG arousals, and of PTT response at the end of respiratory events. There were only 37 events without PTT change. This number represented the limiting factor for selection of events. Statistics:Two-way ANOVA was applied considering the following two major effects: a) RR interval, and b) UARS vs OSAS, PTT vs NO PTT, and EEG vs NO EEG similar two-way ANOVA design was also performed to analyze the sympathetic and parasympathetic component of heart rate variability.Wilcoxon ranked pairs test was applied to compare sympathetic and parasympathetic heart rate components, before and after respiratory events, during NREM and REM sleep.

Results: A total of 1168 respiratory events were identified for all patients. The events were then subdivided according to presence or absence of EEG visually scored arousal (>1.5 sec) and of PTT. Significant increase in heart rate was found after respiratory event termination (p<0.01). Mild OSAS subjects presented persistent shorter RR interval when compared to UARS patients, i.e., OSAS subjects exhibited consistent pattern of increased heart rate (p<0.01). There was no association between RR interval and PTT event. However, when a cortical arousal was visually detected, there was a significant increased heart rate following the respiratory event (p<0.01). The analysis of heart rate variability showed consistent changes after respiratory events during NREM sleep. There was a significant increase in sympathetic, and decrease in parasympathetic components in response to abnormal breathing effort (p<0.01). However, no significant changes could be detected during REM sleep. The parasympathetic component distinguished UARS from mild OSAS subjects. The formsers presented a significant decrease in parasympathetic component after respiratory events.PTT was associated with significant decrease in parasympathetic component of heart rate after breathing events (p<0.01). The presence of PTT event and EEG arousal, for both group of subjects, was not associated with significant change in the sympathetic component of heart rate neither during NREM nor during REM sleep.

Conclusions: NA

Acknowledgement: Dr Poyares is recipient of grants from FAPESP, Sao Paulo-Brazil. The authors would like to thank Sunrise Medical Inc.
Psychosocial Improvements after Continuous Positive Airway Pressure (CPAP) Treatment for Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) adversely affects physical, cognitive, and psychological functioning. Although CPAP treatment reduces excessive daytime sleepiness caused by OSA, less is known about how treatment affects psychosocial variables such as mood, social functioning, and marital adjustment. Furthermore, it is a well-known clinical phenomenon that OSA impacts the patient’s bedpartner, yet few studies have investigated the effect of OSA on spousal relations. This study investigates changes in psychosocial and marital adjustment associated with the initiation of CPAP treatment in patients with OSA.

Methods: Patients undergoing routine diagnostic polysomnography (PSG) for OSA in an accredited sleep disorders center were eligible to participate. Participants had no co-existing sleep disorders, no current or past psychiatric disorders, and were not taking psychotropic medications. Patients completed the following questionnaires prior to diagnostic PSG and 3 months following initiation of CPAP: Beck Depression Inventory (BDI), State-Trait Anxiety Inventory, T-scale (STAI), Fatigue Severity Scale (FSS), Dyadic Adjustment Scale (DAS), Social Adjustment Scale-Self Report (SAS). CPAP compliance data were collected at follow-up. When possible, spouses of patients also completed the DAS and SAS at baseline and posttreatment. To date, 57 patients and 22 spouses have enrolled in this on-going multi-site study. Preliminary data from 29 patients (86% male; mean age=56.6 years) and 11 spouses (91% female) who have completed follow-up are presented here. CPAP compliance data are available on 19 patients.

Results: Changes in questionnaire scores from baseline to posttreatment (Table 1) were analyzed with paired t-tests, using a Bonferroni correction of α=0.01. Significant improvements over time were found for BDI (t[28] = 2.81, p < .01) and STAI (t[28] = 4.18, p < .01). Although the FSS, DAS, and SAS demonstrated trends towards improvements at posttreatment for patients (and spouses), low baseline scores restricting the range of data and the small number of participants may have impeded our ability to detect significant effects. To analyze changes related to CPAP compliance, patients were divided into “high adherers” (>4.5hrs CPAP use/night; n=10) and “low adherers” (< 4.5hrs/night; n=9). Scores on the 5 questionnaires and SAS subscales were analyzed using 2 (Groups: high adherers, low adherers) X 2 (Times: baseline and post-treatment) repeated measures ANOVAs with baseline scores entered as covariates. There was a significant group by time interaction for the SAS Family Unit subscale (F[1, 12] = 9.29, p = .01), suggesting that after 3 months, high CPAP adherers express less feelings of inadequacy regarding the functioning of their immediate family, whereas low CPAP adherers express increased guilt and worry about their family (Figure 1).

Conclusions: Preliminary results from this on-going investigation support previous research indicating that psychological variables such as depression and anxiety improve after CPAP treatment. Furthermore, patients who are more compliant with CPAP enjoy greater satisfaction with family functioning after treatment than those who are partially or non-compliant with CPAP. As more data are collected, we will be able to further clarify psychosocial benefits related to CPAP and further assess marital adjustment from the perspectives of the patients and their spouses.

Positive Beliefs about Continuous Positive Airway Pressure (CPAP) Treatment are Strongly Related to Compliance Behaviour

Macdonell G1 Sasse A2 Conduit R1
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Introduction: CPAP treatment of OSA has reported rates of adherence as low as 46% (1). Current medical adherence research suggests that three primary illness representations should be compared when assessing treatment compliance (2). These three attributes are time-line (individual beliefs about illness duration), consequences (the experienced or expected personal effects of the illness), and control (beliefs about the impact of interventions on the illness and the potential for control of the illness) (2). It has also been proposed that adherence is strongly related to beliefs about specific treatments, and adherence can be predicted from the two core themes of specific treatment beliefs, necessity and control. Hence, patients who strongly believe in the necessity of a treatment are more likely to adhere to that treatment. Patients who hold strong concerns about a treatment are less likely to adhere (2). The Illness Perception Questionnaire (IPQ) and Beliefs about Medicines Questionnaire (BMQ) were developed to assess such beliefs regarding illness and its treatment (2). Previous research has also found that the use of
behavioural techniques of self-control or learned resourcefulness are also predictors of adherence behaviour (3). The Self-Control Schedule (SCS) was developed to assess the use of such behaviours (3). The present study investigated CPAP adherence together with measures of illness representations (2), beliefs about treatment (2), and learned resourcefulness (3) in OSA patients.

Methods: Questionnaire packages were mailed in August 2000 to 103 males and 25 females OSA patients previously diagnosed by a sleep disorders clinic in Melbourne from 1995-1998. The questionnaire package contained an explanatory statement, informed consent form, a Demographic/CPAP Usage questionnaire, IPQ (2), BMQ (2), SCS (3). Physiological sleep laboratory data regarding each participants OSA was obtained from hospital medical records.

Results: Response Rate: 25 males and 6 females participated in the study by returning the questionnaire package with all sections completed. Ten subjects returned incomplete packages and five subjects responded declining to participate. CPAP Adherence: CPAP counter measures were found to be unreliable as only 11 subjects reported admissible clock times. Therefore, self-reported CPAP use was utilized as the adherence measure. 19 subjects were classed as Adherent if they reported CPAP use during all sleep times. The remaining 12 subjects were classed as Non-Adherent, as they reported discontinued or partial use of CPAP. Correlates of CPAP Adherence: Adherent and Nonadherent groups were not significantly different in BMI (tt(29)=0.59, p>0.05), RDI (tt(29)=0.74, p>0.05) or CPAP setting (tt(29)=0.52, p>0.05). A direct logistic regression was performed on CPAP adherence as an outcome of scores on five predictors: 1) IPQ time-line, 2) IPQ consequences, 3) IPQ control, 4) BMQ necessity-concerns and 5) SCS learned resourcefulness. A test of the full model with all five predictors against a constant-only model was statistically reliable (Chi-square(5)= 16.2, p < .01), with 84.2% of participants in the adherent category and 66.7% of participants in the non-adherent category correctly predicted, for an overall success rate of 77.4%. According to the Wald criterion, perceived necessity-concerns regarding CPAP was the only reliable predictor of CPAP adherence of the five variables (z = 5.753, p < .05).

Figure 1

Conclusions: This result suggests that practitioners and sleep technologists should try to promote beliefs in treatment necessity and decrease concerns about CPAP treatment in order to increase adherence.

References:

470.J

Screening and Diagnosis of Obstructive Sleep Apnea from Continuous Nighttime Electrocardiogram Recordings

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Introduction: Obstructive Sleep Apnea (OSA) represents a major disor-
Average Face of the Japanese Patients with Obstructive Sleep Apnea

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Introduction: Asian patients with obstructive sleep apnea hypopnea syndrome (OSAHS) are less obese than Caucasian patients when controlled for AHI (1). Craniofacial anatomical abnormality was suggested as a cause of the difference (2). We made an average face of Japanese patients with OSAHS from digital photographs in order to determine whether the facial anatomic abnormality is emphasized or not.

Methods: 48 patients (all males, mean age: 51.0±11.4 years, mean BMI: 26.9±5.1 kg/m² mean AHI: 59.2±26.6/hr) with OSAHS were studied. Each digital photograph of the patients was outlined for analysis using a software (Face tool; Information-technology Promotion Agency, Japan), and average face was calculated using the software (Heikingao; Harashima & Naemura Laboratory, Course of Information & Communication Engineering, University of Tokyo). Figure 1 showed a sample of outlined face of a patient. And patients were divided into 2 groups by AHI>30 and AHI<30, and analyzed in the same way.

Results: Figure 2 showed the average face of all 48 patients. It appeared that facial abnormality was not emphasized. Even when compared 2groups with AHI>30 and AHI<30, facial width was greater in the group with AHI>30, but the facial structures seemed to be similar.

Conclusions: Average face of the Japanese OSAHS patients did not emphasize craniofacial anatomical abnormality in our results.

References:

Driving Simulator Performance in Patients With Obstructive Sleep Apnea Syndrome (OSAS) and Normals

(1) University Hospital Bergmannsheil, Department of Internal Medicine, Division of Pneumology, Allergology and Sleep Medicine, (2) University Hospital Bergmannsheil, Allergology and Sleep Medicine, Department of Neurology

Introduction: In patients with OSAS accident rate is at least 2-3 fold higher than in healthy subjects. Data on automobile accidents can be obtained by patients’ self-report and independent data banks (police, insurance companies). However, it can be assumed that part of the accidents may not be reported especially when the driver has to fear punishment or unemployment. Driving simulators are an additional tool in the assessment of accident rates in patients with OSAS. The present study compares driving simulator performance in patients with OSAS and normals.

Methods: Driving simulator performance was investigated in 31 patients [age 55.3±10.2 years, BMI 29.8±6.2 kg/m²] with polysomnographically confirmed OSAS (Alice 4, Healthdyne) and 10 healthy controls [age 55.1±7.8 years, BMI 23.1±3.2 kg/m²]. Driving simulator conditions were as follows: 60 minutes highway driving, mean speed 100 km/h, monotonous conditions with only few obstacles (steer, pedestrian, other vehicles) and different weather conditions (rain, sunshine, snow, mist) and different daytimes. All driving simulator tests were conducted in the early afternoon. The following driving simulator parameters were examined: total number of accidents and concentration faults such as light, intermittent light, windscreen, red light and off-road driving.
Results: OSAS patients normals p-value
accident rate 2.7 ± 2.0 1.3 ± 1.5 <0.05
concentration faults 12.4 ± 5.1 7.1 ± 3.2 <0.01

Conclusions: Accident rate and concentration faults in the simulated driving situation were 2 fold higher in patients with OSAS as compared to controls. Thus the driving simulator used in the present study is able to measure objectively the increased driving risk in patients with OSAS. Additionally objective measurement of driving performance may identify OSAS-patients with normal driving skills and thus avoid needless driving restrictions in those patients.

473.J

Neurobehavioural Impairment in Mild Sleep Apnea Patients Compared To Control Subjects.

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(1) Austin and Repatriation Medical Centre, (2) Daw Park Repatriation General Hospital

Introduction: In the management of mild sleep disordered breathing it is important to assess the impact of the disease on daytime function as well as measuring the apnea hypopnea index (AHI). In this study the daytime function in a group of subjects with mild obstructive sleep apnea syndrome (OSAS) was assessed and compared to that of a screened control population.

Methods: Control subjects were recruited through random telephone calls and screened for symptoms of OSAS and co-morbidities. OSAS subjects were recruited from routine presentations to physicians if an initial overnight polysomnogram showed an AHI 5-30 and there were no other causes of daytime neurobehavioural dysfunction. All subjects had repeat polysomnography, maintenance of wakefulness test (MWT) and comprehensive neuropsychological and quality of life assessments. Comparisons were made using independent measure T-tests and linear regression analysis with independent predictors being age, sex, anthropometry and symptom score.

Results: We recruited 28 control subjects (23 males, 5 females) and 112 OSA subjects (88 males, 24 females) of similar ages. The OSA subjects were more obese and had more sleep-disordered breathing than the control group, but oxygen desaturations and arousals did not differ (Table 1). Daytime sleepiness was subjectively and objectively increased in the OSA group, but oxygen desaturations and arousals did not differ (Table 1). Neuropsychological function was impaired in the OSA group, with significant decrements in vigilance, psychomotor function and short term auditory memory (Table 2). Quality of life was impaired in OSA subjects, and they had mild mood depression (Table 2). Linear regression analysis showed that when age, sex, obesity and symptom score were controlled for, control subjects performed better than OSA subjects in the areas of vigilance (PVT lapses R2=0.11, p=0.03), divided attention tasks (PASAT R2=0.12, p=0.06) and had less daytime sleepiness (MWT R2=0.17, p=0.10, ESS R2=0.30, p=0.1).

Conclusions: There is significant excess daytime sleepiness and impairment of neuropsychological function and quality of life in a group of 112 subjects with mild obstructive sleep apnea compared to a group of control subjects.

Research supported by National Health and Medical Research Council of Australia

474.J

The Vestibular-in-line Pressure System (VIPS); A Comparative Home Trial with Nasal CPAP

Khanna R, Kline LR
Western Pennsylvania Hospital, Pittsburgh, Pa.

Introduction: CPAP remains the treatment of choice for Obstructive Sleep Apnea Syndrome (OSAS). Since the inception of this treatment, pressure has been applied primarily via the nose (nCPAP). Despite improvements in mask interfaces, many patients dislike nCPAP for a myriad of reasons. Complaints include skin abrasions, air leaks, conjunctivitis, sinus congestion, rhinorrhea, claustrophobia, and limitation of sleeping position. Such negative experiences could contribute to the 40% of patients who ultimately abandon therapy within the first three months. We wondered if patients would prefer CPAP provided via the oral route, using a new interface, the VIPS (Fisher-Paykel, “Oracle”). The VIPS might have some inherent advantages, with less annoying side effects. Accordingly, a home trial was designed to compare the VIPS to nCPAP.

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Methods: A total of 18 patients with suspected OSAS underwent a diagnostic PSG. Subjects with OSAS (RDI>15/h.) returned for CPAP titration. Patients were randomized to receive either nCPAP or the VIPS. The VIPS, a strapless butterfly-shaped device, rests in the oral vestibule between the lips and teeth; tubing from the interface attaches to the CPAP unit. All received heated humidification (Fisher-Paykel HC100). Subsequently, subjects were given the same interface for home use. Patients were provided CPAP devices with a heated humidifier and hour counter meter (Fisher-Paykel HC201). Subjects were unaware that compliance was a major outcome of the study. Adjustments in interfaces, humidification, and pressure levels were made in the usual clinical fashion. After the first month, a respiratory therapist visited each patient to check the hour counter meter. The average hours use per day was calculated. A questionnaire (33 questions, 1 – 5 scale) also gauged patients’ reactions to treatment. Comparisons between groups were made with t-tests.

Results: Ten patients (RDI 44.7±26.8/h) were enrolled in the oral and 8 (RDI 46.5±17.8) in the nasal groups, respectively. All patients completed one month of study. After one month, patients with the VIPS averaged 4.0±1.7 h (SD); those with nCPAP averaged 4.2±2.6 h (p>0.5). No significant differences were observed in the therapeutic pressure (VIPS, 9.8±1.0 cmH2O; nCPAP 10.3±2.1 cmH2O; p>0.05). Six of 10 patients using the VIPS and 1 of 8 nCPAP patients had airway dryness. Eight VIPS patients had either painful gums or lip irritation; 2 nCPAP patients had skin irritation. Five nCPAP patients had nasal congestion, 2 patients reported claustrophobia, and 3 had significant air leaks; no patients in the oral group had these complaints. Annoying dislodgments of the masks were noted in 3/8 nCPAP patients and 2/10 with the VIPS. Five patients required refitting of their nasal masks, and only one patient required a change to a smaller oral interface.

Conclusions: These data demonstrate that the VIPS is a suitable alternative to nCPAP. Compliance with the VIPS was similar to nCPAP. The VIPS group noted more airway drying, and some lip and gum irritation. However, there were fewer complaints of air leaks, nasal congestion, skin irritation, and claustrophobia than with nCPAP. Future improvements in the implementation of the VIPS may further enhance patient satisfaction.

Supported by Fisher & Paykel Healthcare

475.J

Comparing the Acceptance of CPAP Between Split-night Studies and all Night CPAP Titration

Rosenberg CE
University Services, Philadelphia, PA

Introduction: One controversy in sleep medicine is using split night sleep studies in patients in with OSA needing CPAP. The goal is to reduce costs and expedite treatment. Published studies have shown that there is no significant difference between the CPAP pressure setting or compliance when comparing the two night studies (TNS) vs. single or split night studies (SNS). Our study compares the acceptance of CPAP in split night studies as opposed to a diagnostic then all night CPAP sleep study.

Methods: Patients were referred to the Sleep Laboratory directly by their physician or by seeing one of the Sleep Center physicians. Laboratory technicians were instructed to perform a SNS if they estimated an RDI of 30 or more, or at their discretion if they saw deep desaturations or arrhythmias. Adult patients were entered into the study if they 1) never had a CPAP sleep study, 2) never been on CPAP, 3) were cognitively intact, and 4) had no psychiatric diagnoses. The first 110 patients not excluded and referred for sleep studies were entered into the following study. The pre-CPAP RDI (RDI), CPAP pressure (CPAP), and Sleep Efficiency (SE) was collected from each study. A CPAP titration was conservatively scored as SUCCESSFUL if the RDI fell by at least 50% or under 10 with CPAP, REFUSED if the patient refused CPAP from the beginning of the study, NOT TOLERATED if the patient demanded that CPAP be stopped, INSUFFICIENT TIME if the patient tolerated CPAP but the titration was not SUCCESSFUL and INSUFFICIENT SLEEP if the patient could barely sleep once CPAP was started.

Results: See tables

Table 1

<table>
<thead>
<tr>
<th>Method</th>
<th>SE</th>
<th>RDI</th>
<th>CPAP</th>
</tr>
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<tr>
<td>TNS</td>
<td>Mean</td>
<td>62.22</td>
<td>14.55</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>23.98</td>
<td>15.70</td>
<td>5.72</td>
</tr>
<tr>
<td>SNS</td>
<td>Mean</td>
<td>64.99</td>
<td>44.16</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>19.06</td>
<td>25.70</td>
<td>6.30</td>
</tr>
</tbody>
</table>

Significance P<.05: 3 Yes

Conclusions: The differences in CPAP acceptance is dramatic between those having a SNS and those with a TNS with a much greater acceptance in the latter. These two populations are not identical: the SNS population has a higher RDI as expected from the technician’s instructions. The higher CPAP pressure in the TNS population is surprising considering the lower RDI, possibly indicating more time to titrate CPAP. Importantly, both populations slept equally well. The population differences, RDI and CPAP pressure do not seem to explain the difference in acceptance. Patients with higher RDI’s have a tendency to be more accepting of CPAP. There is no compelling evidence that a higher CPAP pressure increases CPAP tolerance. Most likely the difference is in patient preparation. It may be more difficult to adjust to the combination of wires and CPAP in one night, than wires one night and CPAP on the second. Possible solutions include: very strict criteria for SNS virtually eliminating them, careful patient education, and/or sending patients who might need CPAP home with at least a mask to get used to it prior to the study.

References:
**Is Elevation of Serum Vascular Endothelial Growth Factor Concentrations a Reliable Surrogate Biological Marker in Patients With Obstructive Sleep Apnea?**

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**Introduction:** Obstructive sleep apnea (OSA) is associated with intermittent hypoxia during sleep. Vascular endothelial growth factor (VEGF) has detectable levels in the circulation and its expression is highly regulated by changes in oxygen tension. We hypothesized that serum VEGF levels are elevated in OSA, and may serve as a biological marker for OSA.

**Methods:** Blood samples were collected at random times during the day from 68 adults and 41 children who were clinically suspected for the presence of OSA, and who underwent an overnight diagnostic polysomnographic evaluation within 7 days of blood drawing.

**Results:** For both children and adults, serum VEGF levels were significantly higher in polysomnographically confirmed OSA when compared to those with mild or no disease (P<0.0001). Furthermore, significant correlations were found between VEGF concentrations and respiratory disturbance index and sleep time spent at SpO2 <90%. In addition, VEGF levels in children were higher for any given duration of hypoxia during sleep (P<0.0001). No differences in VEGF emerged between evening and morning samples. However, temporal delays in blood sample processing were associated with spuriously increased VEGF concentrations. Exploratory analysis of the data revealed adequate OSA predictive values for serum VEGF concentrations of > 150 pg/ml in adults (AHI > 40/hr TST) and > 100 pg/ml in children (AI>5/hr TST).

**Conclusions:** Circulating VEGF levels are frequently elevated in OSA patients, and provide a reliable biological marker in more severe OSA patients. We postulate that VEGF elevations may play a role in the regulation of tissue oxygen delivery.

**References:**
(3) Lee JK, Hong YJ, Han CJ, Hwang DY, Hong SIClinical usefulness of serum and plasma vascular endothelial growth factor in cancer patients: which is the optimal specimen? Int. J. Oncol. 2000, 17:149-152.

Research supported by National Institutes of Health HL-65270, HL-63912 and HL-66358 the American Heart Association AHA-0050442N.

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**Continuous Positive Airway Pressure (CPAP) Interface and Compliance**

Massie CA,1,2 Ahrens SC,1,2 Hart RW1,2
(1) Suburban Center for Sleep Medicine of Suburban Lung Associates, Central DuPage Hospital, (2) Alexian Brothers Medical Center

**Introduction:** Many types of interface are available, and can be classified into nasal, nasal pillows or prongs, naso-oral and oral mask. The first two being the most commonly employed. Side effects related to interface include air leak, pressure sores and general discomfort, all of which may compromise a patient’s ability to utilize CPAP. One prior study examined compliance and side effects as a function of interface. Patients were more compliant with a nasal mask compared to a naso-oral mask, and rated the nasal mask as more comfortable. The present study compares the Respironics Contour (nasal mask [NM]), with the Mallinckrodt Breeze (a new type of interface utilizing nasal pillows [NP]).

**Methods:** To date, 28 patients (25 men and 3 women), mean age 47.7 ± 8 yrs, mean BMI 35.1 ± 5.5 kg/ M², with polysomnographically confirmed OSA (RDI ≥ 10) have completed the study. A randomized crossover design was employed. Patients were assigned to the NM or the NP during the titration, and subsequently initiated on CPAP (mean pressure 8.9, range 6-14) with the appropriate mask type and heated humidity. All patients utilized the Mallinckrodt GoodKnight 418A, in fixed pressure mode, which detected apneas and hypopneas during treatment. Each treatment period lasted 3-weeks. Pre-treatment Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) scores were obtained. Objective compliance, ESS, FOSQ, and self-report of general and specific side effects (12-item inventory, 4-point scale and 100 min VAS) were obtained at the conclusion of each treatment period. Sleep diaries were maintained daily for the first week of each treatment.

**Results:** Paired t-tests revealed that objective compliance across the 3-weeks and on days used did not differ between the two masks (p-values ≥ 0.14). However, patients utilized the NP on a greater percentage of days (94 vs. 85; p = 0.03). Repeated measures ANOVA was used to analyze FOSQ and ESS data. The FOSQ total score (F[6,54] = 19.4; p < 0.001) increased with treatment and the ESS score decreased (F[6,54] = 24.9; p < 0.001), but no differential treatment effects were observed. Patients reported fewer overall side effects (sum of 12-item inventory; p = 0.001) and greater satisfaction (VAS; p = 0.005) with the NP. Patients reported waking more refreshed during the first week of treatment with the NP (VAS; p = 0.02), but they also reported greater air leak (VAS; p = 0.002). No differences were observed for apnea index or hypopnea index (p-values ≥ 0.09).

**Table 1**

<table>
<thead>
<tr>
<th>Selected Outcome Measures, Pretreatment and during NP and NM Use</th>
<th>Compliance % days used</th>
<th>FOQ Side Effects</th>
<th>ESS</th>
<th>Refreshed</th>
<th>Air Leak</th>
<th>HI</th>
<th>Satisfaction w/mask</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NM</td>
<td>510 min</td>
<td>94</td>
<td>18.4</td>
<td>3.9</td>
<td>4.3</td>
<td>68</td>
<td>83</td>
</tr>
<tr>
<td>NP</td>
<td>514 min</td>
<td>85</td>
<td>18.5</td>
<td>6.6</td>
<td>8.7</td>
<td>59</td>
<td>66</td>
</tr>
</tbody>
</table>

**Conclusions:** The NP interface system was associated with fewer adverse side effects, with the exception of air leak. This did not appear to affect residual sleep disordered breathing, as apnea and hypopnea indices were acceptably low, and comparable to the NM. Although no compliance differences were observed, patients utilized the NP on a greater percentage of days, and were more satisfied with this type of interface. These findings may predict improved long-term compliance with CPAP.
Radulovacki MN, Pavlovic S, Rakic A, Janelidze M, Carley DW

Rats

5HT2 receptors evoked dose-dependent reflex apnea following intra-

Results

breaths (spontaneous apneas) or following a sigh (post-sigh apneas).

sis. Apneas were detected as cessations of phasic respiration for more

schedules. Obstructive sleep apnea was diagnosed at an RDI >= 5, per the

Introduction: In the rat model of sleep apnea, we have shown previ-

ously that 5-HT3 antagonists suppress spontaneous sleep apnea. In anes-

thetized rats, Yoshioka et al. demonstrated that agonists of 5-HT 3 or

5HT2 receptors evoked dose-dependent reflex apnea following intra-

venous injection. These effects were blocked by pre-treatment with

appropriate receptor antagonists, suggesting that 5-HT3 or 5HT2 recep-

tors may initiate apnea. In view of these studies, we conducted the pres-

ent experiment to determine the effects of endogenous tone at 5HT2

receptors on sleep-related apneas in rats.

Methods: Twelve adult Sprague-Dawley rats, maintained on a 12hr/12hr

light/dark cycle, were instrumented for recording EEG and nuchal mus-

cle EMG and were allowed 7 days to recover. Respiration was recorded

by single-chamber plethysmography. 15 minutes prior to each 6-hour

recording, each animal received, in random order, one of the following:

1) saline solution (control); 2) 0.1 mg/kg ketanserin; 3) 1.0 mg/kg

ketanserin; 4) 10.0 mg/kg ketanserin; or 5) 100.0 mg/kg ketanserin.

Behavioral state was staged as Wake (W), non-rapid eye movement

(NREM) sleep or rapid eye movement (REM) sleep by computer algo-

rithm. Breath by breath parameters were extracted by automated analy-

sis. Apneas were detected as cessations of phasic respiration for more

than 2.5 seconds and were observed to occur as pauses between tidal

breaths (spontaneous apneas) or following a sigh (post-sigh apneas).

Results: Intrapertoneal injection of ketanserin suppressed post-sigh

apneas (1.0 mg/kg, p = 0.03; 10.0 mg/kg, p = 0.0001; or 100.0 mg/kg, p

< 0.0001) in NREM sleep, whereas spontaneous apneas during NREM

sleep were suppressed only by a dose of 100.0 mg/kg (p < 0.0001) (Fig.

1). During REM sleep, ketanserin at all doses (0.1 mg/kg, p <0.005; 1.0

mg/kg, p <0.001; 10.0 mg/kg, p <0.001; or 100.0 mg/kg, p < 0.001) sup-

pressed post-sigh apneas, whereas spontaneous apneas were suppressed

only by the 100.0 mg/kg, (p < 0.00 1) dose of the drug (Fig. 2).

Figure 1

Conclusions: Our data implicate activity of endogenous serotonin at

5HT2 receptors in the genesis of sleep-related apnea. These novel observ-

ations parallel and extend our previous findings that 5-HT3 receptor

activation in the peripheral nervous system promotes sleep apnea gener-

ation.1-2 The widely differing doseeresponse profiles observed for

ketanserin suggest at least partially distinct mechanisms for spontaneous

versus post-sigh apneas. Especially at the highest dose, nonspecific

effects of hypotension or crosstalk with other receptor types cannot be

ruled out. Still, the present data provide a rationale for further evaluation

of the pharmacotherapeutic potential of 5HT2 receptor antagonists in the

treatment of sleep related breathing disorders.

References:


(2) Carley DW, Radulovacki M. Role of peripheral serotonin in the regu-


Supported by National Institute on Aging grant AG 14564.

479.J

Prevalence of Sleep Apnea in a Population of Women with Polycys-

tic Ovarian Syndrome

Gopal M, Uhles M, Duntley SP, Attarian HP

Washington University School of Medicine

Introduction: Obstructive Sleep Apnea (OSA) is a prevalent condition

that, if untreated, is associated with significant mortality and morbidity.

Obesity is a major risk factor for developing OSA and so is male sex.

One third of patients with OSA, however are not obese. The prevalence

of OSA is poorly recognized, especially among women. Polycystic

Ovarian Syndrome is an endocrine disorder of women characterized by

a hyper androgenic state and obesity. We wanted to determine the preva-

lence of obstructive sleep apnea in premenopausal women with PCOS

and compare it to those of the general population and those in the obese

population of each sex, in order to establish PCOS as a risk factor for

developing OSA independent of weight.

Methods: This was a prospective observational pilot study using histor-

ical controls. 20 premenopausal obese women with documented PCOS

and no prior diagnosis of a sleep disorder were given a sleep question-

naire and underwent overnight polysomnography in a sleep lab. The pre-

dictor variables were presence of PCOS and gender. The dependent vari-

ables were respiratory disturbance index (RDI) and self-reported hyper-

somnolence, measured with, respectively, interval and categorical

scales. Obstructive sleep apnea was diagnosed at an RDI >= 5, per the

International Classification of Sleep Disorders.

Results: All patients were obese with BMI range 31.8 to 46. 14 of 20 met criteria for sleep apnea, of who 4 required treatment. 6 of 20 did not have sleep apnea. The prevalence of OSAS in this small group then was about 70%. (as of 11/25/00, study is still ongoing)

Conclusions: The prevalence of symptomatic OSAS in the general female population is 2% and it is 4% in the general male population (1). The prevalence of symptomatic OSAS in the obese female population is 3.7% (2.3) and 40-77% in the obese male population (2.3). In our group of patients with PCOS the prevalence was 70%. This is higher than the prevalence in the obese female population and closer to the prevalence in the obese male population. PCOS is therefore an independent risk factor for developing sleep apnea. We postulate that this is because of a combination of factors including obesity and hyperandrogenic state. There is a higher prevalence of obstructive sleep apnea in obese patients with PCOS compared with the general population of women, men and obese female controls. A heightened awareness among physicians will lead to a rapid diagnosis and treatment to prevent significant mortality and morbidity.

References:

480.J

The Effect of an Oral Appliance (KlearwayTM) on Obstructive Sleep Apnea and Hypopnea Syndrome (OSAHS).
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Introduction: OSAHS is a common chronic sleep and breathing disorder that may present as pathological sleepiness with respiratory and/or cardiovascular complications. The treatment of OSA depends upon the severity of symptoms, magnitude of clinical complications and etiology of the upper airway obstruction. Nasal CPAP (n-CPAP) is the most common treatment, but some patients are unable to tolerate it on a long-term basis, particularly those with mild OSAHS with no somnolence. Maybe this could be risk factor for n-CPAP low compliance. Oral appliances (OA) and surgical procedures have been proposed as alternative therapeutic approaches. OA are indicated for use in patients with primary snoring or mild OSA and for patients with moderate to severe OSA who can not tolerate or refuse n-CPAP. There are two groups of OA: tongue retainers and the mandibular advancement devices. The adjustability and retention are the most important factors for the success of this treatment, particularly for mandibular advancement devices. KlearwayTM is a titratable oral appliance described by Lowe3 with an excellent retention.

Methods: Thirteen patients with snoring complaints were attended by the medical staff of the Sleep Institute, Sao Paulo, Brazil. They were submitted to a diagnostic polysomnography on an Oxford System. They were indicated for treatment with oral appliance. Some of them (38.5 %) were moderate or severe OSA patients who refused n-CPAP treatment, and 61.5 % were primarily indicated to OA. All of them presented good odontological conditions and absence of TMJ problems and/or periodontal problems. Thus, they underwent a treatment with the OA (KlearwayTM) described earlier3. After a variable adaptation period and OA titration, they were again submitted to a polysomnography (with OA).

Results: Before treatment: mean RDI = 18.8 (sd = 9.5); median RDI = 15.0; minimum = 5.0; maximum = 38.0 mean minimum desaturation = 79.85 (sd = 9.92);median minimum desaturation = 84.0; minimum = 57.0; maximum = 95.0 With oral appliance: mean RDI = 7.5 (sd = 5.2); median RDI = 6.3; minimum = 0.0; maximum = 21.5 mean minimum desaturation = 81.77 (sd = 9.28); median minimum desaturation = 84.0; minimum = 57.0; maximum = 97.0 Using paired Student’s t-test, marked statistically significant differences in RDI values (p < 0.05) before and after treatment were observed. For minimum saturation values there were no statistically significant differences.

Conclusions: Following this results, we can conclude that Klearway appliance is a good option of treatment to OSAHS patients, particularly considering on RDI.

References:

Financial support: Associacao Fundo de Incentivo a Psicofarmacologia (AFIP).

481.J

Evaluations of Efficacy and Compliance of CPAP and UPPP in Treating Patients with Obstructive Sleep Apnea
Sleep Disorders Center, Beijing Chaoyang Hospital

Introduction: Perfect efficacy of treatment for obstructive sleep apnea(OSA) should normalize breathing during sleep, improve sleep quality and be with good compliance and without risk or side effects. In order to evaluate efficacy and compliance of continuous positive airway pressure(CPAP) and uvulopalatopharyngoplasty(UPPP) in treating patients with OSA.

Methods: We reviewed 475 patients with OSA who underwent CPAP or UPPP treatment from 1990 to 1997 in our sleep center. There were 159 patients received UPPP therapy(UPPP group), 316 received CPAP therapy(CPAP group). We divided these patients into four subgroups depended on AHI was below or above 30 before treatment. All patients underwent PSGs before and after (1 to 6 months) treatment.
Results: In CPAP group: Patients with AHI<30 showed lower compliance. Only 23/113 (20.3%) patients used their CPAP devices about 4 hours per night. 59/113 (52.2%) patients terminated CPAP treatment within 1 to 5 months after initially used because that CPAP preventing them entry into deeper sleep stages and very frequent arousals made them poorer sleep quality although CPAP normalized sleep related breathing. 35/113 (30.9%) patients refusing this therapy after a single night’s use in the lab. The high incidence of side effects mainly centered on nasal problems which may alter long-term compliance to CPAP. Whereas, patients with AHI>30 showed high compliance who may be with or without extremely obese, chronic CO2 retention, mandibular deficient, hypertrophied tongue or tonsil.. 153/203 (78.3%) are tolerant of using CPAP every night. 48/203 (23.6%) patients with severe OSA were too uncomfortable attempting to sleep without CPAP.

Table 1 Mean Values of PSGs Before and After Treatment

<table>
<thead>
<tr>
<th></th>
<th>CPAP group 113</th>
<th></th>
<th>UPPP group 159</th>
<th></th>
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<tbody>
<tr>
<td>(AHI&lt;30)</td>
<td>(AHI&gt;30)</td>
<td>(AHI&lt;30)</td>
<td>(AHI&gt;30)</td>
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</tr>
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</table>

In UPPP group: 97/110 (82.7%) patients with AHI<30 received remarkable improvement after the operation. 19/110 (17.3%) patients with limited efficacy because of obesity, mandibular deficient or hypertrophied tongue. In 49 patients with AHI>30, 33 (67.3%) patients showed limited improvement. 18 (36.7%) patients finally had to received CPAP therapy.

Conclusions: Although the evaluation of clinical feature improvement may be multifactorial, there are greatly differences in efficacy and compliance of CPAP and UPPP between OSA patients with an AHI<30 and AHI>30. Compliance with CPAP maybe low in patients with AHI<30. And efficacy of UPPP is limited among patients with AHI>30. Patients with hypertrophied tongue, sleep-induced posterior tongue motion and severely mandibular deficient are not favor to UPPP. If maxillo-mandibular osteotomy or mandibular advancement are not available, or UPPP fail to eliminate apnea, CPAP should be consider. Educational efforts and technical and medical follow-up are necessary when OSA patients receive treatment.

482.J

Unusual Presentation of Sleep Apnea

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Introduction: Sleep apnea typically presents with complaints of sleepiness, fatigue or a concern on the part of bed partners. In children the most common presentation of sleep apnea are snoring, poor performance at school, nightmares and hyperactivity or sleepiness. Here we present a case of a 6 year old girl with secondary enuresis after being completely dry for 2 years. Enuresis was nightly and often several times a night. She had 4.9% stage 1 (increased); 24.5% stage 2 (decreased) and increased sleep deep. Her respiratory disturbance index (RDI) was 7.1/hour (fulfilling the recognised criterion for sleep apnea of one event per hour in children). Most of the respiratory events occurred in REM sleep. Immediately after the tonsillectomy the enuresis stopped completely and a subsequent sleep study showed normal sleep architecture (qualitatively and quantitatively). There were no abnormal respiratory events during her sleep.

Conclusions: The learning point of this case vignette is that secondary enuresis may be a primary presentation of sleep apnea in children. In adults and children enuresis as a feature of sleep apnea is recognised but we are not aware of any accounts of enuresis being the presenting complaint in children.

483.J

Craniofacial Characteristics of Patients with Sleep Apnea: A Study with the Enlows CounteParts Analysis

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(1) Department of Orthodontics - Federal University of Ceara, (2) Department of Psychobiology - UNIFESP, Sao Paulo, Brazil

Introduction: Obstructive Sleep Apnea and Hypopnea Syndrome (OSAHS) is a breathing disorder characterized by repetitive obstructions of the upper airway during sleep. The cephalometry has demonstrated a variety of different abnormalities of craniofacial anatomy that may predispose to a narrow of upper airway in OSAHS patients. The Enlows cephalometric analysis evaluates the patient individually with points corresponding to areas of growth and remodelling, avoiding comparison to the standard population.

Methods: A sample of 49 brazilian patients with mild, moderate and severe OSAHS was selected and divided in two groups: a mild to moderate and a severe group. Twenty patients were considered to have mild (10<RDI<20) and moderate (20<RDI<40) OSAHS and twenty nine severe OSAHS (RDI>40). All patients were submitted to a cephalometric roentgenograms with teeth in occlusion and a conventional polysomnography on Oxford system. The correlation between anatomic structures of the craniofacial complex was analyzed by means of the Enlows counterpart analysis. From variables studied and results achieved we can conclude: 1. The dimensional and rotation compromise were revealed by representative cephalometric variables of the middle cranial floor and mandibular ramus that may cause an unfavorable influence in the pharyngeal air space. These are counterparts of growth that establish a craniofacial architecture that contributes for a reduction of the anteroposteri-
or airway dimension. The behavior of cephalometric variables was similar in the groups of mild to moderate and severe apnea. Unbalanced skeletal craniofacial characteristics were present in both groups, which shared the same intrinsic alterations. As the apnea and hypopnea index increases we observed an increase in obesity, the narrowing of the mandibular ramus in relation to the horizontal dimension middle cranial floor and a reduction of arterial oxygen saturation during sleep.

References:

Financial support: Associacao Fundo de Incentivo a Psicofarmacologia (AFIP).

484.J

Polysomnographic Evaluation in Interstate Bus Drivers

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Introduction: In shift-work or prolonged working journeys, human mistake may be the major determinant of accidents. Lack of attention, inadequate observations and cognitive mistakes make up to approximately 40% of the cases. The present study sought to evaluate, by means of polysomnography (PSG) the sleep pattern and complaints of professional interstate bus drivers from a commercial company.

Methods: The study was carried out in two phases, distributed as follows: In the first evaluation, the driver spent a first night of adaptation to the exam (PSG), followed by a whole PSG recording night and a multiple sleep latency test (MSLT) two hours after waking up. In the second evaluation, the driver underwent the PSG recording immediately after a working journey and, at least, 4 days after returning to the normal working schedule; two hours after waking up, the driver was submitted to the MSLT. Were evaluated 31 bus drives.

Results: Table 1

Table 1

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency</td>
<td>17 (minutes)</td>
<td>18.2 (minutes)</td>
<td>0.01</td>
</tr>
<tr>
<td>REM sleep latency</td>
<td>81 (minutes)</td>
<td>77 (minutes)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>414 (minutes)</td>
<td>380 (minutes)</td>
<td>0.08</td>
</tr>
<tr>
<td>Time awake</td>
<td>42 (minutes)</td>
<td>79 (minutes)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>84%</td>
<td>78%</td>
<td>0.05</td>
</tr>
<tr>
<td>Excessive somnolence</td>
<td>30% *</td>
<td>50% **</td>
<td>n.a.</td>
</tr>
<tr>
<td>Periodic limb movements (PLM)</td>
<td>10% *</td>
<td>20% ***</td>
<td>n.a.</td>
</tr>
<tr>
<td>Apnea/hypopnea index (AHI)</td>
<td>40% ***</td>
<td>42% ***</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

*: % of drivers who presented excessive somnolence
**: % of drivers who presented a PLM index above 5%
***: % of drivers who presented AHI above 5%

Conclusions: It is possible to conclude that the drivers exhibited high levels of excessive somnolence, AHI and PLM either on the first or on the second phase. Although the total sleep time was undistinguishable between the phases, a lower sleep efficiency was observed on the 2nd phase, due, mainly to the longer waking time. This fact shows that drivers may be sleep deprived and shift-work may be causing sleep disturbances, since sleep was not refreshing on the second phase of the study, thus becoming a risk factor for accidents. This study will pursue, with the purpose to analyze the sleep pattern, by means of PSG, and complaints of all drivers of the company.

Financial support: AFIP, CEPID/FAPESP, NACIONAL EXPRESSO LTDA.

485.J

Use of a 6-channel Esophago-pharyngeal Pressure Probe with Automatic Analysis in the Diagnosis of Obstructive Sleep Apnea

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Introduction: To provide the best treatment for patients suffering from sleep apnea syndrome it is essential to know the site of obstruction. But up to now an ideal method for detection of the site of obstruction during an apnea has not been found. Multichannel esophago-pharyngeal probes have been described previously to be helpful, but problems exist concerning positioning of the transducers, artefacts and analysis of the pressure data. In the following, we describe the use of a new developed automatic analysis of the data derived from a 6-channel probe.

Methods: Ten patients with snoring or suspected sleep apnea were examined using polysomnography and measurement of the esophagog-pharyngeal pressure. Our pressure probe with a diameter of 1.8 mm, the first pressure transducer placed in the esophagus, the other five in the pharynx, was similar to the probe used by Skatvedt. The pressure data were analysed by a new software (developed for our department) which determined the pressure amplitude of every breath for the 6 channels during the whole night. The disperment and the mean amplitudes during normal breathing, apneas and hypopneas were calculated. For further analysis the relative pressures of the 5 pharyngeal transducers were determined based on the esophageal pressure. The data derived during normal breathing and apneas were compared.

Results: After a short time of habituation all patients tolerated the probe well and reported only little disturbance. On the average 7988 ±870 breaths were analysed for each patient. 5 Patients had more than 50 apneas during the night. The comparison of the relative pressures during normal breathing and sleep apnea in these patients showed distinct differences between the transducers. For example, in patient 5, 7320 pressure amplitudes during normal breathing and 309 during obstructive apnea were determined. The relative pressures during apnea compared to normal breathing for the 6 transducer were 100% (esophagus), 102% (hypopharynx), 112% (tongue base), 108% (middle of oropharynx), 112% (velum) and 38% (nasal pharynx). Based on these results we concluded that in this case the main obstruction was located at the level of the velum. Other patients showed obstruction at the hypopharynx or the tongue base in a similar way.

Conclusions: Automatic analysis of multichannel esophago-pharyngeal pressure measurement seems to be a helpful tool in detecting the site of obstruction during sleep apnea. More data and postoperative re-examination will be needed to determine the accuracy of our findings.

References:
Comparison of Maintenance Wakefulness Test and Multiple Sleep Latency Test in Obese Apnea Patients.

Valencia-Flores M,1,2 Recendiz M,1,2 Casiano VA,1,2 Santiago V1,2 Campos RM,2 Montes J,1 Rosales M,1 Blilisie DLJ
(1) Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán, (2) PUIS-Facultad de Psicología, UNAM, México, D.F., Sleep Disorders Center, Emory University, School of Medicine, Atlanta, GA, USA.

Introduction: Sleepiness is a cardinal symptom in Obstructive Sleep Apnea Syndrome (OSAS), the standard test for assessing excessive daytime sleepiness is the Multiple Sleep Latency Test (MSLT). Maintenance of Wakefulness test (MWT) also appears to be useful in evaluating disability from daytime sleepiness, although some have hypothesized that the MSLT measures sleep tendency while the MWT measures ability to stay awake.

Methods: The MSLT and the MWT were administered on the same day to 41 consecutive obese patients whose full-night polysomnography (PSG) demonstrated obstructive sleep apnea as defined by an Apnea/Hypopnea Index (AHI) (number of apneas and hypopneas per hour of sleep) ≥ 5. The MWT consisted of five 20 min trials, separated by 2 h intervals, and beginning about 2 h after previous night’s PSG. Subjects were sitting in bed in a dimly lit room and instructed to try to remain awake. The trial was terminated after 20 min if sleep did not occur, or 15 min after sleep onset. The MSLT, was administered under standard conditions after MWT. During intervals between sleepiness tests, subjective daytime sleepiness was measured with Epworth sleepiness scale (ESS) and the sleepiness scale of Sleep-Wake Activity Inventory (SWAI), the Beck Depression Inventory (BDI) and Sleep Disorders Questionnaire (SDQ) were also administered. For comparisons between patients with different reported level of daytime sleepiness we classified the apnea patients into two groups ESS < 11 (Non-Sleepy-Group, n=28) and ESS ≥ 11 (Sleepy-Group, n=13).

Results: There were not statistically significant differences between the groups in total sleep time, sleep efficiency, awakenings, sleep architecture or Apnea/Hypopnea Index. A significant correlation between the MWT and the MSLT was found (r=0.66, p<0.001). ESS correlated significantly with MSLT (r=-0.52, p<0.002), MWT (r=-0.48, p<0.005) and SWAI (r=-0.63, p<0.001). Interestingly BDI correlated with MWT (r=-0.40, p<0.02) but not with MSLT (r=-0.24, p=0.19).

Table 1

| Variable          | Non-Sleepy Group | Sleepy-Group | P<  
|-------------------|-----------------|--------------|-------
| Age (yrs)         | 47.5±11.5       | 36.6±12.1    | 0.03  
| Body Mass Index   | 46.2±18.8       | 39.7±36.1    | ns    
| AHI               | 15.0±6.1        | 8.9±5.4      | 0.0005 
| MWT min           | 6.3±3.7         | 2.6±1.3      | 0.0001 
| ESS               | 5.2±2.8         | 15.9±4.4     | 0.0001 
| SWAI              | 61.4±13.3       | 47.5±13.8    | 0.005  
| SDQ item 21       | 2.5±1.5         | 3.7±1.2      | 0.02   
| SDQ item 157      | 1.1±0.3         | 1.8±1.4      | 0.02   
| BDI               | 15.5±9.7        | 23.5±7.1     | 0.02   

Conclusions: In obese sleep apnea patients there is a significant association between MWT and MSLT, the subjective sleepiness scales (ESS and SWAI) correlated significantly with objective measurement of sleepiness. Interestingly depression seems to be a factor that might affect MWT.

Research supported by DGAPA-IN207397 and NIH AG-10643

Coping Styles, Psychogenic Attitudes and Psychosomatic Correlates in Obstructive Sleep Apnea Syndrome: A Descriptive Pilot Study of the MBHI in Sleep Medicine

Bell EA
Methodist Hospital Sleep Center

Introduction: Previous research has indicated that patients with obstructive sleep apnea syndrome may share certain psychological characteristics, such as somatic concerns and depressive symptoms (1), as well as various degrees of neuropsychological impairment (2). The Millon Behavioral Health Inventory (MBHI) is a 150 item, forced-choice, psychological instrument which has been utilized in health psychology settings for several years and Millon, Green and Meagher (3) have indicated that this instrument had been developed for use with medical patients, rather than psychiatric populations. Some relevant applications of the MBHI include facilitating an understanding of the patient, describing a probable manner of the individual’s relating to health care personnel and also to promote a comprehensive treatment plan.

Methods: In the present prospective, yet descriptive study, 62 consecutively physician-referred normal weight patients (mean age = 48.8; sd = 9.8; male = 48, female = 14) were evaluated in our sleep disorders center following clinical interview with the author. Each patient underwent a standard polysomnogram, immediately followed by an MSLT-MWT. During the MSLT-MWT evaluation, each patient completed the MBHI, responses were keyed into a computer system (NCS scoring) and interpretative profiles were derived. Obtained PSG and MSLT data were entered into spreadsheet format, along with MBHI data. As this was a pilot study and previous MBHI data with OSAS patients had not been reported, means and standard deviations of basal rate (BR) inventory scores are provided below.

Results: Mean polysomnographic data revealed an overall sleep efficiency of 82.6% (sd=11.4), waking frequency of 11.79 events/sleep episode (sd=6.29), an apnea index of 25.9/hour sleep (sd=24.4), the number of transient arousals of 123.41 events/night (sd=76.5) and an overall MSLT score (measured as the mean latency to stage one sleep) of 5.46 minutes (sd=3.10). In descending order, mean BR responses from our patient group are as follows (mean, sd): Basic Coping Style: Introversion (60.3,22.9), Respectful (58.6,17.8), Inhibited (52.3,32), Cooperative (51.6,26.6), Sensitive (43.8,28.7), Sociable (38,26), Confident (37.7,22.2) and Forceful (32.2,24.8). Psychogenic Attitudes: Somatovisceral Insomnia (49.2,20.8), Social Alienation (46.6,24.9), Future Despair (46.6,22.5), Premorbid Pessimism (46.5,24.6), Recent Stress (43.8,25.9) and Chronic Tension (41.6,28.3). Psychosomatic Correlates: Gastrointestinal Susceptibility (62.2,18.4), Cardiovascular Tendency (59.6,19.7) and Allergic Inclination (59.2,16.9). Prognostic Indices: Life Threat Reactivity (58.20.9), Pain Treatment Responsivity (43.3,28.6) and Emotional Vulnerability (29.2,27.4).

Conclusions: The primary aim of this research was to provide additional physiological assessment data (MBHI scores) with a heterogeneous group of OSAS-EDS patients. Within this patient sample, mean BR data were not consistently elevated with any particular scale, suggesting substantial variance existed among our patient group in their manner of responding to MBHI items. Furthermore, ongoing research with other patient groups (i.e., snoring without OSAS + excessive sleepiness and psychophysiological insomnia) will be reported separately. Lastly, clinical applications of the MBHI in sleep disorders medicine will require addi-
Referential research from other investigators.

References:

Radiofrequency Volumetric Tissue Reduction Of The Soft Palate And Tonsils: A New Therapy For Snoring And Obstructive Sleep Apnea

(1) Sleep Disorders Center, Beijing Chaoyang Hospital, sleep@mail.com, (2) Sleep Disorders Center of Bergen, Norway

Introduction: Snoring and obstructive sleep apnea process with a high prevalence. Obstructive tonsils, palatal webbing, and an enlarged uvula require surgical approaches including the soft palate and tonsils. Radiofrequency has been investigated as a treatment for sleep-disordered breathing. In order to improve snoring and obstructive sleep apnea, soft palate tissue and tonsils have been treated with Coblation.

Methods: 32 subjects with simple snoring and 41 with mild obstructive sleep apnea (mean AHI 15.5, b7.2) were selected for radiofrequency thermal ablation with Coblation (Arthrocare, USA) and bipolar reflex 55 electrode. All of these patients were selected according to mainly narrow and obstructive level of soft palate, uvula and tonsils. Nocturnal polysomnograms (Respironics, USA) were performed before and after operation.

Results: All subjects underwent radiofrequency thermal ablation under local anesthesia successfully. 41 OSA subjects with a mean AHI of 15.5, b7.2 and mean lowest SaO2 of 81.8 ± 7.6%. Six to two months after RF operation, the mean AHI decreased to 7.3, b5.4(p<0.01), the mean lowest SaO2 increased to 87.1, b4.9%(p<0.05). The percentage of slow wave sleep among total sleep time increased from 2.6, b3.5% to 5.8, b4.7%(p<0.05). An alternative to nasal CPAP was needed for 6 subjects with OSA. 7 subjects combine with dental device to release the obstruction of base of tongue. The mean snoring degree decreased from 6.4 to 2.1 among snorers.

Conclusions: Our study indicated that snoring and obstructive sleep apnea could be significantly improved by using radiofrequency thermal ablation in some subjects at least on a short-term basis. These results can be obtained without complications related to speech, taste or swallowing. The treatment can be administered as an outpatient procedure. The determination of which patients will benefit most from these procedures will require further multi-center, placebo-controlled and long-term studies.

Daytime Sleepiness Among Patients With OSAS: MSLT Findings With Those Who Admit or Deny Sleepiness While Driving

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Introduction: Excessive daytime sleepiness (EDS) remains one of the most significant symptoms associated with OSAS and both objective (i.e., MSLT) and subjective (i.e., interview, questionnaire) measures are available for assessment purposes. Essentially, the former (MSLT) provides physiologic data, while the latter rely upon self-report and self-perceptual processes. Although the ICSD-R (1) clearly indicated that MSLT studies should be performed with OSAS-EDS patients, another report (2) did not concur with this viewpoint. Because subjective measures can be unreliable (3) and patients with moderate to severe OSAS may be at considerable risk for motor vehicle accidents, this study was conducted in order to evaluate physiologic sleepiness with OSAS patients who either admitted or denied sleepiness while operating a motor vehicle. It was hypothesized that significant differences with daytime sleepiness would not exist between the two (admit/deny) groups.

Methods: Two hundred thirty-seven (237) physician referred patients (males = 185; females = 52) completed an initial sleep history with the author and subsequently underwent a routine diagnostic polysomnogram followed immediately by a four nap MSLT. Sleep stages and other polysomnographic variables were scored according to standard criteria and MSLT scores were derived from the latency to stage one sleep. Relevant data are presented below (mean, sd).

Results: Group One: Denied sleepiness while driving (n=59; m=45, f=14); Age (53.67, 12.3), apnea index (26.16,21.04), lowest oxygen saturation (76.49, 12.56), total number of transient arousals per sleep episode (135.54, 108.68), MSLT (6.59, 4.16).Group Two: Admitted sleepiness while driving (n=178; m=140, f=38); Age (48.11,10.59), apnea index (34.57,39.89), lowest oxygen saturation (76.39, 13.44), total number of transient arousals per sleep episode (162.92,126.07), MSLT (5.16,3.53).

Conclusions: Significant statistical differences with mean MSLT scores, as well as other data, were not observed with these groups of physician referred patients. Importantly, both groups exhibited clinically significant objective sleepiness, yet this level of hypersomnia was not accurately identified through simple questioning. Similar findings have been observed with another sample of 157 patients with the chief complaint of snoring (Bell, unpublished data). Given the likelihood that wakefulness may be unstable among OSAS patients and that inattention may play a substantial role with driving performance, gaining objective measures of daytime sleepiness with similar patients appears warranted.

References:
(1) ICSD-R (1997), ASDA.
≤ 5) at the Stanford Sleep Disorders Clinic. Patients: The cohort consisted of 30 patients (24 males, 6 females) with mean age of 49.7 (SD 8.27), mean body mass index of 33.09 (SD 7.09), mean AHI of 32.42 (SD 21.44). (See Table 1) Treatments: Patients chose one of the following treatments: n-CPAP or Bi-level treatment (n-CPAP=23, Bi-level n=1), oral appliance (n=2), UPPP/nasal surgery/genioglossus (Phase I) surgery (n=3), mandibular advancement (Phase II) surgery (n=0), T&A (n=1), tracheotomy(n=0). Measurements: Epworth Sleepiness Scale, Medical Outcome Short Form (SF-36) questionnaire, Calgary Sleep Apnea Quality of Life Index (SAQLI), and Preference Utilities by Visual Analog Scale (VAS) and Standard Gamble (SG) of the following health states: current health, nasal CPAP, oral appliance, Phase I & II surgery, and tracheostomy were assessed at between 1-6 months after treatment.

Results: Total group: The Epworth Sleepiness scale reflected a significant improvement for the entire group before 11.8 (SD 5.08), after 6.22 (SD 3.71) (p<0.001). Analysis using paired t-tests showed significant improvement in all SF-36 categories except bodily pain and role-emotional (see Figure 1). Vitality showed the normalized group mean to be below that of general population (50). There was no significance measured by SAQLI. VAS demonstrated a trend in utilities of improvement of current health only. Standard gamble approach showed a significant decrease in utilities of Phase II surgery. Subgroup: The n-CPAP patients were the predominant contributors to the improvements of the SF-36 subscales, but patients who selected other treatments accounted for the improvement in physical functioning (p<0.04). The n-CPAP group accounted for the decline in attitudes towards phase II surgery.

Table 1

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Total (n=30)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>24.6%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Age median</td>
<td>49.7 (8.27)</td>
<td>50</td>
<td>50.5</td>
</tr>
<tr>
<td>BMI median</td>
<td>33.09 (7.09)</td>
<td>50.5</td>
<td>48</td>
</tr>
<tr>
<td>AHI median</td>
<td>32.42 (21.44)</td>
<td>35.65</td>
<td>35.67</td>
</tr>
<tr>
<td>Epworth median</td>
<td>11.80 (5.09)</td>
<td>19.8</td>
<td>12.33 (2.94)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian=26</td>
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<td>Native American =1</td>
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</tr>
<tr>
<td></td>
<td>Native American =1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1

Conclusions: The health-related quality of life scales currently available yielded different results during repeat testing in these one-month comparisons. Although SF-36 is not a disease-specific instrument, it demonstrated more significant changes. Patients with OSA perceived their vitality below normal. Patient also perceived a general higher utility with treatment of their OSA when assessed by VAS. Since only one re-assessment was performed, it would be difficult to determine if the disease-specific QoL scales would reflect a similar degree of change. Previously reported significant improvements in utilities of OSA patients undergoing n-CPAP use was not seen here except for the health state for mandibular advancement. This may reflect the anticipatory attitudes of n-CPAP patients towards surgical options. This study demonstrates that the quality of life of patients with OSA measurably improved with treatment. A larger scale study would help categorize better the preferences and attitudes of the surgical subgroup, and will help determine cost-effectiveness of these procedures.

References:

Additive Effects of Circadian Rhythms and Sleep on Respiration in the Rat

University of Toronto

Introduction: Sleep is associated with reduced respiratory responsiveness to CO2. We have shown that respiratory chemoreflex characteristics oscillate with an endogenous circadian rhythm in humans and rats (Stephenson et al., 2000; Peever and Stephenson, 1997) but studies have been performed only in wakefulness. We hypothesized that the effects of sleep and circadian time are additive. Capitalizing on the polyphasic sleep-wake pattern of freely behaving rats, we measured ventilation (VI) and CO2 production (VCO2, as an index of metabolic rate) in each of wakefulness, rapid-eye-movement sleep (REM) and non-REM sleep (NREM) in each 2 h time bin across the day and night (12:12 h light dark cycle).

Methods: At least 7 days before experiments, 6 male Sprague-Dawley rats (359±19g) were implanted with a radiotransmitter for measurement of electroencephalogram (EEG), neck electromyogram (EMG) and body temperature by telemetry. VI and VCO2 were measured non-invasively using whole body plethysmography. Recordings began 10 h after placing the animal in the plethysmograph and continued for a further 24 h. Each rat was studied twice and data were pooled across days. Data were normalized (deviations from 24 h mean), pooled across animals, then subjected to least squares sinusoidal regression.

Results: Statistically significant circadian rhythms were observed in VI (p<0.005) and VCO2 (p<0.05) in each of wakefulness, NREM sleep, and REM sleep. Amplitudes (mean to peak difference) and phases of the rhythms were similar across sleep-wake states (p>0.2). That is, the state-specific circadian rhythms were in parallel. The amplitudes of the circadian rhythms were approximately 9% of the respective 24-h mean values and the rhythms peaked mid-way through the dark phase of the LD cycle. The circadian rhythm in VI was mediated by a rhythm in respiratory frequency (fR) (p<0.002). Tidal volume (VT) was unrelated to time of day in all sleep-wake states (p>0.999). In addition, there were significant overall effects of sleep-wake state (p<0.001). Comparing 24-h mean values revealed that VI was significantly greater during wakefulness (363.5 ±18.5 ml.min-1) than during NREM sleep (284.8 ±11.1 ml.min-1) and REM sleep (276.1 ±13.9 ml.min-1). fR was significantly lower in NREM than in wake and REM (p<0.013). VCO2 and VT each significantly decreased from wake to NREM to REM (both p<0.001). Thus, VT contributed to the state-dependent effect but not to the circadian effect on VI.

Conclusions: These data show for the first time that VI and VCO2 exhibit circadian rhythms during NREM sleep and REM sleep as well as...
wakefulness. The amplitudes and phases of the circadian rhythms in respiration and metabolic rate were similar across sleep-wake states, implying that the masking effect of sleep-wake state on VI and VCO2 is not dependent on time of day. We conclude that the circadian timing system and sleep-wake state have separate and additive effects on respiration in the rat.

References:

Research supported by NSERC Canada, MRC Canada, Ontario Graduate Scholarship in Science and Technology.

492.J

Morning Hypotension and UARS
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Introduction: Orthostatic intolerance (OI) and orthostatic hypotension (OH) cause a diminished quality of life and an increased incidence of falls. This study examines the presence of OI, OH, and low blood pressure in 4409 subjects referred for sleep studies (overnight 18-channel polysomnography). A low resting arterial blood pressure (systolic blood pressure less than 105 mmHg, diastolic blood pressure less than 65 mmHg) was present in 101 subjects (2.3%). Low blood pressure was observed commonly in subjects with UARS [(23%)], but was uncommon in subjects with OSAS [(0.6%)], parasomnia [1/ 127, (0.7%)], restless leg syndrome [(9.9%)], and psychological insomnia [(0.9%)].

Methods: In order to investigate blood pressure homeostasis, 15 subjects with OI and the upper airway resistance syndrome (UARS), 15 subjects with OSAS (matched for age and BMI), 5 insomniac subjects with low blood pressure, and 15 control subjects underwent tilt-table testing. Fifteen subjects with UARS and OI and fifteen control subjects also underwent 24-hour ambulatory blood pressure monitoring.

Results: Subjects with OI and UARS had lower mean daytime systolic blood pressure (119 ± 28 mmHg) and lower mean daytime diastolic blood pressure (75 ± 18 mmHg) than control subjects (131 ± 35 mmHg and 86 ± 19 mmHg, respectively) (p < 0.05). During tilt-table testing, subjects with UARS and a history of OI had a greater drop in blood pressure (27 ± 3 mmHg), than control subjects (7.5 ± 1.6 mmHg), subjects with OSAS (7.5 ± 1.6 mmHg) (p < 0.01), and insomniacs (9.4 ± 1.5 mm Hg) (p<0.01).

Conclusions: We conclude that a fifth of subjects with UARS have low blood pressure and complain of OI in the morning. Morning tilt-table testing of these subjects demonstrates resting tachycardia and OH consistent with hypovolemia. Low early morning blood pressure may increase the risk of stroke in older patients.

493.J

CPAP Adherence: The Role of Self-Prediction
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Introduction: Despite a multitude of studies over the last decade examining potential predictors of adherence with nasal continuous positive airway pressure (CPAP), no reliable predictors have been found to date (Collard et al., 1997). It has been suggested that researchers have overlooked the potential accuracy of patient’s forecasting their own level of compliant and noncompliant behaviors (Kaplan & Simon, 1990). This study prospectively investigated the relationship between self-prediction and objectively measured CPAP adherence over a one-month time period.

Methods: Fifty-one consecutively presenting patients (49 men) to the Pulmonary Clinic at the Veterans Affairs San Diego Healthcare System participated. All participants were diagnosed with sleep apnea and were prescribed the Respiromics Aria LX CPAP machine (Respiromics, Inc., Pittsburgh, PA), which recorded objective adherence information. Adherence was measured at one-month. Self-predicted nightly use (in hrs/night) was assessed both at CPAP fitting and at one-week post CPAP-fitting. Hierarchical regression analysis was performed between the number of hours of CPAP usage per night and self-predicted use. CPAP pressure was chosen as the covariate in the analyses because it has been shown that CPAP pressure is in large part a function of body mass index (BMI) and AHI.

Results: Table 1 shows background information. Mean self-predicted use measured at CPAP fitting was 7.0 hours per night ± 1.4 (range 3.6-10.0) and measured at one-week post CPAP fitting was 6.5 hours per night ± 2.1 (range 0-10.0). No significant relationship was found between self-predicted use measured at CPAP-fitting and CPAP adherence. Table 2 shows the results of the analyses regressing self-predicted use measured at one-week post-fitting on CPAP adherence. At step 1 R² = .047, adjusted R² = .025 (p = .148). At step 2 R² = .152, adjusted R² = .113 (p = .029). The change in R² between the two steps was .105 (p = .026), meaning that self-predicted use measured at one-week post CPAP-fitting accounted for a statistically significant amount of variance in objective CPAP adherence measured at one month.

Conclusions: Eleven percent of the variance in CPAP adherence can be predicted by knowing the scores on the self-predicted use scale at one-week post CPAP-fitting, over and beyond that accounted for by CPAP pressure (and thereby BMI and AHI). No relationship was found between self-predictions made on the day of CPAP-fitting and adherence. These results suggest that the patient may be a valuable source of information concerning level of future CPAP adherence, but only when the patient has had experience (in this case, one week) with the CPAP regimen. These data support Kaplan & Simon’s review findings that patients can be surprisingly accurate in predicting adherence particularly when: 1) they have personal experience with the medical regimen and 2) in situations that they understand clearly.

References:

Research supported by NIA AG02711, NCI CA 85264, VISN 22 MIRECC, and the Research Service of the VASDHS.
Cognitive Deficits in Obstructive Sleep Apnea

Koves P, Szakács Z, Bernáth I, Molnár M
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Introduction: Patients with OSA frequently complain about daytime symptoms (excessive daytime sleepiness impairment of general intellectual functioning, of attention, of working, episodic prospective and procedural memory and of the executive functions as well. Complaints related to sleep fragmentation proved to be normalized by adequate treatment, while deficits might be caused by hypoxemia and thought to result from frontal lobe dysfunction, which could be only relieved partially. Many SPECT and TCD studies coupled with PSG referred to the harmful impact of sleep fragmentation on the frontal lobe function mostly accompanied by regional (frontal and parietal) impairment of the cerebral blood flow. The aim of our study was to obtain further data about the mental/cognitive deficits occurring in OSAS patients reflected by specific neurophysiological examination and by HMPAO SPECT.

Methods: Patients: males, age < 60 yrs., RDI: between 20 and 50, Epworth < 10, htc < 0.5, stroke free patient’s history and negative CDS finding, right handedness. Protocol: Complete sleep lab examination, vascular laboratory tests, CDS, CT, HMPAO SPECT; neurophysiological examination based on internationally accepted test battery. Protocol was repeated after a 6-month period of controlled CPAP/BiPAP treatment.

Results: Until this time 17 pts have undergone the first (A) and 6 pts the second (B) session. A. 16 of them developed significant premotor deficits, impairment of manual dexterity, of eye-hand coordination, of intended verbal attention/memory, of unintended visual attention/memory, deficits in episodic, prospective memory, impairment of executive functioning and of mental flexibility. There were no deficits of parietal and of other cerebral lobes. In each pt. values of Beck scale remained below 14. CT: normal in 15 pts., parietal lacunar focuses in 2 pts. SPECT showed frontal hypoperfusion in 11 pts. (in 9 pts. on the left side), in 3 pts. frontoparietal, in 1 pt. parietal hypoperfusion. Normal finding could be found in 3 pts. B. The 6 pts. undergone repeated protocol developed significant improvements in all elements of the frontal deficits except for manual dexterity, eye-hand coordination and kinetic melody in 5 pts., and for procedural memory and focused attention in 2 pts. Characteristic regional hypoperfusion had been completely normalized by effective CPAP treatment in all cases.

Conclusions: Changes observed in the neurophysiological tests and HMPAO SPECT in the relation of CPAP treatment of OSAS pts. confirms the vulnerability of the frontal lobe in OSAS -proves the curative effect of CPAP treatment started in the early period of it -might refer to the excessive vulnerability of premotor function -highlights the important role of specific neurophysiological examination (and SPECT) in the diagnostical protocol of OSAS pts. Calls our attention to the need for taking into consideration many mechanisms (sleep fragmentation, local disorder of vascular autoregulation and lacunar vascular lesions) in the interpretation of cognitive and psychomotor deficits in OSAS.

References:

Recovery Sleep Patterns Following Treatment of Patients With Obstructive Sleep Apnea

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Introduction: There is controversy about the degree to which chronic and acute sleep deprivation increase different sleep stages during recovery sleep. Studies of acute sleep deprivation in humans generally report prominent recovery of SWS with modest changes in REM sleep, while longer-term deprivation in animals may lead to more prominent REM rebound. Experimental studies of chronic sleep deprivation in humans are not possible. Obstructive sleep apnea (OSA) can, however, lead to chronic sleep disruption and deprivation. Recovery sleep following successful treatment may serve as a naturalistic experiment to assess which sleep stages have priority during recovery from chronic sleep loss.

Methods: Following a night of polysomnographic recording for diagnosis, twenty-two men and one woman (47.0 ± 10.7 years) were treated with CPAP during a second recording night. Paper sleep records were scored manually for apneas/hypopneas and sleep architecture for the diagnostic and treatment nights. A period of 6 h from sleep onset was analyzed for each record, and ANOVA followed by paired t-tests with Bonferroni correction were used to compare the time courses of REM and SWS during the two nights. Latency data were square-root transformed before analysis.

Results: Patients showed mild to severe OSA (apnea/hypopnea indices of 10-121) on the diagnostic night. SWS and REM sleep increased significantly during the recovery night (Figure 1), while median latencies to SWS and REM sleep decreased by 33 min (p=0.01) and by 30 min (p=0.01), respectively. Figure 2 illustrates the hourly amounts of SWS and REM sleep throughout the two nights. On the recovery night, 20 patients entered SWS first while 3 entered REM sleep first. While there was little REM sleep in the first hour during the diagnostic night, REM sleep was phase advanced during the second night and increased in the first two hours as well as later in the night. SWS also increased dramatically early in the night and less so later.

Figure 1

Effect of CPAP on six hours of recovery sleep following Sleep Onset

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Wake</th>
<th>I/II</th>
<th>SWS</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>150</td>
<td></td>
<td></td>
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<tr>
<td>200</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
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</tr>
</tbody>
</table>
Conclusions: Both SWS and REM sleep increased during the treatment night, following presumed chronic sleep deprivation, as previously reported. The advanced timing of REM sleep during the night suggests a significant amount of REM pressure that was expressed when sleep disruption was reduced by successful CPAP treatment. The analysis is complicated, however, by the fact that ultradian sleep cycles affect sleep expression. Thus, hourly plots of sleep stages reflect rebound sleep pressures interacting with the gating function of an ultradian regulatory system as well as the normal trend toward increasing REM and decreasing SWS over the night. The modulating roles of circadian phase and ultradian cyclicity will need to be considered in future analyses of recovery sleep parameters.

References:

496.J

Cerebral Oxygenation During Sleep in Chronic Obstructive Pulmonary Disease

Jasani RR, Sanders MH, Nemoto EM, Hajduk IA, Atwood CW, Strollo PJ
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Introduction: Cognitive dysfunction has been recognized in chronic obstructive pulmonary disease (COPD) patients who are hypoxic during wakefulness. Although COPD patients with acceptable arterial oxygen tension (PaO2) during wakefulness may experience arterial oxyhemoglobin desaturation to < 85% during sleep whether cerebral oxygenation is compromised is unknown.

Methods: Patients with non-oxygen dependent COPD with or without suspected sleep apnea were studied after informed consent in an IRB approved protocol. All subjects had simultaneous PSG recording with pulse oximetry and cerebral oximetry. Only patients with AHI < 15 by full-night PSG were included in this analysis. Bilateral rSO2 was measured using the INVOS4100 Cerebral Oximeter (Somanetics Corp., Troy, MI). Statistical analysis was performed by one-way ANOVA with a p value of 0.05 as significant. Data are expressed as mean ± SD.

Results: Six male patients with mean age of 63.7 ± 10.6 years and BMI of 28.3 ± 3.8. PSG Data: Sleep Efficiency: 51 ± 26%, AHI: 5.9 ± 2.7, FEV1: 59.7 ± 11.7% predicted (1.79 ± 0.56), SpO2: 94 ± 2.5%, Desaturation Event Frequency (pulse oximeter): 13.3 ± 31.3. Cerebral oxygenation decreased bilaterally with arterial desaturation (Table). Interhemispheric asymmetries in rSO2 were observed in 4 of the 6 patients. In one patient the asymmetry was especially marked during the episodes of arterial desaturation indicating compromised cerebrovascular reserves.

Table 1

<table>
<thead>
<tr>
<th>Period (N)</th>
<th>LrSO2</th>
<th>RrSO2</th>
<th>SaO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturation (16)</td>
<td>62 ± 8*</td>
<td>62 ± 9*</td>
<td>93 ± 3**</td>
</tr>
<tr>
<td>Desaturation (20)</td>
<td>55 ± 9</td>
<td>55 ± 10</td>
<td>89 ± 3</td>
</tr>
</tbody>
</table>

**p=0.0001, *p=0.01, *p=0.03.

Figure 1

Left (LrSO2) and right (RrSO2) hemispheric cerebral oxygenation during sleep in a patient with COPD is shown. Note asymmetry in LrSO2 and RrSO2 with exacerbation of asymmetry during arterial desaturation (arrows).

Conclusions: 1) Cerebral oxygenation decreased during arterial desaturation episodes in COPD. 2) Asymmetries between left and right hemispheres in cerebral oxygenation were observed. Arterial desaturations and/or apnea may accentuate those asymmetries suggesting compromised cerebrovascular reserve and possible stroke risk. 3) Pattern and frequency of cerebral desaturation events may determine stroke risk and may be responsible for neuronal fallout eventually leading to neurocognitive dysfunction in COPD.

498.J

Preliminary Findings From The First Prospective, Randomized Trial Of Surgery For Sleep-Disordered Breathing

Terris DJ, Chavoya M
Stanford University Medical Center

Introduction: Prospective, randomized trials of the surgical management of sleep-disordered breathing have not been performed. We report preliminary findings from the first such protocol.

Methods: 20 patients with mild sleep-disordered breathing who failed conservative treatment were identified and consecutively enrolled into an IRB-approved surgical protocol. They were randomly assigned to undergo either radiofrequency ablation of the palate or laser palatoplasty-
ty. Parameters assessed included severity of SDB (PSG), loudness of snoring (SNAP recording), sleepiness (Epworth) and anatomic changes (videoendoscopy), as well as demographic factors (age, gender, BMI).

**Results**: 12 patients with a mean age of 53.6 years, a mean BMI of 28.5, a mean preoperative AHI of 6.9, and a mean preoperative Epworth score of 6.8 underwent a total of 15 laser palatoplasty procedures. Six patients achieved a satisfactory resolution of their snoring, 4 failed and were salvaged with laser palatoplasty, and 2 have not yet completed the protocol. 8 patients with a mean age of 49.1 years, a mean BMI of 26.5, a mean preoperative AHI of 4.9, and a mean preoperative Epworth score of 6.7 underwent a total of 31 RF ablation procedures. Five patients achieved a satisfactory resolution of their snoring, one was cured, but suffered a relapse and was salvaged with RF ablation, one patient failed and was salvaged with nasal surgery, and one has not yet completed the protocol.

**Conclusions**: Prospective, randomized trials of surgery for sleep-disordered breathing are possible. Preliminary findings from the current protocol reveal a slight advantage of laser palatoplasty over RF ablation, but with a greater degree of discomfort postoperatively.

**References**:

**A Cephalometric Study of the Effects of UPPP using Ricketts’ Method**

**Introduction**: Before treating patients who had obstructive sleep apnea, we took cephalograms in order to analyze the cephalometric differences between patients for whom uvulopalatopharyngoplasty (UPPP) proved effective and those for whom it proved ineffective.

**Methods**: We divided 26 adult patients who had undergone UPPP into two groups: the effective group and the ineffective group. The effective group (n = 17) consisted of those whose apnea-hypopnea index (AHI) after UPPP decreased more than 50%. The ineffective group (n = 9) included those whose AHI after UPPP decreased less than 50%. We digitized the patients’ lateral cephalograms using Ricketts analysis and examined the facial patterns and airways, comparing the results of the two groups.

**Results**: There was a significant difference (p < 0.005) between the effective group and the ineffective group in terms of PNS-P (length of soft palate: effective 41.3mm ± 4.5, ineffective 47.1mm ± 4.0). Significant differences (p < 0.05) also existed in terms of PTA (anterior protruding length of maxilla: effective 3.5mm ± 4.2, ineffective 6.6mm ± 2.4), McNamara-Pog (distance from McNamara line to mandible: effective -4.0mm ± 7.4, ineffective -10.7mm ± 8.4), and the H-point y-coordinate (distance from Frankfurt plane to hyoid bone: effective -106.6mm ± 7.8, ineffective -116.2mm ± 11.4).

**Conclusions**: The patients for whom UPPP was ineffective had retruded mandibles, long soft palates, and low-positioned hyoid bones.

**References**:

**500.J**

**Relationship Between The Use of Nasal CPAP and Chronic Sinusitis In Patients With Obstructive Sleep Apnea**

**Tabba MK**

Sleep Disorder Center, Department of Neurology, University of Missouri-Columbia, Columbia, Missouri

**Introduction**: Obstructive sleep apnea (OSA) is common and usually treated effectively with nasal CPAP. However, compliance is a significant problem. Claustrophobic feeling, nasal congestion, nasal obstruction, upper airway allergies and infection can contribute toward this non-compliance. The incidence of chronic parasinusitis (CS), post nasal drip (PND), and their relationship to the use and tolerance of nasal CPAP is not well understood. The purpose of our study was to evaluate: the incidence of CS in patients with OSA, the occurrence of CS relative to development of symptoms of OSA (snoring & apnea), the effect of CPAP on the clinical course of CS, and the impact of sinusitis exacerbation on the CPAP use.

**Methods**: Randomized study of patients with OSA from our sleep center who met the following inclusion criteria: age >18 yrs with documented OSA and on CPAP. Data collected included: age, sex, apnea/hypopnea index, CPAP pressure, history of CS or PND and onset of symptoms relative to onset of OSA symptoms (snoring & apnea), effect of CPAP on the clinical course of CS, and effect of CS on CPAP usage. This data was collected by using a questioner and the patients were interviewed in the clinic or over the phone.

**Results**: A total of 71 patients were contacted. Of these, 43 agreed to participate in the study. Of the 43 patients, 30 (69.7%) had OSA and CS, and 13 (30.2%) had OSA without CS. Among patients with OSA and CS, 28 (93.3%) reported onset of CS prior to the development of symptoms of OSA (snoring & apnea). 24 (79.9%) patients reported symptoms of CS more than 6 years prior to the onset of OSA symptoms. 19 (63.3%) patients reported improvement of CS after using the CPAP, and the rest didn’t notice any change. 21 (70%) patients reported difficulty with using the nasal CPAP when there was exacerbation of CS.
Table 1

THE STUDY DATA

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic sinusitis</td>
<td>29 (96.6%)</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>25 (80.6%)</td>
</tr>
<tr>
<td>Chronic sinusit &amp; Post nasal drip (both)</td>
<td>(76.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Course of CS</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>29 (96.6%)</td>
</tr>
<tr>
<td>Seasonal</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The occurrence of CS relative to the development of OSA symptoms (snoring &amp; apnea)</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>28 (93.3%)</td>
</tr>
<tr>
<td>After</td>
<td>2 (6.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The occurrence of CS relative to the diagnosis of OSA (years)</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>5-10</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>11-30</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>9 (30%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPAP</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves CS</td>
<td>19 (63.3%)</td>
</tr>
<tr>
<td>Worse CS</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>No change</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Difficulty in using the CPAP during sinusitis exacerbation</th>
<th>Number of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>No</td>
<td>9 (30%)</td>
</tr>
</tbody>
</table>

Conclusions: Based on our small study, chronic sinusitis is common among patients with OSA (70%). Chronic sinusitis symptoms start many years prior to the development of OSA symptoms. CPAP treatment improves CS symptoms in majority of patient. However, when exacerbation of CS occurs, it causes difficulty in using CPAP.

501.J

Risk of Coronary Artery Disease in Veterans Affairs Patients with Sleep Disordered Breathing

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Introduction: The association between sleep disordered breathing (SDB) and coronary artery disease (CAD) is increasingly recognized. However, a direct causal relationship between SDB and CAD remains to be determined. The risk of CAD in Veteran Affairs (VA) patients with SDB has not been defined. The purpose of this study is to determine the risk of CAD in VA patients with SDB.

Methods: We retrospectively reviewed the records of 115 patients who were referred to the Pulmonary sleep apnea monitoring unit between 1996 and 2000 to assess the prevalence of CAD. Only patients undergoing their first apnea study were included in the analysis. Followup studies and incomplete records were excluded. The study population (n=70), was composed predominantly of male veterans (n=67), representative of the larger population of patients studied in the monitoring unit during this period of time. The following information was obtained from the medical records: age, sex, body mass index (BMI), neck size, Epworth sleepiness Scale scores, respiratory disturbance index (RDI), and the presence or absence of CAD. Six channel unattended apnea monitoring (Edentrace) was performed. The RDI data was used to subdivide the sample into 2 groups: 1) normal group with RDI ≤ 5 (n=10), 2) abnormal group with RDI >5 (n=60). An odds ratio and the nonparametric Mann-Whitney U Test were used for between group comparisons.

Results: The normal group, (n=10), consisted of 1 female, 9 males, mean age 56 years (SD ± 13), and mean BMI 30 kg/m2 (SD ± 8). The characteristics of the abnormal group, (n=60), consisted of 2 females, 58 males, mean age 55.8 years (SD ± 11.4), and mean BMI 34 kg/m2 (SD ± 6). Although, as expected, there were significant differences between the two groups for RDI (p < .0001) and Epworth (p = .01) there were no significant differences between groups for age, neck size, and BMI. We observed an increased incidence of CAD in the abnormal group (RDI >5) as compared with the normal group (RDI ≤ 5). In the normal group (n=10), 1 patient had CAD. In the abnormal group (n=60), 13 patients had CAD. The odds ratio of CAD in patients with SDB compared to normal (Odds 0.28/0.11) is 2.5.

Conclusions: There is a significant association of CAD in our veteran patients with SDB, compared to patients without SDB. Patients with sleep disordered breathing may warrant further surveillance for coexisting CAD; we are planning to further examine this issue with a large prospective study.

References:


502.J

Breathing Patterns in the Arousal in Patients with Obstructive Sleep Apnea-Hypopnea Syndrome

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Introduction: It is well known that patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) demonstrate the cessation of airflow by repeated occlusions of the upper airway during sleep. Increased upper airway collapsibility is considered to be an important mechanism leading to occlusion and ultimately cessation of airflow. However, it is difficult to evaluate the upper airway collapsibility in the arousal by using conventional pulmonary function testing. We hypothesized that the upper airway collapsibility affects breathing pattern in patients with OSAHS. The aim of the present study is to examine whether abnormality of breathing pattern exists even in the arousal in the patients with OSAHS.

Methods: Ventilatory volume was measured by the spirometry with the calibrated respiratory inductive plethysmography (RIP) for 48 male patients who enforced the polysomnography (PSG) by suspected OSAHS in our laboratory. We excluded the patient whose body mass index (BMI) was over 30 in the present study. In high sitting and supine position, we recorded the breathing pattern during stable ventilation for 2 minutes and maximum ventilation for 1 minute continuously. As an index to the breathing pattern, we used respiratory frequency (f), tidal volume (VT), minute ventilation (Vmin), mean inspiratory flow (VT/TI), maximum inspiratory flow (VImax), maximum expiratory flow (VEmax), fractional inspiratory time (TI/Ttot), the ratio of ribcage contribution to tidal volume (RC/VT) and the ratio of the maximum compartmental amplitude to tidal volume (MCA/VT). These indexes were compared between group with the sleep apnea (OSAS group: AHI>10, n=24, 52.1±13.1 years old) and group without the sleep apnea (simple snorer group: AHI<10, n=24, 54.1±12.3 years old).
Results: The mean value of BMI in OSAHS group (25.6±2.3) was not different from that in simple snorer group (25.2±2.1). The mean value of AHI was 28.2±13.1 in the OSAHS group and 4.4±3.1 in the simple snorer group. In the OSAHS group, VT/TI, Vmax and MCA/VT were significantly higher than simple snorers in the high sitting position, and TI/Tot and RC/VT were significantly low. In supine position, VT was significantly high, and RC/VT was significantly low. In the other index, the significant difference was not recognized between both groups.

Conclusions: In the OSAHS patient, it became clear that abnormality of breathing pattern also existed in the arousal. The upper airway collapsibility may contribute to the mechanism leading to the abnormality of breathing pattern.

References:

503.J
St. Luke’s Medical Center Obstructive Sleep Apnea Clinical Score

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Introduction: Obstructive sleep apnea syndrome is a relatively common disease, with an estimated prevalence in the general population of between 0.3% and 4%. However, among high-risk groups the prevalence is 45%. The gold standard for diagnosing obstructive sleep apnea, nocturnal polysomnography is time-consuming, expensive, labor-intensive and a limited resource in the Philippines. The purpose of our study is to devise a clinical prediction rule for obstructive sleep apnea from clinical parameters of Filipino adult patients that can be used to identify either high-risk patients requiring full nocturnal polysomnography or low-risk patients in whom unnecessary sleep studies could be avoided. No prediction rule using non-Caucasian subjects are reported to this date.

Methods: This is a cross-sectional study of all Filipino adult patients with clinical suspicion of obstructive sleep apnea referred to the St. Luke’s Medical Center Sleep Disorders Laboratory from January 1993 to December 1999. Patients were excluded if they have previously been assessed or treated for sleep apnea, specific sleep disorder other than sleep apnea. All patients completed a general sleep questionnaire and underwent nocturnal polysomnography. Multiple regression analysis which include 13 clinical variables (age, body mass index, neck size, sex, chief complaint affecting daily activities, perception of too much sleep, perception of too little sleep, daytime fatigue, bothersome daytime sleepiness, snoring, snoring affecting others, smoking and hypertension) were used to develop the clinical scoring system. A p value < 0.05 was considered statistically significant.

Results: Only 344 Filipino adult patients with a mean age of 46.4 ± 14.05 were included in the study. The prevalence of obstructive sleep apnea in our patients was 62%. Body mass index, snoring affect others and bothersome daytime sleepiness were found to be significant predictors of obstructive sleep apnea in Filipinos (p<0.05). A sleep apnea clinical score of 7 was determined as the cut-off value to predict the presence of obstructive sleep apnea (sensitivity = 75%, specificity = 70%, positive predictive value of 80%, Overall accuracy rate of 73%, likelihood ratio = 2.5 and posttest probability of 80%). A score of <7 has a likelihood ratio of 0.36 and a corresponding posttest probability of 30%.

Conclusions: Body mass index, snoring affect others and bothersome daytime sleepiness were found to be significant predictors of obstructive sleep apnea in Filipinos. In the diagnostic workup of patients suspected of having obstructive sleep apnea, the clinical prediction rule can simply and accurately determine the immediate need and benefit of nocturnal polysomnography for further assessment and management.

504.J
Breathing Disorders in Patients with Congestive Heart Failure

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Heart Institute - InCor, Sao Paulo Medical School, University of Sao Paulo, Sao Paulo, Brazil.

Introduction: The occurrence of central (Cheyne-Stokes breathing - CSH) and obstructive sleep apnea (OSA) in patients with congestive heart failure (CHF) requires careful and consistent investigation. The main objective of this study was to analyse the incidence of CSH, OSA and hypopnea during sleep in patients with CHF caused by idiopathic, ischemic or chagias’ heart disease.

Methods: Overnight polysomnography was performed in 30 patients with severe stable CHF (left ventricular ejection fraction < 40%), using EMBLA digital system (17 channels, Flaga hf. Medical Devices). The studies were performed and scored based on the guidelines for sleep studies (Rechtschaffen & Kales, 1968).

Results: The sleep studies showed the following features: age = (mean ± SD) 54 ± 11 years, mean sleep efficiency index = 72 ± 23%, and sleep total time = 309 ± 99 min. Apnea-hypopnea index was considered normal below 5 events per hour of sleep. CSH was present in 60% of patients and OSA was present in 16.6%. The patients were divided according to etiology of the CHF: in 15 patients (50%) with idiopathic heart disease (in these group 10 patients had CSH and 2 had OSA); 5 patients (17%) with ischemic disease (in these group 4 patients had CSH and 1 had OSA); 9 patients (30%) with chagias’ heart disease (in these group 4 patients had CSH and 2 had OSA).

Conclusions: These preliminary results suggest a high occurrence of breathing disorders in patients with CHF. The CSH pattern was particularly prevalent in most patients, including the patients with chagias’ heart disease.
N=16) was invited for nocturnal sleep studies, MWT and driving simu-
lator (STSIM, Systems Technology Inc, USA) tests.

**Results:** Prevalences, based on the questionnaire, of suspected OSAS in
different professions were bus drivers 26.3 %, tram drivers 17.2 %, office workers 7.8 %, service personnel 23.1 %, middle- or upper managers 11.4 %, other workers 16.8 %. In the sleep recordings 17 bus driv-
ers of the 22 (77.3 %) had OSA (ODI4 > 10). On the other hand four (25 %) of the controls had ODI4 >10 in the recordings. Using the Bayes the-
orem we can compute that the minimum prevalence of OSAS among
city bus drivers was 20.3 %. Using only the results of the sleep recordings the lower limit of prevalence would be 9.3 %, and the upper limit would be 24.3 %. Using a limit of S1-latency of 12.9 minutes for 40 minutes MWT the prevalence of sleepy subjects with sleep apnea was 7.9 %. The prevalence of OSAS with ODI4 > 30 was 3.5 %. Five bus drivers of the 38 (13.2 %) had periodic limb movements in the sleep recordings. They all had also OSAS. In the driving simulator the median of the reaction
times to the additional tasks was 1.3 s (SD 0.2; range 0.9 – 1.8 s). The apnea indices and the oxygen desaturation index (ODI4) correlated
(r=0.356) statistically significantly (P=0.042) with the reaction times. There were no statistically significant differences in the number of acci-
dents (in the simulator or in the past history of real life driving)

**Conclusions:** Obstructive sleep apnea is common among city bus driv-
ers. However, subjects with sleep apnea may perform as well as the
controls, while driving a car. This is important information. Thus the decision of driving licence of OSAS patients should be made focusing on the
daytime sleepiness of the driver.

506.J

**Community-Based Study on the Association between Snoring and Blood Pressure in Japanese Men**

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sei Hospital Sleep Medical Center

**Introduction:** Several population-based studies in the US. and Europe have shown that snoring may increase the risk of hypertension, but only limited data are have been documented in Asian countries.

**Methods:** One hundred and fifty men (22 to 59 years, mean age: 48 years) without anti-hypertensive medication use completed a self-report-
ed questionnaire on snoring at the annual health check-up in a rural com-

**Results:** Mean age-adjusted diastolic blood pressure (DBP) was 90.5mmHg in every-night snorers, 83.1mmHg in snorers of once to 5
nights per week, 83.7mmHg in snorers of less than once per week and 86.3mmHg in never snorers (p for difference by ANCOVA=0.02). Sig-
nificant differences in mean DBP were found between every-night snor-
ers and snorers of once to 5 nights per week (p=0.002) and between
every-night snorers and snorers of less than once per week (p=0.03). This difference in diastolic BP became small, but remained of borderline statistical significance when adjusted further for body mass index (89.5mmHg in every-night snorers, 83.2mmHg in snorers of once to 5 nights per week, 84.3mmHg in snorers of less than once per week and 86.7mmHg in never snorers, p=0.07). No association was observed between the frequency of snoring and systolic BP levels.

**Conclusions:** Every-night snorers have higher mean DBP levels than occasional snorers in this Japanese population. This association is partly explained by the confounding of overweight. However, the possibility of an effect of snoring per se on increased BP levels is not ruled out.

Research supported by Grant-in-Aid (12877066) for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

507.J

**Oral Appliance Treatment: Polissonographic Results in 29 Mild to Severe OSAHS Subjects**

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**Introduction:** Sleep-disordered breathing ranges from partial airway collapse and increased upper-airway resistance manifested as loud snor-
ing and brief arousals to total or partial recurrent airway collapse. Obstructive sleep apnea/hypopnea syndrome (OSAHS) leads to risks of
motor vehicle accidents, increased cardiovascular morbidity and mortal-
y1. Therefore, even mild degree OSAHS demands an effective treat-
ment. Although nasal CPAP is therapeutically effective, its compliance rate varies among different patient populations. Hence, removable intra-
oral appliance therapy has become a treatment alternative for OSAHS. The objective of this study is to assess treatment effectiveness of the MLRD2 in 29 OSAHS subjects.

**Methods:** 29 PSG-confirmed OSAHS patients were included, 23M/6F, age= 36 to 68, (avg=52), avg BMI = 27.32 ±4.35. Two RDI subgroups were created. Group 1 OSAHS: RDI>30 (range 113.4 to 33.7), n=19, and Group 2 OSAHS: 29.9>RDI>4.9 (range 28.9 to 5.0). Pre- and post-
treatment indexes were obtained at approximately 4 months later for both groups: RDI, Epworth Sleepiness Scale (ESS) subjective daytime sleepiness scores2, min.SatO2%. Student’s-t test were employed to compare groups. Mimal treatment outcome criteria were RDI<10 event/hour, min.SatO2%> 90% and ESS < 10 points.

**Results:** The results are presented in Table and graphic below.

**Table 1**
Figure 1

Conclusions: Discussion: Pre- and post-treatment RDI, ESS, min Sat O2.% were statistically different confirming the MLRD efficiency in this patient population. However, the RDI was the only parameter that reached a statistically significant difference between group 1 and 2. This confirms intraoral appliances are more efficient in lower RDI patient populations. The pattern of post-treatment improvement ranked ESS score<10 points, RDI<10, minSatO2%> 90% and lastly, minimal treatment outcome criteria for both groups. MLRD-induced improvement in ESS-measured subjective sleepiness has been reported2. Yet, the degree of oxygen desaturation relates to respiratory event duration. This suggests that the intraoral appliance fitted in this patient population is more efficient in reducing the number of arousals, and in reducing the number than reducing the duration of abnormal respiratory events. Conclusion: ESS and RDI intraoral appliance-induced clinical improvement is more robust than min Sat O2.

References:

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508.J

Serum Cortisol and Catecholamines in Untreated and Treated Obstructive Sleep Apeanov

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Introduction: High serum cortisol and catecholamines may be associated with arterial hypertension. Patients with obstructive sleep apnea (OSA) were suggested to be at high risk for arterial hypertension.

Methods: We measured serum levels of cortisol (COR), epinephrine (E), and norepinephrine (NE) at 9 p.m., 6 a.m. (after waking up), and 9 a.m. (after getting into the upright position) in 17 patients with polysomnography-confirmed severe OSA (apnea-hypopnea-index at least 30 per hour total sleep time) before treatment, after short-term (one or two nights) with nasal continuous positive airway pressure (nCPAP) and after at least 3 months nCPAP treatment, and in 7 age- and sex-matched patients without OSA (controls).

Results: COR was similar in untreated patients with OSA and controls. In OSA patients COR, NE and E levels were significantly (p < 0.05, Wilcoxon-Test) reduced at 9 a.m. after short-term nCPAP treatment compared to the time before treatment. Furthermore, E levels were significantly (p < 0.05, Wilcoxon-Test) reduced at 6 a.m. after short-term nCPAP treatment compared to the corresponding time before treatment. COR, NE and E levels were similar after long-term nCPAP treatment compared to untreated OSA.

Conclusions: These preliminary results of our ongoing study show a significant early morning reduction of serum COR, NE and E after short-term nCPAP treatment. However, there was no significant long-term effect of nCPAP therapy on COR, NE, and E. This suggests 1, that moderate to severe OSA does not influence serum COR or plasma catecholamine levels and 2. OSA associated hypertension is not primarily based on elevated serum COR or plasma catecholamines.

509.J

Comparison Between Presenting Complaints And Diagnosis After Sleep Study

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Introduction: Sleep disorders have increasingly been recognised as an important cause of morbidity but a systematic review of patterns of presentation and diagnosis has not been undertaken for UK patients. Primary complaints are an important clue in making the diagnosis but they may be misleading. The aim of this study was to compare the complaints of the patients and the final diagnosis after sleep study to reveal possible causes of misdiagnosis without sleep study.

Methods: 299 patients consulting the Sleep Disorders Centre, St. Thomas’ Hospital in 1999 were analyzed. 218 patients underwent sleep study; the primary complaint at presentation and the final diagnosis after sleep study were compared.

Results: The presenting complaints were categorized into three groups; hypersomnia, insomnia and parasomnia and the final diagnosis after sleep study is shown in the table.

Table 1

<table>
<thead>
<tr>
<th>Presenting complaints</th>
<th>Hypersomnia</th>
<th>Insomnia</th>
<th>Parasomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=167)</td>
<td>(n=32)</td>
<td>(n=19)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Hypersomnia</th>
<th>Insomnia</th>
<th>Parasomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyssomnias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic sleep disorders</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic insomnia</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic hypersomnia</td>
<td>123</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Sleep related breathing disorders</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PLMD / RLS</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Circadian rhythm disorders</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Parasomias</td>
<td>6</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Other conditions causing sleep disorders</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: This study shows that presenting symptoms may not be a reliable guide to final diagnosis and a sleep study may be necessary to distinguish the individual sleep pathologies.
510.J

Assessment Of Sleep Disordered Breathing In Neuromuscular Disease Patients By Heart Rate Variability

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Introduction: Respiratory failure develops in neurological disorders when the load on the respiratory pump exceeds its capacity. Hypoventilation, which occurs in normal sleep, is magnified in patients with pulmonary and neuromusculoskeletal disease and leads to prolonged nocturnal hypoxaemia. Spectral analysis of heart rate variability allows detailed assessment of individual components of the periodic fluctuations in the heart period and thus provides information about sympathovagal balance. The high frequency (HF) band of the frequency spectrum reflects vagal tone, while low frequency (LF) reflects mainly sympathetic activity.

Methods: 17 patients (age 27-70 years, M:F ratio 9:8) with neuromuscular disease and nocturnal oxygen desaturation participated in this study. All subjects underwent overnight full polysomnography including ECG recording (sampling rate=100 Hz). Sequential segments of 256 seconds were extracted and analysed using power spectral analysis. From 900 segments, spectral power in the LF band (0.002-0.15 Hz) and HF band (0.15-0.4Hz), and LF/HF ratio were calculated.

Results: The presence of obstructive and central apnoeas produced distinct changes in heart rate variability. Compared with uninterrupted sleep, obstructive apnoea increased HF to 115% (111-118%), LF to 135% (130-140%) and LF/HF to 117% (113-121%). In non-obstructive apnoea, HF remained the same, LF increased to 127% (118-137%) and LF/HF increased to 133% (124-143%)[mean change per 10 seconds apnoea / segment (95% confidence interval), p<0.01]

Conclusions: 1. There is an immediate sympathoactivation during any type of apnoea as evidenced by the increase in LF & LF/HF ratio. 2. A simultaneous increase in the HF suggests an obstructive apnoea, while no change or a decrease suggests a non-obstructive apnoea. 3. Heart rate variability is an important but simple and non-invasive investigation, which should be used to screen all neuromuscular disease patients with possible respiratory insufficiency.

511.J

Incidence of Sleep Disordered Breathing (SDB) in a Population-Based Sample

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Introduction: Although a number of studies have reported prevalence ratios for SDB, little is known regarding the incidence of the disorder, and how incidence varies with demographic factors, exposures, and comorbidity. In this study, we assessed the incidence of SDB, and predictors of incident SDB, among individuals studied as part of the Cleveland Family Study, a longitudinal genetic-epidemiological study.

Methods: In a cohort of 373 subjects studied both at baseline and after 5 years, a sample of subjects >18 years of age and without SDB (respiratory disturbance index, RDI, <5) at baseline was identified (n=232). At both visits, subjects underwent overnight in-home sleep monitoring (Edentec I/II, recording chest wall impedance, oximetry, heart rate, airflow and position), blood pressure and physical measurements, and assessment of medical history, symptoms and exposures with a standardized questionnaire. Ordinal logistic regression using a proportional odds model was performed with the dependent variable as the follow-up RDI categorized as <5, 5-10, >10-15, ≥15.

Results: The sample was 72% female, 22% African American, and had a mean age of 36.7±11.8 (SD) years. 48% of the sample had been recruited because a family member had SDB, and the remaining were recruited as neighborhood controls. At baseline, 28% reported current smoking and 22% reported consuming alcohol more than once per week, 19% were hypertensive, and 17% reported cardiovascular disease or diabetes (CVD-Di). Baseline and follow-up RDI were 2.0±1.4 and 6.2±7.9, respectively. On follow-up, 40% subjects were identified with a RDI≥5, 17% with a RDI≥10, and 10% with a RDI≥15. A greater proportion of males (19%) than females (7%) had a follow-up RDI≥15 (p<0.01). Univariate analyses also showed that higher follow-up RDI was significantly associated with body mass index (BMI), waist/hip ratio (WHR), and CVD-Di at baseline. Ordinal logistic regression analysis showed that incident SDB was independently associated with age, male gender, BMI, WHR, and CVD-Di. The odds ratios, relating the likelihood of SDB of any given category above the reference (RDI<5), compared to all lower categories (e.g., ≥15 vs. <5; ≥10 vs. <10, and ≥5 vs. <5), for significant risk factors were: male: 3.37 (1.52,7.46; 95% C.I.), BMI (per 1 kg/m2 change): 1.14 (1.08,1.19), age (per year): 1.05 (1.02,1.07), WHR (upper quartile): 2.47 (1.18,5.13), and CVD-Di: 2.18 (1.04,4.59). In subjects identified with a baseline RDI<5, race, hypertension, alcohol, smoking, and family membership did not predict follow-up RDI.

Conclusions: Risk factors for 5-year incident SDB were similar to those identified previously for prevalent SDB, and included obesity, body fat distribution, and age. After adjusting for these factors, baseline CVD-Di increased the risk of follow-up SDB approximately 2-fold. The latter suggests that metabolic factors or other host risk factors associated with CVD-Di also predispose to SDB.

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512.J

Changes in Dreaming in Patients using Continuous Positive Air Pressure(CPAP) for Documented Obstructive Sleep Apeana(OSA)

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Introduction: OSA is usually associated with significant disruption of the nocturnal sleep with decreased proportions of slow wave sleep(SWS) and Rapid Eye Movement(REM) sleep.Treatment of OSA is accompanied by restoration of SWS and REM sleep.Dreaming is considered to be predominantly associated with REM sleep.Treatment of OSA,then,should result in increased dreaming as an association of increased REM sleep.We studied the effects of resolution of OSA with CPAP on dreaming patterns of OSA patients.

Methods: Patients were randomly selected from our Sleep Disorders Center.These patients had documented OSA and were on CPAP.Identical pre- and post-CPAP questionnaires were used to assess the presence of dreaming,dream frequency,dream content,dream affect and changes in these parameters after CPAP use.The questions addressed frequency of dreams, content of dreams (relation to faces, places, work, household, past experiences, family and friends), affective content of dreams (happy, sad,of war,illness,death). The questionnaires were completed by interviewing patients in person or over the phone.
Results: A total of 30 patients agreed to participate in the study. Of these, 2 did not remember dreaming before or after CPAP use and 5 patients did not report any have any significant change in their dream pattern after starting CPAP. Of the remaining patients, 3 reported a decrease in the frequency of dreaming. Of these patients, 1 reported cessation of nightmares. The remaining 15 patients had a positive effect on dreaming after CPAP. 7 reported increased frequency of dreams, 4 reported started dreaming and 4 reported positive change in dream affect (more pleasant dreams or cessation of unpleasant dreams). Thus, a total of 23 patients reported change in dreaming. In 15 (65.2%) of these, the change was of a positive nature in that there was either an increase in frequency or improved affective content of dreaming. Another patient while reporting decrease in frequency, had also reported cessation of nightmares.

Conclusions: Our limited study suggests a change in dreaming pattern in patients with OSA after initiating CPAP therapy. While our patient numbers are small, there seems to be a trend towards positive effect on dreaming in that there was either an increase in frequency or change in affective content of dreams with trends towards decrease in nightmares and dreams with unpleasant affective component. It is possible that the increase in REM sleep may be responsible for increased dreaming in some of these patients. Secondly, could the presence of recurrent respiratory pauses during the night may influence dream affect—these issues need to be studied further.

513.J

Ten-Second Breath Holding In Wake And Overnight Oximetry As A Apnea Screen: A Preliminary Report

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Introduction: Pulse oximetry has been used for screening of patients with OSA, but results have been contradictory. Studies have shown different sensitivity and specificity of pulse oximetry which is probably related to individual differences included in different studies. We suggest that oximetry is not consistently reliable because of two main situations. First, oximetry is not sensitive enough (no desaturation for more than 3%) and second, oximetry is too sensitive but not specific (desaturation presents without underlying obstructive respiratory events). In relation to previous work in the field, breath holding has been used in Sleep Medicine to show factors influencing rate of fall of arterial oxygen-hemoglobin saturation in obstructive sleep apnea (1,2). With the aim to increase reliability of oximetry, breath holding test for ten seconds in wake was proposed as a tool for distribution patients to two different groups with oxygen desaturation less than 3% or more than 3% on ten-second breath holding.

Methods: 13 consecutive patients coming to the Sleep Center for evaluation for obstructive sleep apnea underwent pulse oximetry and breath holding during wake for ten seconds in the moment right before inspiration in supine and upright position. Then patients underwent polysomnography and individual analysis of discrepancy between amount of respiratory events (obstructive and mixed apneas, obstructive hypopneas, arousals with desaturation and desaturation only events) and overnight oximetry results. Respiratory disturbances index (RDI) was compared with number of episodes of oxygen desaturation for 3% or more per hour-oximetry disturbances index (ODI).

Results: Ten patients desaturated for less than 3% during breath holding. Six patients of this group have RDI less than 10 (0, 0.1, 1.3, 3.4, 6.6 and 9.8), ODI was subsequently 1.1, 1.2, 1.1, 3.0, 9.2 and 21.0. Two patients have RDI more than 10 and less than 15 (14.9 and 13.0), ODI was 24.3 and 17.4. ODI was more than RDI independently on low wake 02 desaturation in this group. Two patients had severe obstructive sleep apnea, RDI was 56.3 and 52.7, ODI was 34.1 and 29.7. Oximetry was not sensitive and underestimated the number of obstructive events. Three patients desaturated for more than 3% in wake, in supine and lateral position. One patient had negative apnea screen, RDI was 2.4 and ODI was 8.1. Subsequently, oximetry was too sensitive. Two patients had severe obstructive sleep apnea with RDI 90.5 and 61.4 with subsequent ODI 95.5 and 72.0. Oximetry results were close to results of polysomnography, or presented mild overestimation.

Conclusions: For patients with RDI less than 15, independently of results of breath holding test, RDI was close or higher than ODI. However, for patients with severe obstructive sleep apnea in groups with less than 3% oxygen desaturation, ODI was significantly less than RDI and could be the reason for underestimation of the severity of obstructive sleep apnea. Oximetry results were more reliable in the group with severe obstructive sleep apnea with 3% or more oxygen desaturation on 10-second breath holding in wake. Although 3% or more of oxygen desaturation in breath holding for 10 seconds in wake presents in a small percentage of patient population, oximetry without false negative results for this patients could be important. Studies with large sample sizes are needed to confirm these results.

References:

514.J

Severe Obstructive Sleep Apnea during Pregnancy Treated with CPAP and Resolved after Delivery: A Case Study

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Introduction: Exacerbation or developing OSA during pregnancy is a rare entity (1). Less than 20 patients have been described in literature but there is no polysomnographical documentation of resolution of OSA after delivery. In case described by Kowall J. et al, 1989, patient developed OSA in pregnancy and after delivery decreased REI from 78.6 to 25.9.

Methods: A 31 year old 6 month’s pregnant African-American female developed “unbearably loud snoring, choking while sleeping and falling asleep while driving.” The patient has had snoring since childhood, but a sleep study at age of 10 was negative. Tonsils were removed at that time because of hypertrophy and signs of inflammation. The patient continued to have mild snoring after surgery. Snoring significantly increased since the third month of her first recent pregnancy. The patient has TIB of 7.5-9 hours/night with frequent episodes of awakenings with choking sensation, heartburn and periodic headaches. At the same time, she developed sleepiness. Her Sleep-Wake Activity Inventory (SWAI) index at 6 months of pregnancy was 24 (below 45 indicates sleepiness). Her weight was stable at 160 lbs before pregnancy and was increased to 229 lbs during pregnancy. There was no history of thyroid problem or any other medical or psychiatric disorders. During physical exam BP: 116/74, HR: 96, RR: 20, neck: 14.75” in circumference. Oropharynx: tonsils removed, uvula is slightly enlarged, pillar mucosa wide, palatal free margin position moderately low.

Results: Polysomnography showed an unusually high amount of apneas (see Table 1) with the lowest 02 level 74%, very low sleep efficiency.
Acute Handling Stress Induces Respiratory Depression in Rats

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Introduction: Human obstructive sleep apnea (OSA) is associated with elevated stress-related hormones: norepinephrine, epinephrine and cortisol (1). Patients with OSA have abnormalities in autonomic stress tests (2). Changes in autonomic function in OSA may be a consequence of hypoxic stress. Alternatively, stress may contribute to breathing abnormalities. To test this latter possibility, we examined state-dependent respiratory responses of rats to acute handling stress.

Results: Normal I-Is calculated after rats were well-adapted to the recording chamber were 0.31±0.03 seconds during quiet wakefulness and 0.54±0.05 seconds during nonREM sleep. Of 10 rats studied, 9 exhibited repeated episodes of RD during handling. The average latency to RD onset was 54.7±12.8 seconds. The mean I-I interval during RD episodes was 1.43±0.15 seconds. Episodes of RD persisted for an average of 372±67 sec after onset. RD episodes were predominately nonREM sleep-related. Animals cycled between brief episodes of light nonREM sleep and quiet waking in the immediate post-handling period. In 5/9 animals, the initial episode of apnea occurred during transitions from waking to light nonREM sleep. An average of 86±2% of the time spent in RD occurred during nonREM sleep (n=6).

Conclusions: These preliminary results demonstrate that abnormalities in sleep-related breathing can be induced by handling in a majority of rats tested. Acute stress may promote disordered breathing during sleep in rats.

References:

516.J

Adherence to Positive Pressure Therapy in Patients with Obstructive Sleep Disordered Breathing Treated with an Oral-Nasal Mask as Salvage Therapy

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Introduction: Positive airway pressure is the medical therapy of choice for obstructive sleep apnea. Subsets of patients exist that cannot be effectively treated with positive pressure applied solely via a nasal route. Positive pressure via an oral-nasal route has been shown to be effective in treating obstructive sleep apnea in patients who cannot tolerate or in whom a nasal mask is ineffective (1-3). Prior work has suggested that patients treated with positive airway pressure via an oral-nasal mask are less willing to accept and adhere to positive pressure therapy (1). To date, adherence data in patients who have rejected nasal interfaces has not been examined. The purpose of this investigation was to assess the value of oral-nasal masks has salvage therapy for patients treated with.
positive pressure therapy.

Methods: Study design: Retrospective consecutive case series. Study duration: Dec 1998-1999 Inclusion criteria: Age > 18 years, AH1 > 5, Patients in whom on the night of the in-laboratory positive pressure titration therapy via a nasal mask was not tolerated or was determined to be ineffective. Outcome variables examined: average hours per night of use of the oral-nasal mask, by meter read. Three patient groups were examined: 1) Non-adherent (meter read 0 hours), Adherence < 4 hours/night, Adherence > 4 hours/night. An intention to treat analysis was utilized. Statistics: Descriptive, data is expressed as mean ± standard deviation.

Results: Over the study period, 52 patients were prescribed oral-nasal masks. The baseline demographic data for the entire group was: Age 57 ± 14.9 yrs., BMI 40.1 ± 17.7. Epworth sleepiness scale 11.7 ± 5.4, AHI(Dx PSG) 52.9 ± 38.2. Desaturation event frequency(Dx PSG) 23.1 ± 31.6. Forty four patients (84%) were found to be non-adherent to therapy. Six patients (12%) were found to have adherence of > 4 hrs/night. Two patients exhibited adherence of < 4 hrs/night.

Conclusions: 1) In patients with moderately severe obstructive sleep disordered breathing, the salvage rate for treatment with an oral-nasal mask is poor. 2) Only 12% of the patients prescribed oral-nasal masks demonstrated what is generally considered adequate (> 4 hrs/night) adherence to positive pressure therapy. 3) Additional research is needed to identify how adherence can be improved in this difficult to treat group of patients.

References:

Impact of Definition of Hypopnea on Respiratory Disturbance Index

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Introduction: A wide variety of definitions of hypopnea have been used in different sleep centers.1 This study used “auto-detection” software provided with a computerized polysomnography system to determine the impact of different thresholds of definition of hypopnea on the resulting respiratory disturbance index (RDI).

Methods: 32 consecutive clinical polysomnography studies performed in patients presenting with complaints of snoring and daytime sleepiness were analyzed for apnea and hypopnea by repetitive use of proprietary “auto-detection” software. Detection of hypopnea was based on 10%, 30%, or 50% drop in airflow and 1%, 2%, 3%, or 4% drops in oxyhemoglobin saturation. PSG was performed using the Cadvell Easy Sleep II & #61652; system which includes software for automated detection of respiratory events. PSG was conducted using a standard sleep montage. Sleep stages were scored manually using R and K criteria. Respiratory events were recorded based on pulse oximetry, oro-nasal thermistor, and piezoelectric measurement of qualitative changes in chest and abdominal excursion. The presence of cortical arousal was not used to assist the detection of respiratory events.

Results: The above thresholds of detection resulted in widely different values for RDI. At the most sensitive threshold (10% drop in airflow, 1% drop in saturation), RDI values ranged from 46.3 to 128.8. At the least sensitive threshold (50% drop in airflow, 4% drop in saturation), RDI values ranged from 1.5 to 85.5. At the least sensitive level of detection 6 of 32 RDI values were < 5.0. In some cases, the RDI value was well within the normal range on one hand (e.g., 3.6) and severely abnormal on the other (e.g., 94.7). The mean values for each definition level are displayed in Figure 1.

Conclusions: Redline, et al.2, reported that different definitions of apnea and hypopnea significantly influence the prevalence of sleep-disordered breathing found in a population. The present study demonstrates a similar variation in RDI in a small group of patients being evaluated for sleep problems in the setting of a sleep disorders center. Tsai, et al.3, reported that inclusion of arousal criteria caused small changes in RDI. In the present study, it was felt that an automated analysis would be less subjective because the same records were evaluated repeatedly. The resulting range of results was quite striking suggesting the following conclusions: 1) automated analysis of respiratory events should be performed with great caution, at least if the analysis is based on qualitative measures of airflow and respiratory movements; 2) the threshold of definition of hypopnea has a profound impact on RDI; 3) the criteria used for detection of hypopnea should be included in polysomnography reports; 4) efforts to define standards for detection of respiratory events are important.

References:

Testosterone Levels In Sleep Related Breathing Disorders

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Introduction: Sex hormones have been known to alter the regulatory mechanisms involved in breathing. Males with elevated testosterone levels associated with sleep related disordered breathing, and recently females with polycystic ovary syndrome and hyperandrogenism have also been associated with increase risk for obstructive sleep apnea. This linked between sex hormones and sleep related breathing raises the potential that sex related hormones even in normal ranges may play an important role in sleep related breathing disorders.

Methods: To examine this we evaluated the testosternore levels 38 of
patients who were diagnosed with a sleep related breathing disorder. Patients underwent standard diagnostic polysomnography at the University of North Carolina Sleep Laboratory. Subjects also had total and free testosterone levels measured prior to the induction of therapy for their sleep related breathing disorder. Testosterone levels were measured using a commercially available analyzer (competitive immunoassay). Free testosterone level was measured by radioimmunoassay.

Results: We examined 17 females and 21 males. We found that the average total testosterone level for our females was 67.7 ng/dl and for males 293 ng/dl. We found a significant relationship between the free testosterone level and lowest oxygen saturation (r= 0.65). However we did not find a trend between respiratory disturbance index and total or free testosterone. Patients with higher testosterone tended to have greater weight.

Conclusions: These results suggest that testosterone may play a role in sleep related respiration. Although testosterone has been reported to exacerbate respiratory dysfunction during sleep, we found that lower free testosterone levels correlated with greater oxygen desaturation.

References:
(1) Kouchiyama, S, Honda, Y, Kuriyama, T: Influence of nocturnal oxy-
tations without cDNA were negative.
a 21 day-old rat submitted to PCR without RT was positive, and all reac-
tions from each of 5-21 day-old animals, and in 60% (6/10) of mns from one
rats), orexin 2 receptor mRNA was detected in 88-100% of cells sampled

Results:
PCR (44-64 cycles)(Ref. 2). Positive results were verified by both melt-
and polymerase chain reaction (RT-PCR) using either a semi-nested,
in 2 receptors was detected by means of single-cell reverse transcription
expression in motor nuclei obtained from 5-28 day-old rats whose XII mns

Methods:
Type 2 Orexin Receptor mRNA

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atory Neurobiology, University of Pennsylvania, Philadelphia, PA
19104, USA

Introduction: Orexins are excitatory peptides produced by a distinct
group of hypothalamic cells whose axons ramify throughout the nervous
system, including motor nuclei (Ref. 1). Orexins are implicated in the
maintenance of wakefulness, and deficiencies of this system are associ-
ated with narcolepsy/cataplexy. Orexin projections to motoneurons
are associated with narcolepsy/cataplexy. Orexin projections to motoneurons

Methods: XII mns were acutely dissociated from medullary slices con-
taining the XII nucleus obtained from 5-28 day-old rats whose XII mns
were retrogradely labeled with rhodamine-dextran. The mRNA for orex-
in 2 receptors was detected by means of single-cell reverse transcription
and polymerase chain reaction (RT-PCR) using either a semi-nested,
two-stage process (35 and then 10-25 cycles of real-time PCR), or one
PCR (44-64 cycles)(Ref. 2). Positive results were verified by both melt-
ing of the PCR products and gel electrophoresis.

Results: Of the 58 mns studied to date (8-14 XII mns harvested from 6
rats), orexin 2 receptor mRNA was detected in 88-100% of cells sampled
from each of 5-21 day-old animals, and in 60% (6/10) of mns from one
28 day-old rat. In control experiments, none of the additional 8 mns from
a 21 day-old rat submitted to PCR without RT was positive, and all reac-
tions without cDNA were negative.

Conclusions: The presence of orexin 2 receptor mRNA in XII mns sug-
gests that orexins exert direct postsynaptic excitatory effect on these
mns. Interestingly, this effect may be present in mns of animals as young
as 5 days and is then maintained, or only slightly decreased, in mature
rats (28 days). The interpretation and relevance of these findings for
motor control across the sleep-wake cycle hinges, in part, on the ques-
tion of changes in orexin release onto mns in different states of vigilance.
Preliminary studies of this issue done by other groups suggest that orex-
in release is increased during active states. If so, our present results sug-
gest that orexinergic innervation of mns provides them with a wakeful-
ness-related excitatory drive. This hypothalamic drive is probably
reduced during sleep (slow-wave or REM or both), thereby acting in
concert with other mechanisms that originate in the brainstem which
also contribute to reduced motoneuronal excitability during sleep.

References:
(1) 1. Kilduff TS, Peyron C: The hypocretin/orexin ligand-receptor sys-
(2) Comer A, Gibbons HM, Qi J, Kawai Y, Win J, Lipski J: Detection of
mRNA species in bulbospinal neurons isolated from the rostral ventro-
lateral medulla using single-cell RT-PCR. Brain Res Prot 1999, 4: 367-
77.

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520.J

Evaluation of Hypersomnia Frequencies by using DRG in the Hos-
pitalized Population of Lorraine

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(1) Medical Information departement of Nancy hospital, (2) Regional
Hospitalisation Agency of Lorraine, (3) Laffont Company

Introduction: Sleep apnea syndrom is well-known as an entity belong-
ing to hypersomnia. It is essential to diagnose it in order to prevent car-
diovascular and neurological risks and to treat it. To obtain a descrip-
tive approach of this pathology in the Lorraine region, data from the
regional database of the Regional Hospital Agency of Lorraine has been
used. This study intends to determine the number of sleep disorders lead-
ing to hospitalization and to study their hospital impacts in the region.

Methods: According to the medicalisation program (PMSI), medical
activity has to be recorded in each public and private establishment. The
PMSI goal is to modulate money allowances for each establishment in
accordance with its activity. Each stay results in a standardized check-
out summing-up with administrative and diagnostic data as well as data
linked to medical treatment. International Classification of Diseases
(CIM-10) is used to code diagnoses and the PMSI used to code medical
care. Then data are send to the ARH. Five codes about hypersomnia
pathology have been selected and stays in relation with this codee have
been chosen. By comparing with the total number of stays in 1999, it
has been possible to the frequencies of hypersomnia.

Results: The study listed a total of 5939 hospitalizations over the year
1999 corresponding to the selected codes with a great number of patients
(5479) suffering from SAS (codes G47.3) i.e. 92.25% of the stays. The
organic hypersomnia (code G47.1) appears in 4 % of the studied stays.
Sleep disorders (code G47.9 and F51.9) represent 3 % and narcolepsy
(code G47.4) 1 % of the cases. Other selected codes , hypersomnies not
organics (code F51.1) and disorders of the cycle day before-sleep (code
F51.2 and G47.2) are scarce. Sex ratio is 4.05 (4763 male for 1176 female)
but it can vary considerably from one group to another. It is 4.45
for the SAS group. In this last group hospitalizations are more frequent
for people aged between 60 and 70 (1695 hospitalizations is 32.1
%)(table 1).60% of the subjects have between 60 and 80 years (table 2). In 1999, the regional base of Lorraine listed a total of 566 936 stays. For hypersomnia pathology, the hospitalization frequency has been estimated 10 per 1000. As for hospitalization of more than 24 H, the estimation has been 15 per 1000.

### Table 1

<table>
<thead>
<tr>
<th>Gender</th>
<th>&lt;24h</th>
<th>24-48h</th>
<th>&gt;24h</th>
<th>total</th>
<th>sex ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>17</td>
<td>2</td>
<td>3</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>143</td>
<td>91</td>
<td>54</td>
<td>180</td>
<td>234</td>
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</table>

### Table 2

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<tr>
<th>Gender</th>
<th>Code</th>
<th>&lt;24h</th>
<th>24-48h</th>
<th>&gt;24h</th>
<th>total</th>
<th>Sex ratio</th>
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<td>Male</td>
<td>G47.1</td>
<td>143</td>
<td>91</td>
<td>54</td>
<td>180</td>
<td>234</td>
</tr>
<tr>
<td>Female</td>
<td>G47.2</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

Conclusions: Sleep apnea syndrome seems to be the more frequent pathology of hypersomnia. Different studies have evaluated the prevalence of this syndrome at 4%1. In this study, it has not been possible to estimate this prevalence since only hospitalized cases have been taken into account. Measures aiming at avoiding errors by using PMSI in an epidemiology context have been proposed2. Obtained results depend on the quality of the information coding contained in the summing-ups 3. Nevertheless, there is a control of these data coding, which ensure its quality. This study has been carried out as a « exploration » of hypersomnia pathologies in Lorraine. It gives a quick answer for a given problem and allows to obtain indices reproducible indicators. However, it would be necessary to tally the obtained data with others in order to to validate their accuracy.

References:

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521.J

Serotonergic 1B, 2A and 2C Receptor mRNA Expression in Upper Airway Motoneurons in Mature Rats and During Postnatal Development

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Introduction: Serotonin (5-HT)-containing cell activity is maximal during wakefulness and minimal during REM sleep. The corresponding decrements of 5-HT levels around motoneurons (mns) are hypothesized to be a major cause of the upper airway hypotonia characteristic of REM sleep (Ref. 1). 5-HT also modulates mns during stereotyped motor behaviors and plays a role in the development of the motor system. We previously found that 5-HT type 1B, 2A, and 2C receptor mRNA species are present in the hypoglossal (XII) motor nucleus, which innervates important upper airway-dilating muscles. Since individual receptors may mediate either excitatory or inhibitory effects, the net effect of 5-HT at the level of individual cells depends on the expression pattern of distinct 5-HT receptor subtypes, and those may change with development. To elucidate the contribution of 1B, 2A, and 2C receptors to state-dependent postsynaptic effects of 5-HT, we studied the expression of their mRNA in individual XII mns of neonatal and mature rats.

Methods: XII mns were retrogradely labeled with rhodamine-dextran. They were then acutely dissociated from medullary slices containing the XII nucleus. The expression and co-expression of 5-HT type 1B, 2A, and 2C receptor mRNA was determined in 342 XII mns using single-cell transcription and polymerase chain reaction (RT-PCR). On the average, 29±8(SD) mns were studied from each of 12 rats aged 3-28 days (neonatal to mature) obtained from three sequentially processed litters. The percent of mns showing positive results following a standardized, seminested RT-PCR protocol was used to characterize the level of expression of individual mRNA species in mns from rats at different ages.

Results: The proportion of mns with detectable levels of 5-HT receptor mRNA varied with age and receptor type (p<0.002, two-way ANOVA), with the 2A receptor mRNA being most common, and that for 2C receptors (truncated or full isoform) encountered least often (Figure). For all receptors, the expression increased sharply during the first 10 postnatal days, transiently decreased through the subsequent 7 days, and then increased. The 1B and 2A receptor mRNA species were frequently co-expressed.

Figure 1
Conclusions: The presence and parallel developmental changes of the mRNA for 1B and 2A receptors in a high proportion of mns show that 5-HT may postsynaptically both inhibit (1B) and excite (2A) XII mns. The final effect will depend, however, on the process of production and recycling of the corresponding receptor proteins. The transient decrease in the 5-HT receptor mRNA expression suggests that a major reorganization of 5-HT effects on mns peaks near the 14th postnatal day. This may be associated with profound changes in the mode of serotonergic control of orofacial mns and its state dependence.

References:

Research supported by SCOR grant HL-60287 and HL-47600.

522.J

Predicting The Diagnosis of Upper Airway Resistance Syndrome Using Total Arousal Index

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(1) Walter Reed Army Medical Center, (2) Howard University

Introduction: Upper airway resistance syndrome (UARS) patients present with excessive daytime sleepiness or tiredness and do not have obstructive sleep apnea on evaluation by standard nocturnal polysomnography 1. Esophageal pressure (Pes) catheter measurements are the gold standard for diagnosing UARS, but are not available in all sleep labs. Other variables obtained during diagnostic polysomnography (PSG) could be helpful in predicting the diagnosis of UARS. We set out to (1) determine predictability of total arousal index (TAI), body mass index (BMI), and Epworth sleepiness scale (ESS) in diagnosing UARS, and (2) to examine association between TAI, ESS, BMI and respiratory effort related arousals (RERA) index.

Methods: We did a retrospective study among 39 patients who underwent overnight PSG withPes monitoring at Walter Reed Sleep Disorders Center from April 1999 to November 2000. Pes monitoring was obtained in these patients if they had an apnea/hypopnea index (AHI) <5/hour and TAI >7/hour on initial PSG and were symptomatic with excessive daytime sleepiness or tiredness. The subjects consists of 39 patients (25 males and 14 females) with mean age of 38.4 years (21 to 62), mean BMI of 28.3 kg/m2 (20.37 to 39.47) and with mean Epworth sleepiness scale of 12.0 (2 to 23).

Results: Analyses using Pearson’s correlation among the 20 patients with UARS revealed a non-significant association with TAI on diagnostic PSG with the RERA index. However, there was a positive association with TAI on the PSG with Pes and RERA index (r = 0.668; p<.01). Comparison of the mean TAI results between the diagnostic and Pes PSG’s did not show any significant statistical difference. We feel the TAI is lower on the diagnostic PSG due to increased difficulty recognizing arousals without Pes manometry and esophageal pressure shifts. There were no significant associations of RERA index with ESS or BMI. Table 1, illustrates the breakdown of diagnosis after PSG with Pes monitoring.

Table 1

<table>
<thead>
<tr>
<th>Diagnosis after overnight polysomnogram with upper airway pressure monitoring</th>
<th>Total Patients</th>
<th>UARS</th>
<th>NORMAL</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>20</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>(51.3%)</td>
<td>(23.1%)</td>
<td>(25.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Total arousal index is occasionally ignored and not scored during diagnostic PSG. Sleep professionals should strongly consider scoring arousals and microarousals during diagnostic PSG. All patients with UARS had an initial TAI >10/hour. Based on our results, a TAI >10/hour among symptomatic patients with an AHI <5/hour on standard PSG should lead one to consider the diagnosis of UARS. The utility of TAI is a promising tool in predicting UARS especially in sleep centers that do not have Pes monitoring capability. Otherwise, a significant portion of patients suffering from UARS could potentially go undiagnosed and untreated with continued socioeconomic impact.

References:

523.J

Population-based Longitudinal Study of Menopause and Sleep-disordered Breathing

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Introduction: Menopause has been hypothesized as a risk factor for sleep apnea, but there is little evidence to support their association. Longitudinal data are needed to determine whether age related increases in sleep-disordered breathing (SDB) are accelerated by the onset of menopause, independent of body habitus changes. Using a population-based sample of women enrolled in the Wisconsin Sleep Cohort Study, we are investigating how the onset of menopause during a four year period accelerated the incidence of polysomnographically determined SDB.

Methods: The study sample comprises 616 women who have undergone up to three in-lab sleep study protocols at 4-year intervals, for a total of 1127 sleep studies. Menopausal status was determined from self-reported menstrual and surgical history obtained at each lab visit and serum FSH level. SDB was measured by continuous polygraphic recording using 16-channel Grass polygraphs (model 78). Studies were sleep staged according to standard criteria. SDB was determined by the number of apneas (10 seconds with no airflow) plus hypopneas (reduced airflow accompanied by a 4% oxyhemoglobin desaturation) per hour of sleep (Apnea/Hypopnea Index (AHI)). An AHI=5 or above was considered positive for SDB. Conditional logistic regression was used to estimate the relative odds, beyond 4 years of aging, of developing SDB in women who became menopausal compared to those who did not, controlling for change in BMI.

Results: After exclusion of 184 women who were post-menopausal at their first in-lab study, data from 305 pairs of studies were used for this analysis. 168 women remained pre-menopausal at follow-up, while 137 women experienced the onset of menopause (75 peri-menopausal and 62 post-menopausal). Women not changing menopausal status had a mean baseline AHI = 1.33 versus 3.48 for those who changed status (p<0.002). Multivariable regression showed that onset of menopause was strongly related to the development of SDB, independent of change in BMI. Women who experienced the onset of menopause had a 19-fold increase in the odds ratio of developing SDB associated with 4 years of aging. A change in one BMI unit was related to a 1.2-fold increase in the odds of SDB, unadjusted for menopausal change, but the association was insignificant when menopause was accounted for. We investigated HRT use at follow-up as a modifier of the association of menopause and SDB, but study power was limited and we found no significant effect.
Table 1

<table>
<thead>
<tr>
<th>Model Terms</th>
<th>β-Coefficient (se)</th>
<th>P-value</th>
<th>Odds Ratio†</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Menopause</td>
<td>2.973 (1.14)</td>
<td>0.009</td>
<td>19.55</td>
<td>(2.09 – 182.8)</td>
</tr>
<tr>
<td>Change in BMI (Kg/m²)</td>
<td>0.153 (0.13)</td>
<td>0.233</td>
<td>1.165</td>
<td>(0.91 – 1.50)</td>
</tr>
</tbody>
</table>

Only pre-menopausal and peri-menopausal women included at Baseline.
† = Odds Ratios are calculated for one-unit change in BMI and for multiplicative effect on odds ratio associated with 4 years of aging by change in menopausal status versus no change.
§ = Estimated by conditional logistic regression.

Conclusions: Based upon our preliminary analyses, menopausal onset appears to be a risk factor for the development of SDB, independent from change in age or BMI, supporting the hypothesis that women who experience menopause have a greater risk of developing SDB.

Supported by NIH and NIA grants RO1HL62252, RR03186, and RO1AG14124

524.J

Effect of Position on Apnea, Hypopnea, RERA Indices Using the Nasal Cannula Technique

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Introduction: Position is thought to influence upper airway collapsibility and thus the count of respiratory events during NPSG. Recently the AASM proposed standardized definitions for obstructive respiratory events (1). We have shown that the nasal cannula technique provides detection of events essentially identical to those proposed by the AASM using esophageal pressure measurements (2). In the present study, we investigated how the nasal cannula detection combined with the AASM definitions of events affected the relationship of position and respiratory event counts.

Methods: 98 sequential (July to October 2000) full night polysomnograms (no “split-night” studies) performed on adult patients suspected of having OSAS were scored for inclusion. 37 studies had adequate data quality and at least 30 minutes in supine and lateral positions. To date the NPSGs from twelve patients (10 male/2 females) have been analyzed for inclusion in this study. Age ranged from 35-67 and BMI 24.6-60.2. Overall AHI ranged from 8 to 104/hr. The two patients with AHI<10 had significantly higher AHI (99/hr, 102/hr) in REM sleep. Patients with severe OSAS tended to be excluded because of having split studies. NPSGs consisted of digitally recorded (Biologics) central, occipital and frontal EEG, right/left EOG, submental EMG, anterior tibialis EMG, ECG, chest/abdominal piezoelectric strain gauges, nasal cannula (Protech), oral thermistor and finger oximetry. Position was determined from an automatic sensor (Biologic/Protec), reviewed and manually edited. Sleep was scored by R&K criteria on 30-second epochs. Respiratory events >10sec were scored manually from the nasal cannula signal, identifying apneas (airflow <10% of baseline) and hypopneas (airflow <50% of baseline OR 50-80% of baseline with 3 desaturations). As proposed in our prior work, events with airflow 50-80% of baseline with an arousal but no desaturation, were classified as RERAs due to the sensitivity of the nasal cannula (2). Apnea/Hypopnea index (AHI) and Apnea/Hypopnea/RERA index (AHRI) were tabulated by custom software, and reported by position (supine/lateral) and sleep stage (REM/NREM).

Results: In 6/12 patients AHI-lateral was <50% of AHI-supine. One subject had AHI-lateral more than 50% greater than AHI-supine. AHRI (AHI including RERAs) showed the same relationships as AHI. Stage specific data showed that in NREM AHI-lateral was <50% of the AHI-supine in the same 6/12 subjects; however, no subject had AHI-lateral AHI-supine. In REM, the relationship between AHI-lateral and AHI-supine was very variable: 3/10 subjects showed a decrease by >50%, 3/10 increased >50%, 4 showed change <50%. By Mann-Whitney test, those subjects with >50% reduction in AHI with position had lower BMI (median 27.1 vs. 33.8). These same subjects also had lower overall AHI (median 14 vs. 41). There was a significant relation between AHI and BMI (Spearman r=0.5).

Figure 1

Conclusions: In our group of patients with OSA, a significant (>50%) change in AHI with position was found in at least half the patients. These tended to be the patients with lower BMI and AHI. These results applied equally when AHI was defined as recommended by the AASM, or by including the RERAs in the count.

References:
(1) AASM Task Force, Sleep 1999;22:667
(2) Ayappa et al. Sleep 2000; 23:763

Research supported by American Lung Association of NY Foundation for Research in Sleep Disorders NIH-NHLBI - GCRC grant RR00096

525.J

Distinguishing Sleep Apnea from Narcolepsy during the Sleep Onset Period (SOP)

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Introduction: The purpose of this study was to examine the sleep onset periods (SOP) of patients diagnosed with narcolepsy, obstructive sleep apnea (OSA) and clinically non-significant sleep. Following earlier work from this group(1), the research hypothesis was that specific sleep onset signatures, based on latency measures (alpha waves, vertex sharp waves, and sleep spindles), could be used to discriminate among the sub-
types of OSA patients (mild, moderate, severe), the narcoleptic patients and the clinically non-significant sleepers. Specifically, it was predicted that patients with sleep apnea or narcolepsy would have shorter latency measures compared to normal sleepers, and that the pattern of latencies could be used to distinguish among the clinical groups.

Methods: This investigation analyzed clinical data collected between 1994-1998 at the Paris Medical Arts Sleep Clinic, Paris, Ontario. Polysomnographic data from 92 participants included: 60 individuals suffering from OSA (20 moderate, 20 moderate & 20 severe), 12 people diagnosed with narcolepsy and 20 with clinically non-significant sleep patterns were studied. One-way analysis of variance (ANOVA), was utilized to determine which measures could differentiate among diagnostic categories. The participants’ body mass index (BMI) was also used as a predictive measure.

Results: One-way ANOVAs indicated that differences between latency measures for sleep onset (<50% alpha) were significant (F4, 87 = 2.61, p = 0.04). Specifically, differences were found between the severe OSA group and the remaining two subgroups of OSA, and between the clinically non-significant sleepers and the moderate OSA group. None of the other comparisons for latency measures were statistically significant. The BMI differentiated among virtually all groups investigated in this study, (F4, 87 = 9.69, p = 0.001). BMI scores discriminated clinically non-significant sleepers from mild, moderate and severe OSA sufferers, and people with narcolepsy from moderate and severe sleep OSA groups.

Conclusions: The study provided evidence that latency to stage 1 sleep onset can be used to differentiate OSA subgroups from clinically non-significant sleepers. This is important as it implies that changes early in the SOP are sensitive to the influence of certain sleep disorders. Thus latency measures in the sleep onset period may enhance the differentiation of excessive daytime sleepiness. BMI, a known predictor of OSA, was used herein as a benchmark against which the SOP latency measures could be compared. If forced to choose, BMI was clearly more useful than the latency measures in this study, but latency to stage 1 sleep remains an important clinical sleep index.

References:
(1) Chilcott LA, Ogilvie RD, Carll DJ, Powles ACP. Physiological markers per hour of sleep, as a summary measure. The presence of ECG indicated CVD includes ECG evidence of left ventricular hypertrophy (ECG-LVH) as defined by Cornell voltage criteria, and ischemia as defined by ST-T wave changes consistent with ischemia, or Q-waves suggestive of past myocardial infarction. We analyzed the association between SDB and these CVD indicators by using a multivariable model with adjustments for age, sex, body-mass index (BMI) and smoking status. Associations were expressed as odds ratio (OR) and 95% confidence intervals (CI). Generalized estimating equation methodology was utilized to account for intra-subject correlation from repeat visits. Beta coefficients were assessed using Wald Chi-square tests with p < 0.05 indicating statistical significance.

Results: The mean age of study participants was 49.9 years; 55% were men, and 45%, women. The prevalence of ECG-LVH and ischemia was 2%, and 8.5%, respectively. There was no significant association between SDB and ECG-LVH. The prevalence of ECG-LVH was 1.7%, 3.7%, and 1.8% in participants with AHI <5, 5-15, and >15, respectively (p=0.29). The prevalence of ischemia increased over SDB severity categories: 7.3%, 9.8%, and 14.7% in participants with AHI <5, 5-15, and >15, respectively (p<0.03). The unadjusted odds ratio between AHI > 15 vs. <5 and ischemia was 2.17 (95% CI: 1.20-3.95). After controlling for potential confounding factors the adjusted odds ratio between AHI > 15 vs. <5 and ischemia was weaker and lost statistical significance (OR = 1.59, 95% CI: 0.80-3.14). Smoking status and BMI were not significantly associated with ischemia and when dropped from the multivariable model, the odds ratio between AHI > 15 vs. <5 and ischemia was slightly higher and statistically significant (OR= 1.86, 95% CI: 1.01-3.41). When SDB was indicated with AHI as a continuous variable, using Log (AHI +1) to control for the skewed nature of AHI, the association between SDB and ischemia was similar in magnitude to that estimated from the categorical SDB models and was statistically significant. The odds ratio for AHI = 15 vs. 0 was 1.87 (95% CI: 1.01-3.46).

Conclusions: We did not find an association between SDB and ECG indicated LVH. We found a consistent positive association between SDB and ischemia but statistical significance varied. The findings suggest that SDB may be a risk factor for ECG abnormalities indicating past myocardial infarction or ischemia in the general population.

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Effects of Esophageal Pressure Monitoring on Total Arousal Index and Apnea/Hypopnea Index during Nocturnal Polysomnography

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Walter Reed Army Medical Center

Introduction: Esophageal pressure (Pes) manometry is used to aid in the diagnosis of upper airway resistance syndrome (UARS). UARS is suspected on initial nocturnal polysomnography (PSG) when the total arousal index (TAI) is >10/hour with an apnea/hypopnea index (AHI) <5/hour. Pes measurements requires placement of a thin, water-filled catheter through the nasal passageway into the esophagus. Pes monitoring has little effect upon sleep architecture , but little is known about the effect it has upon TAI and RDI. Pes may effect both TAI and AHI and the diagnosis of UARS. The purpose of this study was to determine if there is a statistical difference between total arousal index and respiratory disturbance index as measured on polysomnography with and without Pes.

Methods: We did a retrospective study among 39 patients who underwent overnight PSG with Pes monitoring at Walter Reed Sleep Disorders Center from April 1999 to November 2000. Pes monitoring was obtained.
in these patients if they had an AHI <5/hour and TAI >7/hour on initial PSG and were symptomatic with excessive daytime sleepiness or tiredness. The subjects consisted of 39 patients (25 males and 14 females) with mean age of 38.4 years (21 to 62), mean BMI of 28.3 kg/m2 (20.37 to 39.47) and with mean Epworth sleepiness scale of 12.0 (2 to 23).

Results: Mean value of TAI increased from 22.7/hour on initial PSG to 36.145/hour with Pes. Analysis using paired T-test showed no statistical difference. Mean value of AHI decreased from 2.49/hour initially to 1.74/hour with Pes, again without statistical difference. See table 1.

Table 1

<table>
<thead>
<tr>
<th>Mean TAI and AHI with and without Pes.</th>
<th>Initial PSG</th>
<th>PSG with Pes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TAI</td>
<td>22.7/hr</td>
<td>36.145/hr</td>
</tr>
<tr>
<td>Mean AHI</td>
<td>2.49/hr</td>
<td>1.74/hr</td>
</tr>
</tbody>
</table>

Conclusions: The diagnostic criteria of UARS is an AHI<5/hour, a respiratory effort related arousal index >10/hour with negative inspiratory pressures of -12 cm/H2O on Pes monitoring. During our evaluation of possible UARS patients, we noted a general increase in both TAI and AHI whenPes monitoring was used during standard PSG. However, our study shows no significant difference with Pes manometry. We feel the TAI is lower on the diagnostic study due to difficulty recognizing arousals and microarousals without Pes monitoring and therefore, more TAI’s may go undetected on initial PSG. Consequently, the mean initial TAI is potentially artificially low. Our study shows that Pes monitoring does not significantly effect the TAI nor AHI and therefore does not effect the diagnostic accuracy of esophageal pressure manometry.

References:
(1) Chervin, RD and Aldrich, MS. Effects of Esophageal Pressure Monitoring on Sleep Architecture. Am J Respir Crit Care Med 1997; 156:881-885

528.J

Higher Prevalence of Smoking in Patients with Obstructive Sleep Apnea

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Introduction: Despite the presence of evidence suggesting relationship between smoking and sleep disordered breathing, there is little epidemiological information on the relation between smoking and sleep disturbance. The present study tested the hypothesis that there is higher prevalence of smoking in patients diagnosed to have obstructive sleep apnea (OSA).

Methods: 104 patients were randomly selected from the group of patients diagnosed to have OSA with polysomnogram and had respiratory disturbance index (RDI) of 10 or more every hour. These patients were divided into three groups based on their RDI, those with RDI of less than 20 were classified as mild OSA, 20-40 as moderate OSA and more than 40 as severe OSA. Further assessment was made regarding their smoking habits and three groups were identified, current smokers, former smokers and never smokers.

Results: Out of the 104 patients with OSA, 24 (24%) are mild cases, 33 (34%) are moderate cases and 41 (42%) are severe cases. Smoking status was divided into 4 levels: 45 (43%) who had never smoked, 23 (22%) who are former smokers, 24 (23%) are current smokers with 30 pack-years or less, and 12 (12%) who are current smokers with more than 30 pack-years. A Mantel-Haenszel chi-square test for trend showed no trend in the data (p=0.60). There is no evidence supporting the hypothesis that heavier smokers tend to have more severe sleep apnea. The number in each group is given in the following table.

Table 1 Obstructive sleep apnea by smoking status

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>11</td>
<td>14</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>Previous smokers</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Current smokers (&lt;30 pack years)</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Current smokers (&gt;30 pack years)</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>37</td>
<td>42</td>
<td>104</td>
</tr>
</tbody>
</table>

Conclusions: Prevalence of smoking in patients diagnosed to have OSA found in our study is 35% which is much higher than the prevalence of smoking in the general population which is 20% (1). Cigarette smoking may contribute to upper airway dysfunction during sleep by eliciting mucosal edema and increased upper airway resistance. Some investigators have found a high prevalence of pulmonary function abnormalities in sleep apnea patients (2) and there are a number of detrimental pulmonary and respiratory effects attributable to smoking (3) that may result in an increase in sleep disordered breathing. Our study did not find a positive correlation between severity of OSA and heavier smoking habits, but it definitely showed a higher prevalence of smoking in patients with OSA. This study establishes a link between cigarette smoking and sleep-disordered breathing. This provides a strong rationale for further research attempting to ascertain the precise relationship between smoking and sleep-disordered breathing as the results have important public health implications.

References:

529.J

Females with Sleep Disordered Breathing are more likely to be Treated for Depression than Males

North Shore University Hospital

Introduction: Obstructive sleep apnea (OSA) and depression are associated with similar symptoms including excessive daytime somnolence (EDS). Many patients referred for evaluation for EDS are on antidepressive treatment. Patients are often started on antidepressive treatment without psychiatric evaluation. This study was designed to evaluate the pattern of antidepressive use in patients referred for EDS.

Methods: We reviewed records of patients referred for EDS. Each
Changes in Sleep Stage Distribution During Acute CPAP Application in Obstructive Sleep Apnea Patients

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Introduction: Patients with obstructive sleep apnea have significant sleep disruption, including poor sleep efficiency, increased stage 1 NREM sleep, decreased slow-wave sleep (SWS) and decreased REM. During acute treatment with nasal CPAP there is marked improvement in sleep disruption. Previous studies have demonstrated an acute effect of CPAP on sleep characterized by increased SWS and REM, but this has been in small series. Because of our clinical impression that SWS rebound was rare, we undertook to re-examine the effects on sleep architecture of the first night of CPAP application in a large series of patients with obstructive sleep apnea/hypopnea syndrome (OSAHS).

Methods: All patients seen at the NYU Sleep Disorders Center from August, 1998 to October, 2000 with a new diagnosis of OSAHS who completed both a full night of diagnostic and CPAP polysomnography were retrospectively evaluated. Patients were excluded if they had significant changes in medications affecting sleep between the studies or if split night NPSG was done. CPAP titration was performed manually or with an automated CPAP machine (Mallinckrodt GK 418P). Differences in distribution of sleep stages between the diagnostic and CPAP nights were analyzed by paired t-test.

Results: There were 88 males and 31 females. Average age was 48.7 years (6-86) and average diagnostic AHI was 37.9 events/hour (5-138). Automated CPAP titration was performed in 93 and manual titration in 26 patients. Total Sleep Time (TST) was not significantly different (331 vs 313 min) between diagnostic and CPAP nights; Sleep Efficiency also did not differ (74 vs 76%). During CPAP, there was a significant decrease in Stage 1 NREM (31.6% to 19% of TST, p<0.001), an increase in stage 2 NREM (48% to 56% of TST, p<0.001) and an increase in REM sleep (15.9% to 20% of TST, p<0.001) as well as a decrease in REM latency (124 min to 101 min, p<0.05). Interestingly, SWS increased only minimally (4.4% to 5.5% of TST, p=0.07). There was a weak correlation between the increase in REM on CPAP and initial AHI (r=0.345, p<0.001). No relationships could be shown between changes in sleep distribution and age or gender. The changes in sleep architecture did not differ between manual and autoCPAP titration.

Conclusions: As in previous studies, a significant improvement in sleep architecture was shown during the acute application of CPAP in patients with OSAHS. These consisted of reduction in stage 1 NREM and increased REM. Unlike prior studies, we showed only minimal changes in SWS. We cannot exclude the possibility that this lack of increase in SWS was due to our technique of CPAP titration, although no difference was seen between manual and auto titration.

References:

Research supported by ALA-NY, Foundation for Research in Sleep Disorders, NIH/NHLBI - GCRC Grant RR00096

Prevalence of REM-related Sleep-disordered Breathing in a Sleep Clinic Population

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Introduction: Some patients demonstrate sleep-disordered breathing (SDB) which is largely limited to REM sleep. These patient’s may have daytime sleepiness despite a lower index of severity calculated for the total sleep time. This study was undertaken to determine the prevalence of sleep-disordered breathing among patients in a community-based sleep clinic.

Methods: 202 randomly selected studies were reviewed retrospectively. The patients were being evaluated for problematic snoring and excessive daytime sleepiness. They were considered to have “REM-related” SDB if the RDI in REM was more than twice the RDI in NREM. Polysomnography was performed with a computerized acquisition system employing standard EEG montage for scoring sleep. Sleep stages were scored manually according to R and K criteria. Respiratory events were manually scored based upon recordings of pulse oximetry, oronasal thermistry, and qualitative measures of respiratory excursion of the chest and abdomen. Respiratory events were scored manually by registered PSG technologists and reviewed by a board certified sleep physician. Hypopnea was defined as a 50% drop in airflow regardless of changes in oxygen saturation or arousal.
Results: Of the 202 records, 43 demonstrated an RDI<15 and were not analyzed further. 112/159 (70.4%) patients were studied with a “split-night” protocol. 24/47 full night studies (51.1%) demonstrated REM-related SDB. 19 / 112 split night studies (17.0%) demonstrated REM-related SDB. The overall prevalence of REM-related SDB was 43/159 (27.0%). Not surprisingly, the group with REM-related SDB had a lower overall RDI compared to the group without predominance in REM (27.8 vs. 71.6, P<0.001). There was no significant difference in age between the groups (48.8 vs. 50.0, NS). The group with REM-related SDB had slightly lower scores on the Epworth Sleepiness Scale (11.3 vs. 13.7, P<0.015). There was no difference in BMI between the two groups (46.1 vs. 46.5, NS). There was a higher proportion of females in the REM-related group which was not statistically significant (27.9 vs. 15.9, P=0.095).

Conclusions: The protocol used for split-night studies did not require development of REM sleep during the baseline period. Consequently, the true prevalence of REM-related SDB may have been underestimated. On the other hand, scoring hypopneas without requiring oxygen desaturation or arousal may overestimate the number of events in REM sleep. There were minimal differences between the patients with and without REM-related SDB. They may have been somewhat less sleepy. The pathophysiology of this pattern of sleep-disordered breathing remains to be elucidated. It appears to be reasonably common and may have implications in terms of treatment strategies.

532.J

Screening of Referrals for Polysomnography

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(1) Sleep HealthCenters at National Jewish, (2) National Jewish Medical and Research Center, (3) University of Colorado Health Sciences Center, (4) Good Samaritan Medical Center, (5) Brigham and Women’s Hospital

Introduction: Nocturnal polysomnography is expensive and there are frequently long waiting lists for studies. Several investigators have therefore evaluated pre-polysomnography screening for obstructive sleep apnea (OSA), with sensitivities ranging from 28-92% and specificities from 50-95% (1,2). We hypothesized that a 3 outcome predictive model might have improved accuracy, allowing high probability patients to receive immediate polysomnography, deprioritizing low probability patients, and allowing intermediate probability patients additional evaluation before polysomnography.

Methods: Prospective, nonrandomized study in academic medical center. Subjects - 285 consecutive patients referred for polysomnography. Techniques - Telephone questionnaire: snoring frequency and loudness, witnessed apneas, neck circumference, Epworth score, previous falling asleep while driving, hypertension, gender, age. Followed by formal nocturnal polysomnography. Protocol - univariate logistic regression analysis for each predictor vs. AHI. Significant predictors fitted to multivariate regression model vs. AHI. Probability predicted for 3 outcome groups (high probability, AHI ≥ 25; low probability, AHI < 10; intermediate probability, AHI 10-25).

Results: Significant individual predictors were frequently witnessed apneas, frequent snoring, hypertension, gender, neck circumference, age. Our most accurate model never predicted patients into the intermediate probability group. However, when adjusted to a 2 outcome group model (high probability, AHI ≥ 10, low probability, AHI < 10), test accuracy was 74%, sensitivity was 78%, and specificity was 63%. Similar results were obtained from 2 separate validation groups (120 consecutive NJMRC referrals, accuracy = 77%, sensitivity = 81%, specificity = 60%; 284 consecutive community hospital referrals, accuracy = 73%, sensitivity = 80%, specificity = 57%). A “second stage” morphometric screen (3) subsequently applied to 28 “low probability” patients had an accuracy of only 32%.

Conclusions: 1. We were unable to use pre-polysomnography clinical predictors to separate patients into 3 distinct probability groups. 2. After adjustment to predict only 2 probability outcomes, our model demonstrated accuracy, sensitivity, and specificity in 3 different patient populations similar to those previously reported. 3. The addition of a “second stage” morphometric screen did not improve the accuracy of our testing.

References:

533.J

Comparison of Musculoskeletal Complaints in Patients with and without Sleep Disordered Breathing

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Introduction: In a recent review of sleep in less well-defined chronic rheumatic disease (1) Mahowald et al. stated “…conditions characterized by severe sleep fragmentation such as obstructive sleep apnea are not associated with musculoskeletal symptoms.” It was our impression that patients presenting to our sleep clinic with symptoms of sleep disordered breathing also had a high prevalence of musculoskeletal symptoms. To test this hypothesis we did a retrospective chart review of patients studied with polysomnography after clinical evaluation. We compared the responses to a question about awakening with musculoskeletal pain on a standardized questionnaire from patients with an RDI <10 to those from patients with an RDI ≥10.

Methods: We randomly selected sleep laboratory charts until we had identified 25 patients with an RDI <10 and 25 patients with an RDI ≥10. Each patient had filled out a standardized sleep questionnaire within eight weeks of their polysomnographic study. Responses to the question, “Do you awaken with pain in the joints or muscles/elsewhere?” (Choices: never/rarely, occasionally/sometimes, often, frequently and constantly) were abstracted for comparison between the two groups. We excluded from the analysis patients with a history of a diagnosed rheumatological condition.

Results: One patient in each group had a history of osteoarthritis and was excluded from the analysis. Results for the remaining 24 subjects in each group are shown in the table. Mean age was similar in the two groups but as expected, there was a higher proportion of men and a greater mean weight in the RDI ≥10 group. There was also a slightly higher proportion of African-Americans in the higher RDI group. Combining responses of never and rarely as indicating an absence of musculoskeletal symptoms, 88% of the patients with an RDI ≥10 reported awakening with musculoskeletal pain compared to only 42% of the lower RDI group. This difference was highly statistically significant (p <0.001). There was a significant correlation between presence of nocturnal musculoskeletal symptoms and RDI (r = 0.48, p <0.05). Analyzing responses by the reported frequency of nocturnal awakenings with musculoskeletal pain (never =0, rarely =1, occasionally/sometime =2, often =3, frequently =4 and constantly =5) there was also a significant
correlation with RDI ($r = 0.32, p <0.05$).

<table>
<thead>
<tr>
<th>AGE</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI ≥ 10</td>
<td>44.4 yrs</td>
<td>46.1 yrs</td>
</tr>
<tr>
<td>RDI &lt; 10</td>
<td>27-61 yrs</td>
<td>19-64 yrs</td>
</tr>
</tbody>
</table>

Conclusions: These results suggest there is a high prevalence of nocturnal musculoskeletal symptoms in patients with sleep disordered breathing. There is also a significant correlation of severity of sleep disordered breathing as measured by RDI and musculoskeletal symptoms. Possible mechanisms for this correlation include sleep disruption leading to a decreased pain threshold and muscle tension associated with apneic events. Obesity may also be related to both RDI and musculoskeletal symptoms. Further investigation in a larger sample including determination of whether musculoskeletal symptoms are more frequent in the daytime and whether they resolve with treatment of sleep disordered breathing is warranted.

References:
(1) Mahowald M and Mahowald M. Nighttime sleep and daytime functioning (sleepiness and fatigue) in less well-defined chronic rheumatic diseases with particular reference to the ‘alpha-delta NREM sleep anomaly’. Sleep Medicine, 2000; 1: 192-207

Research supported by NIH Sleep Academic Award K07 HL03897

Immunohistochemical Study of Hypothalamic Projections to the Hypoglossal Nucleus of the Cat

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Introduction: State-dependent synaptic control of hypoglossal and other somatomotor neurons is known to be mediated by multiple transmitter systems (1). For the newly described transmitter hypocretin, we have previously presented immunohistochemical data demonstrating close appositions between hypocretinergic varicose fibers (originating from the hypothalamus) and hypoglossal motoneurons in the cat (2). Contemporary findings suggest that the hypothalamic hypocretin system is involved in a variety of functions and behavioral states, including sleep (3). In the present study, we sought to determine whether hypocretinergic neurons that project to the hypoglossal nucleus are activated during active sleep.

Methods: In the chronic cat, under isoflurane anesthesia, the hypoglossal nucleus was located by recording its antidromic field potential in response to electrical stimulation of nerve fibers that lie within the ipsilateral genioglossus muscle. The retrograde marker cholera toxin b (CTb) was then injected by iontophoresis into the hypoglossal nucleus at a site where the amplitude of the antidromic field potential was maximal. Following a recovery period of 10 days, carbachol (0.8 micrograms in 0.2 microliter saline) was microinjected stereotaxically into the nucleus pontis oralis (P2 L2 H-4.5) to elicit a prolonged period of active sleep (AS-carbachol). This paradigm enabled the activation of neurons during AS-carbachol to be revealed by c-fos expression. Under deep anesthesia with Nembutal, perfusion for immunohistochemical studies was undertaken. Free-floating sections were first incubated with an antibody directed against CTb (dilution = 1:30,000). They were then processed with diaminobenzidine (DAB) and nickel intensification in order to reveal the black granular appearance of retrogradely-labeled hypothalamic neurons. The sections were then divided into two separate series for incubation with a polyclonal antibody directed against either hypocretin-2 peptide (dilution = 1:10,000) or c-fos (dilution = 1:60,000). Finally a non-intensified DAB reaction was used to produce brown stained hypocretin immunoreactive neurons (series 1) and Fos protein (series 2).

Results: The first immunostained series revealed that retrogradely labeled, CTb-containing neurons were present bilaterally in the lateral and medial hypothalamus, and that they were located amongst single-labeled hypocretin-immunoreactive neurons. Double-labeled hypocretinergic neurons that projected to the hypoglossal nucleus contained punctate black CTb granules within a brown-stained cytoplasm. The second immunostained series indicated that both types of single-labeled (Fos-immunoreactive and CTb-containing) neurons were localized within the same areas of the hypothalamus. Less than 6% of the CTb-containing neurons expressed Fos immunoreactivity (i.e., were double-labeled).

Conclusions: Our findings indicate that hypocretinergic premotor hypoglossal neurons coexist with hypocretinergic neurons within the lateral and medial hypothalamus. Since the majority of the hypothalamic neurons that project to the hypoglossal nucleus were not activated during AS-carbachol, the hypothalamus is likely to exert synaptic control of hypoglossal motoneurons principally during wakefulness.

References:

These studies were supported by USPHS grants MH43362, NS23426, NS09999 and HL60296.

Comparison of Nasal Thermister and Nasal Cannula Pressure Transducer for Detecting Respiratory Events in Obstructive Sleep Apnea

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Introduction: Nasal thermisters are one of most common sensors used to evaluate sleep disordered breathing and are the current standard in the sleep industry. Esophageal pressure transducer monitoring is a more invasive and less comfortable technique, although typically more sensitive in detecting mild OSA (Obstructive Sleep Apnea) and UARS (Upper Airway Resistance Syndrome). We were seeking to evaluate a sensitive but less invasive method. Therefore, we chose to monitor airflow via a nasal cannula pressure transducer. Our goal was to see if the nasal cannula pressure transducer would detect more mild events such as UARS than thermisters.

Methods: Fifty patients were randomly selected: 31 male and 19 female with ages ranging from 15 to 79 with a mean age of 47. Patients were
recorded with a full 18 channel polysomnography including using dual nasal thermisters and an oral thermister. Patients were also tested simultaneously with a nasal cannula pressure transducer. This was not a blind study because the scorer could tell by the signal display whether the channel was a pressure transducer or a thermister. Each polysomnogram was manually scored twice by the same registered technologist, first by scoring respiratory events using thermister airflow channels and then removing the airflow channel and scoring with the nasal cannula pressure transducer. Hypopnea scoring was defined as events having arousals, desaturations, and an airflow reduction of 20-75%. Apneas were defined as events having, arousals, desaturations, and airflow reduction of 75% or greater. UARS were scored as events with building respiratory effort, 10-20% decrease in airflow, minor O2 desaturations and arousal.

Results: Our test data illustrated minor and probably insignificant variance in A+H index using thermisters versus nasal cannula pressure transducers, with an average variance of 2.78, with a SD (Standard Deviation)=2.56. However, data correlation between total apneas, hypopneas, and UARS scored showed significant variance between the two airflow monitoring techniques. Total apneas scored using airflow pressure transducers were increased in 88% of total patients tested versus thermister scored apneas. This increase equaled an average total of 26.0 events per patient. The remaining 12% had no change. Total pressure transducer hypopneas decreased in 58% of tested patients versus thermister scored hypopneas, with an average decrease of 30.4 events per patient. 40% of pressure transducer hypopneas reflected an average increase of 21.7 events per patient. Total variance average was 26.3 events per patient.Total UARS scored with pressure transducer were increased over thermister scored UARS in 98% of patients tested, with an average total variance of 30.2 events per patient.

Conclusions: Scored data provided an indication that airflow monitoring via nasal cannula pressure transducers enables greater sensitivity in detecting UARS and obstructive apneas, in comparison to thermister detected UARS and obstructive apneas. The increased number of pressure transducer detected apneas occurred frequently with a concurrent decrease in transducer detected hypopneas. Subsequent A+H index between the two techniques therefore remained nearly identical.

536.J

Compensating for Excessive Daytime Sleepiness: The Epworth Sleepiness Scale and Age

Goldstein DS, Lahey MJ
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Introduction: While the relationship between Excessive Daytime Sleepiness (EDS) and obstructive sleep apnea (OSA) has been well-established, the relationship between EDS and the age of OSA patients needs further investigation. The purpose of this study was to determine if the Epworth Sleepiness Scale (ESS) can help in predicting the presence and severity of Obstructive Sleep Apnea (OSA) when the factor of age is taken into account. Can younger groups with OSA compensate better than older groups and have lower overall Epworth Score (ES)?

Methods: Patients in the study were referred from their primary physician to the sleep disorders center for the purposes of a sleep evaluation. A complete sleep history was obtained on all patients. It was at this point that clinical lab values for the Epworth Sleepiness Scale were obtained on the patients. All patients scheduled for polysomnographic evaluation for the purposes of ruling out OSA had Epworth Scores. A full nocturnal polysomnogram was performed on all patients using a standard 16-channel montage. Patients were considered positive for OSA if the apnea-hypopnea index (AHI) was greater than 10 events per hour. Patients were grouped into age brackets of Less than 35 Years, 35 to 55 Years, Greater than 55 Years. The average ES was calculated for each group. Degree of OSA was grouped into three brackets: Mild (AHI 10-30), Moderate (AHI 31-50), Severe (AHI >50).

Results: Of 186 patients with documented OSA, 66 were mild, 52 were moderate, and 68 were severe. There was a trend in the average ES to increase as the age increased in the same degree of OSA. Most of the increases were within the standard deviation. Of note was that there was no correlation between severity of OSA and ES in the same age bracket.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>&lt;35 Yrs</th>
<th>35-55 Yrs</th>
<th>&gt;55 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI 10-30</td>
<td>8.8 ± 5.6</td>
<td>11.9 ± 6.2</td>
<td>14.4 ± 4.7</td>
</tr>
<tr>
<td>RDI 30-50</td>
<td>9.5 ± 4.7</td>
<td>11.6 ± 6.2</td>
<td>13.8 ± 3.8</td>
</tr>
<tr>
<td>RDI &gt;50</td>
<td>9.4 ± 6.7</td>
<td>12.7 ± 4.9</td>
<td>13.6 ± 7.0</td>
</tr>
</tbody>
</table>

Conclusions: For the same degree of OSA there is a trend for the ES to increase with age. Although the Epworth Sleepiness Scale provided a subjective measure of sleepiness, it offered little correlation with actual OSA severity. Age should be taken into account if using the Epworth Sleepiness Scale as a criterion for evaluating a patient for polysomnography.

References:

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Frequency of Significant Carotid Disease in Patients with Obstructive Sleep Apnea

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(1) Georgetown University Medical Center, (2) Washington VA Medical Center

Introduction: Patients with obstructive sleep apnea (OSA) have a higher incidence of stroke compared to the population without OSA, and recent studies by Friedlander et al. (1998 and 1999) have found that persons with OSA are more likely to have calcified atheromas on their panoramic neck radiographs than are healthy controls (22% in OSA patients versus 3% in controls). This would suggest that persons with OSA have a higher incidence of internal carotid artery stenosis, and therefore a higher incidence of stroke. The diagnosis of carotid disease by radiograph however, is not adequate to assess whether hemodynamically significant internal carotid artery stenosis exists. We undertook this study to determine if there is an increased frequency of hemodynamically significant internal carotid artery disease in patients with obstructive sleep apnea.

Methods: Patients referred for polysomnography due to symptoms suggestive of sleep apnea were evaluated for additional comorbidities to determine their known risk factors for atherosclerosis. They subsequently underwent both polysomnography and bilateral carotid duplex ultrasonography. Polysomnograms were scored using standard criteria. Hemodynamically significant stenosis was defined as greater than 60% stenosis.

Results: Of 40 patients were diagnosed with obstructive sleep apnea with a mean respiratory distress index (RDI) of 35. Concomitant risk factors for atherosclerosis in these patients were obesity (92.5%, with a mean body mass index of 35.1), hypertension (75%), diabetes (42.5%), coronary artery disease (22.5%), hypercholesterolemia (mean cholesterol level 176 with 30% of participants currently on an HMGCOA reductase inhibitor), peripheral vascular disease (12.5%), and tobacco use (10%).
Arterial Stiffness Changes In Association With Obstructive Apneas In Sleep

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Introduction: Obstructive sleep apnea syndrome (OSAS) and systemic hypertension have been extensively linked epidemiologically and through putative physiologic mechanisms. However, while acute hemodynamic and autonomic perturbations have been documented in association with obstructive events during sleep, vasomotor responses with these events have been poorly characterized. We hypothesized that arterial stiffness may acutely increase in association with obstructive apneas in patients with OSAS.

Methods: Four patients (1 F, 3 M; ages 31-55 years; BMI 27-60 kg/m2) with severe OSAS were studied prospectively during a night of standard clinical polysomnography. All patients were diagnosed with systemic hypertension; 2 were on antihypertensive medications (Furosemide, Verapamil). Continuous beat to beat blood pressure (BP) was recorded from the radial artery by applanation tonometry using a non-invasive wrist oscillometric device (Colin Model 7000). As a measure of arterial stiffness, the arterial augmentation index (AAI), a time domain estimate of the contribution of pressure wave reflection to pulse pressure, was calculated as the ratio of augmented systolic BP (late minus early systolic BP peaks) to pulse pressure (systolic minus diastolic BP) using computer analysis software. BP was calibrated to simultaneously recorded brachial cuff BP throughout the studies. Oxygen saturation (SaO2) was measured with finger pulse oximetry. Respiratory effort was measured with piezo sensor bands, and airflow with oronasal thermistors and pressure transducers. Sleep was staged by standard criteria. Ten successive cardiac cycles just prior to obstructive apnea onset (Pre-Apnea); all cardiac cycles during the event (Apnea), and 15 successive cardiac cycles immediately following resumption of ventilation (Post-Apnea) were analyzed for all apneas that demonstrated electrocortical arousal, hypoxemia, and artifact-free pressure waveforms.

Results: Mean nadir SaO2 was 70-88% for the 4 patients. For the group, mean + SD AAI was the following: Pre-Apnea AAI=10+3, Apnea AAI=14+4, Post-Apnea AAI=17+23 (p=.06 by ANOVA). In contradistinction to these strong trends to progressively increased AI during and following apneas, systolic blood pressure (SBP) averaged over the same periods for all subjects did not show such a trend: Pre-Apnea SBP=131 mmHg, Apnea SBP=125 mmHg, Post-Apnea SBP=132 mmHg.

Conclusions: These preliminary data indicate that arterial stiffness, as measured by augmentation of radial artery pressure, acutely and repetitively increases progressively during and after obstructive sleep apneas in hypertensive OSAS patients, prior to decreasing again to pre-apnea levels. These trends, which occurred despite significant heterogeneity among subjects regarding degree of sleep hypoxemia, age, body habitus, and presence of vasoactive medications, suggest that both hypoxemia and electrocortical arousal may contribute to increased arterial stiffness with obstructive apneas. Further, these increases in arterial stiffness in association with obstructive apneas are not consonant with changes in arterial blood pressure in this setting. We speculate that these acute changes in arterial stiffness may have both therapeutic and prognostic implications regarding cardiovascular morbidity in patients with OSAS, independent of changes in arterial blood pressure.

Concurrent Sleep Disorders in Patients with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is a common disorder. Symptoms include snoring, excessive sleepiness and fatigue. These symptoms are not specific to OSA. To decrease costs, some insurers have specified evaluation of suspected OSA patients using a limited polysomnography montage that focuses on sleep and breathing and have denied consultation by a sleep specialist. Thus OSA is emphasized to the exclusion of other sleep disorders. The results given to the ordering practitioner may include only data regarding OSA. The practitioner (who may not have any formal sleep training) is responsible for explaining the results to the patient, deciding on therapy and follow up. There is no reliable way to select for study only patients with sleep apnea; other sleep disorders may be present. Therefore, focused sleep evaluation may miss these conditions.

Methods: We performed a retrospective chart review of 204 consecutive patients seen in Mayo Sleep Disorders Clinic who underwent a split night polysomnogram with CPAP titration in the second half. Patients selected had an apnea-hypopnea index (AHI) of 5/hour or greater. All patients had an initial sleep consultation by a sleep specialist. The charts were reviewed for additional sleep disorder diagnosis given by the consultant after polysomnogram and follow up.

Table 1

| Diagnosis Patient Diagnosis Patient |
|------------------------------------|-----------------------------------|
| PLMS 16                              | Insomnia NOS 17                    |
| PLMS/RLS 15                          | Psychophysologic Insomnia 7        |
| RLS 5                                | REM with atonia 1                  |
| Insufficient sleep 9                 | Narcolepsy 2                      |
| Poor sleep hygiene 6                 | Obstructive hyperventilation 5     |
| Obstructive hyperventilation 2       | Upper airway resistance syndrome   |
| Idiopathic hypersomnia 1             | Hypersomnolence NOS 2             |
| Delayed phase syndrome 1             | Circadian rhythm disorder 1        |
| Nocturnal choking spells 1           | Laryngospasm 1                    |

Results: Twelve sleep specialists were involved. Patients were seen over an 8-week period from Jan 1, 1999 to February 24, 1999. The mean age was 54 ± 13 years (range 17 to 82). There were 60 women. The mean AHI was 41 ± 30/hour (range 5 – 125). Follow up information was
available for 91 patients. There were a total of 125 additional sleep disorders diagnosed in 99 patients (26 patients had two diagnosis). Periodic limb movements of sleep (PLMS) was the commonest diagnosis with 40 patients, restless legs syndrome (RLS) with PLMS in 15, and restless legs without PLMS in 5. Other common diagnosis were insomnia in 24 patients, insufficient sleep in 9, REM behavior disorder (RBD) in 7, poor sleep hygiene in 6 and obesity hypoventilation syndrome in 5. A complete list of diagnosis and frequency is in the following table.

Conclusions: Patients undergoing polysomnography for OSA commonly have other sleep disorders that may be partly responsible for their symptoms. The practice of using focused polysomnography with a limited montage, in essence looking for only obstructive sleep apnea, may systematically miss other diagnosis (PLMS, RBD, narcolepsy, and laryngospasm/choking). Furthermore, excluding formal sleep consultation may fail to diagnose other sleep disorders (restless legs, insomnias, poor sleep hygiene, insufficient sleep, and circadian rhythm disorders). We conclude that formal sleep consultation and standard montage polysomnography is essential for evaluation of patients with symptoms consistent with obstructive sleep apnea.

540J

Prevalence of Sedative Prescription in Patients Before the Diagnosis of Obstructive Sleep Apnea

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Introduction: Sedatives prescriptions are given to about 7% of all patients with difficulty sleeping (Gallup Poll, 2000). However, some of these patients may have undetected obstructive sleep apnea (OSA) that could potentially be worsened by sedatives. We set out to determine the prevalence of sedative prescription in patients before the diagnosis of OSA (Apnea-Hypopnea Index (AHI) ≥ 5 events/hour with symptom of excessive daytime sleepiness) had been made.

Methods: We conducted a telephone survey and retrospective chart review of 100 consecutive patients (96 male) with newly diagnosed OSA. In our patients (age 59 ± 1 years)(+ SE) the AHI was 37.2 ± 2.5 events per hour, and body mass index was 35.6 ± 0.7 Kg/m2.

Results: Twenty nine percent of patients had received a prescription for sedative medications prior to the diagnosis of OSA, and these patients as a group were younger (54 ± 2 years) than the group of patients who did not receive a sedative prescription (61 ± 2 yrs; p = 0.008). There was no difference in the body mass index, AHI, or lowest recorded oxygen saturation recorded during polysomnography (p > 0.3) between the two groups. Women were more likely to receive sedative prescriptions than men (relative risk of 2.76; p = 0.04).

Conclusions: In conclusion, a significant proportion of patients are prescribed sedative medications prior to their diagnosis of OSA. Nevertheless, in patients who have been prescribed sedative medication the recorded severity of OSA is not different than that of patients who were not prescribed sedative medications.

541J

Predictors of Excessive Daytime Sleepiness and Occurrence of REM Sleep Episodes on MSLT in Obstructive Sleep Apnea Patients

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Introduction: Previous studies have shown that the occurrence of SOREMS on MSLT is related with EDS and severity of OSA (1,2). Recently it was shown that the male sex is associated with the occurrence of SOREMS on MSLT (2). Pathophysiological mechanisms of EDS and the occurrence of SOREMS on daytime naps on OSA remain unclear. In order to improve our understanding of factors affecting EDS and the occurrence of SOREMS on MSLT, we analyzed clinical, demographic, polysomnographic and MSLT data in the patients with OSA associated with EDS.

Methods: 227 consecutive patients with OSA and EDS were evaluated. PSG and MSLT studies were recorded and interpreted based on standards of ASDA. Statistical analyses of clinical, demographic, PSG and MSLT data were analyzed using SAS 8.0 (SAS Institute, Inc). Exploratory correlation analyses was performed using Spearman correlation coefficient. The general linear model to analyze MSL as a measure of EDS was used. A multivariate logistic regression model for prediction of the occurrence of SOREMS was developed.

Results: AHI is highly correlated with min 02 saturation (r=-0.715 p<0.0001) and with longest duration of apnea. (r=0.492 p<0.0001) reflecting that the severity of OSA:AHI has significant correlation with MSL (r=0.377; p<0.0001), AHI in NREM was more significantly correlated with MSL than AHI in REM sleep. SOREMS also showed the tendency to occur more frequently in more severe OSA.MSL was strongly correlated with sleep latency in PSG(r=0.419 p<0.0001). As expected AHI has a very strong correlation with arousals index (AI) = 0.91 (p<0.0001). The best multiple regression model indicated that jointly with AHI (p-value-0.001) the following variables were significant predicting the MSL: Age (p-value-0.025), PSG Sleep latency (p-value-0.001) and Epworth scale (p-value-0.027). Multiple R-square for this model equals 0.279, which implies that the 28% variability in MSL is explained by this model. Multiple logistic regression analysis indicated that the MALE SEX (p-value-0.028), AGE in MALE subjects (p-value-0.028), Total sleep time (TST), (p-value-0.004) and REM Sleep LATENCY (p-value-0.014), were significantly associated with the odds of having SOREMS on MSLT. Model implies that the odds of having SOREMS on MSLT are higher in younger males. Decrease of PSG sleep latency is associated with increased odds of SOREMS. From another hand an increase in TST on the night prior to MSLT results in an increase of odds of not having SOREMS on MSLT.

Conclusions: AHI is associated with sleep fragmentation. More severe OSA is causing more arousals and more severe sleep fragmentation. EDS is significantly related with increased AHI and sleep fragmentation. Age and possibly chronic partial sleep deprivation in some patients could be significant factors contributing to EDS. Occurrence of SOREMS on MSLT is more likely in younger males. Decreased REM sleep latency is related to the occurrence of SOREMS on MSLT. Increased TST on diagnostic sleep study decreases the likelihood of the appearance of SOREMS on MSLT.

References:
(2) Chervin R., Aldrich M. Sleep onset REM periods during MSLT in patients evaluated for OSA. Am J RespirCritCareMed2000;161:426-431.
Evaluation of the “Sleep Strip,” a Simple Device to Screen Apnea Patients in the General Population

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Introduction: Sleep apnea is a highly prevalent disease in western countries and it may be difficult to screen large groups of patients with polygraphy or polysomnography (PSG). Sleep apnea patients may have however severe consequences in terms of vascular diseases and automobile accidents. The sleep strip has been proposed by Lavie and col. (2000) to screen sleep apneas in the general population. The sleep strip: The device comprises four components: Three thermosensors, two for sensing nasal flow and one for oral-airflow during sleep; A miniature processing unit to analyse the respiratory pattern of the patient; A 3v lithium cell, which is the power source of the SleepStrip; A non-volatile display for presenting the results to the patient or health-care provider. These components are connected through electronic circuitry, which is fabricated on a film. The entire system is attached just above the upper lip.

Methods: We evaluated the sleep strip compared to full night polysomnography in 20 patients addressed our centre for a suspicion of sleep apnea. Polysomnography was performed the first night and the sleep strip the following night. The PSG was manually analysed according to the Reschtaffen and Kales rules and the RDI was compared to the one automatically proposed by the sleep strip. A non-parametric test was used to compare the results of the two explorations.

Results: We found no significant difference between the two methods regarding the RDI (p = 0.14). Sensibility and specificity for a RDI > 10 were respectively 86.6% and 80%.

Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>PSG RDI</th>
<th>Sleep strip RDI</th>
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<tr>
<td>1</td>
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Mean A: 22.03 ± 19.54
Standard deviation: 25.76

Conclusions: In a first group of 20 patients, the evaluation of the “sleep strip” compared to full polysomnography seems to be positive. The three patients for whom the test was not confident have respectively a PSG RDI of 11.2, 5.7, and 11 and a sleep strip RDI of 8, 12 and 8. These results are thus very close from the sleep apnea definition RDI index of 10. The sleep strip has to be understood as a screening test useful in large group of people to detect and prevent sleep apneas consequences.

References:

Obstructive Sleep Apnea Consultation in Hospitalized Patients: Review of a Center’s Experience

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Introduction: The evaluation and treatment of obstructive sleep apnea (OSA) is typically outpatient-based. Occasions arise in hospitalized patients when known or suspected OSA requires attention. The hospital environment, diagnostic and therapeutic maneuvers for the admitting condition(s), and co-morbidities may impact on inpatient OSA management. Little attention has been paid to this unique aspect of OSA care. Therefore, we reviewed our hospital OSA consultative experience for the purpose of characterizing these patients and their outcomes.

Methods: Retrospective chart review of 50 consecutive patients in Mayo Foundation’s St Mary’s Hospital seen by the Sleep Disorders Center’s staff for possible or previously documented OSA between November 1999 and March 2000.

Results: The 50 patients represented 0.32% of all admissions during the 4-month period. The mean age was 65.8 years (range: 40-90), 17 (34%) were women, and the mean body mass index was 37.8 kg/m2 (range: 21-64). Co-morbidities included cardiac disease in 70% (35/50), pulmonary disease in 26% (13/50), and status-post cerebrovascular accident in 8% (4/50). Services requesting consultation were internal medicine: 26 patients; surgery: 10; physical medicine/rehabilitation: 6; psychiatry: 6; neurology: 2. Median hospital day of sleep consultation was day 5 (range: 1-115). Fifty-six percent (28/50) underwent polysomnography. The mean apnea-hypopnea index was 61.6 (range: 1-114), with 25 patients demonstrating OSA and 3 with mixed central and obstructive apnea. In 11 patients it was deemed safest to conduct the sleep study directly in their hospital room with portable polysomnographic equipment. Sleep architecture in these 11 patients, all during split night studies, was altered: mean total sleep times for the diagnostic and therapeutic portions were 72 minutes (range: 25-148) and 107.7 minutes (range: 0-222), respectively, while the mean rapid eye movement sleep durations were 7.9 minutes (max: 33) and 12.3 minutes (max: 36), respectively. Eighteen percent (5/28) of patients could not tolerate the continuous positive airway pressure (CPAP) titration. CPAP was recommended to 24 patients. Two refused to start CPAP and in the 13 patients with follow-up information, 3 never acclimatized. Nine patients were recommended to pursue polysomnography after discharge, and at least five of these patients did not follow through despite returning to Mayo for other appointments. Seven of the 50 patients were empirically treated with auto-adjusting CPAP in the hospital while awaiting polysomnography. At least 2 of these patients were eventually transitioned to standard CPAP after polysomnography.

Conclusions: Patients seen in our hospital sleep consultative practice are characterized by older age, overweight, and severe OSA. Introduction of inpatients to sleep disordered breathing, hospital-based polysomnography, and initiation of CPAP are all possible but can be challenging. Auto-adjusting CPAP may be a temporizing option for some inpatients before polysomnography.
Is a History of Hypothyroidism a Risk Factor For Obstructive Sleep Apnea?

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Introduction: It has been suggested that patients with hypothyroidism have an increased incidence of obstructive sleep apnea (OSA) (1). A closely related question is whether a history of hypothyroidism, perhaps by virtue of persistent alterations in functional upper airway anatomy increases the likelihood of having OSA (2). To answer this question we conducted this study to determine whether a history of hypothyroidism is an independent risk factor for obstructive sleep apnea.

Methods: We reviewed the records of patients referred for polysomnography (PSG) with a history of hypothyroidism and complaints of excessive daytime somnolence, during the period from January '95 to July '00. The comparison group consisted of a random selection of 120 patients with similar complaints but no history of hypothyroidism, matched to BMI with the study group. OSA was defined as RDI-Sleep >5. Clinical, demographic and polysomnographic characteristics of the group with a history of hypothyroidism were analyzed and compared to the control group.

Results: There were 46 patients in the study group with a mean age of 54.3 years (range 20-75 years) and 50% were males. The mean BMI in the study group was 34.6 (range: 23-51), compared to a mean BMI of 35.4 (range 21-50) in the control group. Mean Epworth Sleepiness Scale (ESS) was 12.8 and the mean neck size was 16.7 inches in the study group. The mean RDI was 28 compared to 47.8 in the control group. The incidence of OSA in the study group was 87% and in the control group was 88.4%. The mean duration of hypothyroidism was 8.7 years and the mean euthyroid duration was 3.05 years.

Conclusions: There is a high incidence of OSA in patients with a history of hypothyroidism. However, the incidence is not significantly higher than in a BMI matched control group. A history of hypothyroidism does not, in itself, confer additional risk for the presence of OSA.

References:

Neuropsychological Functioning in Patients with Obstructive Sleep Apnea Syndrome, Treated with CPAP

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Introduction: Problems with attention, concentration and memory are well known complaints in patients with an Obstructive Sleep Apnea Syndrome (OSAS). Usually these complaints disappear after treatment. However, in some patients these complaints persist. Within our Center of Sleep and Wake disorders we asked ourselves whether we (1) could objectivate these complaints with the aid of a neuropsychological test-battery, and (2) if the results were associated with sleepiness and the Respiratory Distress Index (RDI). The group also received four personality questionnaires.

Methods: Patients were recruited on a yearly patient-information-day at the Center. For inclusion patients had to be on CPAP treatment for over a year and persisting complaints of cognitive disfunctioning. Individuals with major neurologic, psychiatric or systemic disease or with a history of headinjury were excluded. Fifteen subjects were chosen at random from this sample to participate in the present study. The study was conducted at the Center. The subjects were given a neuropsychological test-battery, the Epworth Sleepiness Scale and four personality questionnaires on the same day. At three times during the testing the patient had to indicate their subjective sleepiness on a Visual Analog Scale. The RDI before and during treatment was determined on the basis of a polysomnography. The results were compared to the normative data of the tests, as there was no control group.

Results: The mean age of the group was 51.5 years with a mean period of CPAP treatment of 3.6 years. As expected the ESS score became normal during CPAP-treatment (mean: 5.7; sd:3.4). The subjective sleepiness based on a visual analog scale remained constant during the testing. So in our study sleepiness did not seem to be a possible explanation for the following testresults. Verbal learning as measured by the WMS-r and the first trial of the 15-word-test were significantly decreased. As was division attention measured by stroop chart II and III. Mazes showed a small but not significant decrease. On the personality tests we found that almost half of the subjects showed signs of depression (Zung). They also had higher scores on negativeism. Statistically we did not find a correlation between RDI and Zungscore. If we controlled for depression significance of the neuropsychological results disappeared. Patients with more depressive signs also had more passive in stead of active coping strategies.

Conclusions: We observed a significant decrease on verbal short term memory learning and a divided attention test in patients who received CPAP for more than three years and who still complained of cognitive disfunctioning. Signs of depression as measured by the Zung seemed to have more of an impact on the neuropsychological testresults than was subjective sleepiness. As for its cause, depression seems to be more important than severity of the OSAS or of persisting sleepiness.

Hypersomnia with Decreased Hypocretin Level after Removal of Hypothalamic Astrocytoma

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Introduction: Hypocretin /Orexins (Hcrt) are newly discovered hypothalamic peptides that have aroused interest in view of two recent reports linking dysfunction of the Hcrt peptide/receptor system in animal models of narcolepsy (1). Nishino et al. reported that Hcrt-1 /Orexin-A levels in cerebrospinal fluid (CSF) were decreased in human narcolepsy (2). However, the potential role of Hcrt in other sleep disorders has been unidentified. We describe a girl with a destruction of the mid- and posterior hypothalamus that resulted in hypersomnia and a decreased Hcrt level.

Methods: Discovery of a suprasellar astrocytoma in a 16-year-old girl with a headache prompted neurological trans-lamina terminalis resection. Surgical reports revealed that the tumor was intraaxial poor-circumscribed arising in the left hypothalamus. The tumor and its gliotic rim were partially removed throughout the prechiasmatic cistern. She had no history of neurologic, psychiatric or sleep-related problems prior to surgery. We investigated the influence on her vegetative functions, sleep characters and Hcrt-1 level in the CSF. Hcrt-1 was extracted from CSF with a reversed phase SEP-PAK C-18 Columns (Waters Associates, Inc., Milford, MA). Iodine-125 Hcrt-1 radioimmunoassay kit (Phoenix Pharmaceuticals, Mountain View, CA) was used to measure levels.

Results: Tumor removal resulted in hypothalamic injury to the ventromedial, dorsomedial nucleus, and perifornical regions, as well as a part of the lateral or posterior nucleus of the hypothalamus, as identified by the pathologiscal and radiological studies. Postoperatively, she exhibited diabetes insipidus, hypothyroidism, a mild left hemiparasis, right partial oculomotor paralysis, and left incomplete homonymous hemianopsia. Her weight gained mildly with an increase in hunger. Her body temperature, pulse rate, and blood pressure were normal. She experienced an intermittent daytime hypersomnolence without cataplexy. Multiple sleep latency tests revealed rapid sleep onset (100 seconds) without a sleep onset REM period. EEG showed a slight slowing of the basic rhythm (7-8 Hz) with a lazy pattern in the right hemisphere. Neither periodic limb movements nor sleep apnea were observed during the daytime two-hour recording. Her comprehensive neuropsychological testing indicated cognitive functions remained intact; verbal IQ was 100 with performance IQ of 90, though there was mild anterograde amnesia. Hcrt-1 in CSF decreased (102pg/ml) compared with five healthy controls aged 15-19 year-old (252-344pg/ml).

Conclusions: Hcrt cells are discretely localized in the perifornical nucleus, dorsal and lateral hypothalamic areas. They have also diffuse projections concentrating on monoaminergic cell groups implicated in arousal systems (1). In our patient, Hcrt-producing cells in the perifornical and lateral nucleus, as well as part of the abundant axonal projections in posterior hypothalamus might have been damaged by removal of the hypothalamic astrocytoma, therefore resulting in decreased Hcrt level in CSF. A dysfunction of the Hcrt system, as seen in narcolepsy, could account for a disturbance in wakefulness in some patients after removal of hypothalamic tumor.

References:
(1) Kilduff TS, Peyron C. The hypocretin/orexin ligand-receptor sys-

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No Relevant M.R.I. Findings in Narcolepsy

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Introduction: In 2 MRI studies (Basetti et al. 1997, Frey et al. 1997) no evidence was found for pontine or other brain stem related structural lesions in narcoleptics. Previous cases studies reported narcolepsy associated with thalamic hemorrhage, vascular lesions in the pontine tegmentum, arteriovenous malformations around the third ventricle and with hyperintensities in the midrostral pons. As some of these case studies lack clear diagnostic criteria for narcolepsy and a description of the MRI protocol used, we studied the occurrence of narcolepsy specific abnormality on MRI in a larger patient group with the same narcolepsy criteria and investigated with the same MRI protocol.

Methods: 19 patients (6 females,13 males; mean age: 40.84y.; range 16-63y.) were diagnosed as narcoleptics according the I.C.S.D.criterias, so including nighttime polysomnography. A MRI protocol was set up with specific reference for the sleep-wake and REM-sleep regulatory centers. All investigations took place in the University Hospital on a ‘Symphony’ MRI apparatus. Following sequences were used and interpreted by MRI unit staff members: ax TSE T2; ax Flair; sag T1; ax GRE T2* (Flash); cor TSE T2 (small coupes through brainstem).

Results: All MRI exams show a symmetric brain with clear cortico-medullar differentiation and normal gyri. The midline is in a normal position. Sagittal images show a normal morphology and signal intensity of the corpus callosum, mesencephalon, pons, medulla oblongata and cerebellar vermis. On coronal images a normal structural aspect of the hippocampus is noted. No abnormalities in the craniocervical transition and the Sylvic duct. In two patients some enlarged perivascular Virchow-Robin liquor space was seen, a non-pathological finding. So, no MRI abnormalities were found in 14 patients. In five patients small nodular or merging lesions situated subcortical or perivascular in the white matter are visible, most notable on Flair sequences. These lesions are nonspecific and most probably of vascular, ischemic origin. In 2 of these 5 patients the gradient echo images evidenced a lower signal intensity of the basal ganglia (a.o. the globus pallidus) probably caused by calcium deposits.

Conclusions: In 5 patients brain abnormalities on the MRI were found. These are situated in several locations of the white matter and have a vascular-ischemic origin. These abnormalities can also be evidenced in diabetes, hypertension, migraine or other conditions associated with microvascular pathology. The lesions are non-specific and cannot be related to the narcoleptic symptomatology. Only two patients show structural abnormalities that can be related to sleep-wake regulatory processes: calcifications in the globus pallidus, an abnormality also seen in elderly or Parkinson patients. On the MRI these abnormalities present as low signal intensity of the basal ganglia. These findings are not considered as specific to the studied pathology. We conclude from these 19 case studies that no specific narcolepsy related brain lesions could be evidenced on the MRI exam.

References:

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Dose Sparing Effects of Fluoxetine on Methylphenidate for the Treatment of Sleepiness in Narcolepsy

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University of Toronto

Introduction: The use of higher doses of stimulant medications for the management of excessive daytime sleepiness (EDS) in narcolepsy syndrome may be associated with excessive side effects(1). Fluoxetine has been found to be an effective agent for the treatment of cataplexy with minimal side effects(2). Furthermore, there are reports that it may have alerting effects(3). The goal of this study was to determine whether the addition of fluoxetine to the treatment regimen of individuals with narcolepsy would allow for a lower dose of methylphenidate for effective treatment of EDS.

Methods: A retrospective chart review was performed on all patients diagnosed with narcolepsy between 1998 and 2000. Patients were included if baseline and post treatment sleep studies were available and their final treatment was either methylphenidate alone or the combination of methylphenidate and fluoxetine. The 23 patients meeting this criteria were separated into two groups: methylphenidate alone and methylphenidate and fluoxetine treatment. They were then compared across demographics, pre and post treatment sleep parameters, clinical features, completed questionnaires, and the methylphenidate dose required for control of EDS. The group results were analyzed using T-tests and chi squared tests.

Table 1

<table>
<thead>
<tr>
<th>DEMOGRAPHICS</th>
<th>fluoxetine and methylphenidate</th>
<th>methylphenidate alone</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>38(19)</td>
<td>35(14)</td>
<td>0.68</td>
</tr>
<tr>
<td>Male/Female</td>
<td>5/7</td>
<td>11/16</td>
<td>0.90</td>
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<table>
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<tr>
<th>PRE-TREATMENT</th>
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<tbody>
<tr>
<td>Sleep efficiency %</td>
<td>85(4)</td>
<td>85(14)</td>
<td>0.98</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>40(73)</td>
<td>79(61)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean Multiple Sleep Latency Test</td>
<td>3.2(2.5)</td>
<td>5.2(4.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of SOREMS</td>
<td>3.0(82)</td>
<td>3.0(89)</td>
<td>1</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>6/7</td>
<td>7/16</td>
<td>0.06</td>
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<tr>
<td>Hypnagogic hallucinations</td>
<td>2/7</td>
<td>3/16</td>
<td>0.60</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>3/7</td>
<td>5/16</td>
<td>0.51</td>
</tr>
<tr>
<td>Beck depression inventory</td>
<td>10(12)</td>
<td>8(8)</td>
<td>0.75</td>
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<tr>
<td>Epworth Sleepiness Scale</td>
<td>31(10)</td>
<td>25(8)</td>
<td>0.21</td>
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<table>
<thead>
<tr>
<th>POST TREATMENT</th>
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<tbody>
<tr>
<td>Fluoxetine Dose (mg)</td>
<td>15.7(7.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate Dose (mg)</td>
<td>16.1(9.1)</td>
<td>35 (18.9)</td>
<td>0.002</td>
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<tr>
<td>Sleep Efficiency %</td>
<td>82(9)</td>
<td>87(7)</td>
<td>0.17</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>63(62)</td>
<td>74(62)</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean Maintenance of Wakefulness Test (20 min protocol)</td>
<td>15.7(4.7)</td>
<td>18.2(3.2)</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Results: As presented in table 1, the group treated with fluoxetine required a mean dose of 16 mg of methylphenidate which is significantly lower than the mean dose of 35 mg required by the group treated with methylphenidate alone (p<.002). Although prior to treatment cataplexy appears to be more prevalent in the fluoxetine group (p=.06), the groups do not otherwise appear significantly different with respect to demographics, and severity of sleepiness both pre-treatment and following stabilization on medication.

Conclusions: Although the sample size is limited and the study retrospective, these preliminary results suggest that the use of fluoxetine may result in a lower dose requirement of methylphenidate for the treatment of excessive daytime sleepiness in narcolepsy syndrome. Further work will be required to replicate this finding and determine whether this stimulant reduced regimen results in an overall better side effect profile.

References:

Value of Epworth Sleepiness Scale, Ullanlinna Narcolepsy Scale, and a new developed Score in the Diagnosis of Narcolepsy

Sturzenegger C, Mathis J, Guerrer M, Bassetti CL
(1) Department of Neurology, (2) Division of Pneumology, University Hospital, 3010 Bern, Switzerland

Introduction: In a study of 25 narcoleptics an Ullanlinna Narcolepsy Scale (UNS) score >14 was shown to have a sensitivity of 100% and a specificity of 99% for the diagnosis of narcolepsy (1). The value of the Epworth sleepiness score (ESS) in discriminating narcoleptics from normal subjects was recently emphasized (2).

Methods: We prospectively studied by questionnaire 57 narcoleptics (N, mean age=43 years, SD=18 years) and 56 non-narcoleptic hypersomniacs (H, mean age=45, SD=9). The diagnoses of narcolepsy with and without cataplexy were made according to international criteria. Our questionnaire included questions about sleep-wake habits/disturbances, whereas cataplexy-like symptoms are reported also by normal subjects. The differentiation between cataplexy and cataplexy-like symptoms remains a matter of controversy.

Results: ESS and UNS were significantly higher (p<0.001) in N (17, SD=5; 24, SD=9) than in H (15, SD=4; 13, SD=6). A UNS score >14 had a sensitivity and specificity for narcolepsy of 98% and 56% respectively. A new score based on five questions was found to have a high sensitivity and specificity for the diagnosis of narcolepsy.

Conclusions: UNS and ESS do not always help to discriminate narcoleptics from other patients with hypersomnia. A new score based on five questions was found to have a high sensitivity and specificity for the diagnosis of narcolepsy.

References:

Cataplexy and Cataplexy-like Symptoms in Narcoleptics, non-Narcoleptic Hypersomniacs, and Normal Controls

Sturzenegger C, Mathis J, Guerrer M, Bassetti CL
(1) Department of Neurology, (2) Division of Pneumology, University Hospital, 3010 Bern, Switzerland

Introduction: Definite (true) cataplexy is pathognomonic for narcolepsy, whereas cataplexy-like symptoms are reported also by normal subjects. The differentiation between cataplexy and cataplexy-like symptoms remains a matter of controversy.

Methods: We prospectively studied by questionnaire 41 narcoleptics with clear-cut cataplexy (N, mean age=43 years, SD=18 years), 56 non-narcoleptic hypersomniacs (H, mean age=45, SD=9) and 40 normal controls (No, mean age=42, SD=14). Clear-cut (definite) cataplexy was diagnosed following current suggestions (1). Answers concerning frequency (in N, H, and No), triggering emotions and involved body parts (in N and H) of cataplexy and cataplexy-like symptoms were analysed.

Results: Sudden buckling of knees following emotions was significantly more common in N (80%) than in H (19%) and No (8%). Sagging of the jaw and nodding of the head were more frequent (p<0.001) in N (83%; 75%) than in H (2%; 4%) and No (both 0%). Narcoleptics reported cataplexy more commonly following surprise (63% vs 0% in H, p<0.001), sudden joy (81% vs 27%, p<0.001), while being tickled (54% vs 0%, p<0.001), and in the presence of known persons (81% vs 23%, p<0.001). Hypersomniacs had more commonly cata-
plexy-like symptoms with stress (50% vs 31% in N) or unpleasant feelings (64% vs 30%, p=0.02).

**Figure 1**

Conclusions: Triggering characteristics and involved body parts are helpful in discriminating cataplexy-like symptoms from true cataplexy.

**References:**

552.K

**SPECT Investigations of Striatal Dopamine Transporters in Narcolepsy**

Eisensehr I, Linke R, Tatsch K, Lindeiner H, Trenkwalder C, Wetter TC, Eberle R, Schuld A, Pollmaecher T, Noachtar S (1) Department of Neurology, University of Munich, Germany, (2) Department of Nuclear Medicine, University of Munich, Germany, (3) Max Planck Institute of Psychiatry, Munich, Germany, (4) Department of Internal Medicine, Rotkruz-Clinic, Munich, Germany

**Introduction:** The pathophysiological basis of narcolepsy is still unknown. Autoradiographic studies of post-mortem human narcoleptic patients revealed increases of D2-receptor binding in the basal ganglia. In vivo single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies in narcolepsy revealed no abnormalities of striatal postsynaptic D2-receptor binding. Presynaptic striatal dopaminergic function has not been evaluated in narcolepsy so far.

**Methods:** We therefore studied striatal presynaptic dopamine transporters with (N) (3-Iodopropene-2-yl) -2beta-carbomethoxy -3beta(4 chlorophenyl) tropane (123I-IPT) using SPECT in drug-free patients with narcolepsy (n=10) and 10 age- and sex-matched controls without a history of sleep disorders.

**Results:** There was no statistical difference in IPT-binding between patients and controls. Narcoleptic patients showed a wider variance of IPT-binding than controls. Three of the four patients with the lowest IPT-binding values were pretreated with modafinil (n=2) and amphetamins (n=1), which were discontinued at least 5 days prior to the SPECT. There were significant negative correlations (Spearman correlation coefficient r=-0.68, p<0.001) of age and duration of the disease with IPT-binding of every investigated striatal area only in narcoleptics.

**Conclusions:** We conclude from our preliminary results, that striatal presynaptic dopaminergic function is unlikely to play a major role in human narcolepsy. However, mechanisms underlying the narcoleptic syndrome or treatment with stimulating agents might influence presynaptic dopamine transporters over the course of life.

553.K

**Comparison of Driving Simulator Performance and Neuropsychological Testing In Narcolepsy**

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**Introduction:** Accidents occur in patients with narcolepsy due to daytime sleepiness and cataplexy. Physicians are often asked to assess an individual’s ability to drive a car. Still there is no consensus about the best diagnostic tool. The present study compares driving simulator performance and neuropsychological test results in narcolepsy.

**Methods:** 13 patients with narcolepsy (10 men, 3 women, age: 41.5 ± 12.9 years) and 10 healthy controls (9 men, 1 woman, age: 55.1 ± 7.8 years) were investigated. By computer-assisted neuropsychological testing vigilance, alertness and divided attention were assessed. Test results are expressed as percentage related to normative data. Patients and controls underwent a driving simulator test. They had to drive on a highway for 60 minutes with a mean speed of 100 km/h. Different weather and daytime conditions were presented. Obstacles occurred infrequently.

**Results:** Scores of the Epworth Sleepiness Scale were significantly raised (16.7 ± 5.1 in narcolepsy, 6.6 ± 3.6 in controls, p<0.001). Besides the total number of accidents concentration deficits like tracking errors, deviation from speed limit, disregard of traffic lights, incorrect use of headlights were scored. Compared to controls accident rate was increased (3.2 ± 1.8 vs 1.3 ± 1.5, p<0.01). Significant differences in concentration faults could not be revealed (9.5 ± 3.5 vs 7.1 ± 3.2, p.n.s.). Regarding neuropsychological performance patients showed significant deficits in alertness (percentage 32.3 ± 28.6). Mean percentage
scores of divided attention (56.9 + 25.4) and vigilance (58.7 + 26.8) were in normal range. There was a high individual difference, however. Reaction time correlated with accident rate (r=0.61, p<0.05). There was no other correlation regarding driving performance and neuropsychological test results or ESS-Score.

**Conclusions:** Narcolepsy patients' difficulties remaining alert and attentive may account for sleep-related motor vehicle accidents which occur 1.5-4 times more in hypersomnolent patient groups than in control groups. Computerized neuropsychological testing should especially be used for intradividual follow-up investigations. Neuropsychological deficits could be demonstrated concerning alertness. Driving simulator investigations are an additional diagnostic tool closer related to real traffic situations. They should especially be used when expert opinions regarding driving licence are necessary.

**References:**
(1) Narcolepsy
(2) driving simulator

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**554.K**

**REM Sleep Deprivation in Narcoleptics**

Hurni C, Vu MH, Roth C, Mathis J, Bassetti CL

Department of Neurology, University Hospital, Bern, Switzerland

**Introduction:** Narcolepsy is characterized by REM sleep abnormalities. The aim of this study was to test the hypothesis of disturbed REM sleep homeostasis in narcolepsy.

**Methods:** Six patients with narcolepsy and six healthy subjects were studied. The protocol included habituation night, baseline night (B), 1st (D1) and 2nd REM deprivation night (D2), and recovery night (R). During D1 and D2 subjects were awakened at the first signs of REM sleep and kept awake for two minutes. Sleep latency and sleep onset REM periods (SOREMs) were determined on multiple sleep latency tests (MSLT) after B and D2.

**Results:** There was a significant difference in number of interventions between controls and narcoleptics during D1 (p=0.002) and D2 (p<0.001). In both groups interventions increased from D1 to D2. Selective REM deprivation was successful in controls (mean reduction of REM to 2% of total sleep time) more than in narcoleptics (4%). In both groups no significant differences were found between the sleep EEG of R and B. However, the number of SOREMs increased from the first to the second MSLT by 50% in both narcoleptics (p=0.009) and controls (p>0.05).

**Conclusions:** REM sleep propensity is higher in narcoleptics than controls, REM sleep homeostasis appears however to be similar in the two groups.

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**555.K**

**Idiopathic Hypersomnia and Narcolepsy without Cataplexy: A Multimodal Diagnostic Approach in 21 Patients including Cerebrospinal Fluid Hypocretin Levels**

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(1) Department of Neurology, University Hospital, Bern, Switzerland, (2) Division of Pneumology, University Hospital, Bern, Switzerland, (3) Center for Narcolepsy, Stanford University Medical Center, Palo Alto, CA, USA, (4) Department of Psychiatry, University Hospital, Bern, Switzerland

**Introduction:** The nature and diagnosis of idiopathic hypersomnia (IH) and narcolepsy without cataplexy (syn. monosymptomatic narcolepsy, MN) remain a matter of controversy [1]. The aim of this study was to assess the clinical spectrum of IH and MN using a multimodal diagnostic approach.

**Methods:** We prospectively studied 15 patients (pts, 9 women, 6 men; median age of 27 years, range 18-53) with presumed IH fulfilling following criteria: 1) excessive daytime sleepiness (EDS) >6 months and Epworth sleepiness score >10; 2) no definite cataplexy; 3) Apnea-Hypopnea Index <10; 4) Periodic Leg Movements Index <10; 5) no clear-cut improvement of EDS following sleep extension; 6) no other evident cause of EDS; 7) all pts personally interviewed by one of the investigators (CB); 8) MSLT with 0-1 sleep onset REM periods (SOREMPs). The diagnosis of MN was presumed in 6 additional pts (2 women, 4 men; median age of 43 years, range 16-47) fulfilling criteria 1-7 but with >1 SOREMPs on MSLT. In all 21 pts assessment included a standard sleep questionnaire, conventional polysomnography, MSLT, 1-week actigraphy, pupillography, steer clear test, HLA-typing, clinical and psychometric evaluations, and measurement of hypocretin levels in the cerebrospinal fluid (CSF).

**Results:** Polysomnography (19 pts analyzed at the time of abstract submission): a sleep efficiency >95% and/or slow wave sleep amounts >18% (of total sleep time) were found in 12 pts. MSLT (n=19): mean sleep latencies were <3 min in 3 pts, between 3-10 min in 10 pts, and >10 min in 3 pts. Sleep onset REM periods (SOREMPs) were noted in 9 pts, 6 of them had MN with >1 SOREMPs. Pupillography (n=12): was abnormal (>8 mm mean diameter variability) in 5 pts. Steer clear test (n=13): was abnormal (>2% errors) in 5 pts. Actigraphy (n=16): in 9 pts the average time “asleep” was >35%. HLA (n=13): DR2/DQ6 positivity was present in 4 pts. Sleep questionnaires, clinical and psychometric evaluations, and CSF-levels of hypocretin are currently analyzed.

**Conclusions:** Preliminary results of this ongoing project confirm the clinical heterogeneity of functional hypersomnia without cataplexy (IH, MN). We are currently testing the hypothesis that psychometric evaluations, CSF-levels of hypocretin or a combination of different tests may help differentiating subgroups of pts fulfilling the current diagnostic criteria of IH or MN. This differentiation may have implications for a better understanding and management of these pts.

**References:**

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**A316**

**SLEEP, Vol. 24, Abstract Supplement 2001**
Clinical and Genetic Characteristics of Korean Narcolepsy Patients

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Introduction: Narcolepsy, a neurological disorder characterized by excessive daytime sleepiness and abnormal REM sleep, is known to be tightly associated with the human leukocyte antigen (HLA) DQB1*0602. Especially cataplexy is linked with HLA DQB1*0602. It has not been studied about HLA DQB1*0602 in Korea yet. This study is designed to investigate the frequency of HLA-DQB1*0602 of Korean narcolepsy patients and controls.

Methods: We selected 16 patients (mean age: 29.9±13, 10 men and 6 women) who were confirmed to have narcolepsy depending on the polysomnography and multiple sleep latency test (MSLT) as well as clinical history and symptoms at the St. Vincent’s hospital and Korea University hospital sleep disorders clinic. Any subjects co-morbid with other hypersomnic sleep disorders such as sleep apnea or periodic limb movements during sleep were excluded. All patients and 19 control did HLA typing for the presence of DQB1*0602. Clinical variables were collected by semi-structured interview for narcolepsy patients.

Results: 1) Average sleep latency was 1.9±4.17 minutes and average frequency of REM was 3.3±1.6 minutes by MSLT. 2) Characteristic symptoms of narcolepsy were investigated as follows: excessive daytime sleepiness (100%), cataplexy (93.8%), sleep paralysis (62.5%), hypnagogic hallucination (68.8%). 3) Prevalence of involved regions when cataplexy was developed was knee and leg (100%), head and shoulder (86.7%), arm and hand (73.3%). 4) Sturred speech (80%) and paralysis (40%) were reported during cataplexy attack. Among the emotional factors, laughing and excitement are proved to be the most powerful triggering emotions for cataplexy. 5) Cataplexy-positive narcolepsy patients demonstrate high HLA-DQB1*0602 positivity (91%) compared to cataplexy-negative narcolepsy patients (0%).

Conclusions: High frequency HLA-DQB1*0602 in Korean narcolepsy patients suggest that HLA-DQB1*0602 could be a strong genetic marker in all ethnic groups. Cataplexy can be a predictive factor for the presence of HLA-DQB1*0602.

References:

This study was supported by St. Vincent’s Hospital, Catholic University of Korea

Is the Health Related Quality of Life Different between People who have Classical Narcolepsy and those with Narcolepsy without Cataplexy?

Morrish E, King MA, Smith IE, Shnerson JM
Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK

Introduction: Narcolepsy has been sub-divided as to whether or not cataplexy is present. The aim of this study was to assess whether self-reported health related quality of life and mood is different between people who have narcolepsy with cataplexy and those who have narcolepsy without cataplexy.

Methods: We mailed surveys to 500 members of the UK association for narcolepsy (UKAN). The survey included the two questions; (a) Do you have to sleep in the daytime?, and (b) Do you have cataplexy (periods of muscle weakness brought on by strong emotions)? It also included the short form 36 (SF-36); a self-report questionnaire divided into eight scales regarding functional and emotional status and general well being, the Beck Depression Inventory (BDI), and demographics. The age and sex distribution, SF-36 scale scores and BDI scores were compared using non-parametric tests between people who responded positively to questions (a) and (b) and those who responded positively to question (a) and negatively to question (b). The SF-36 scale scores of the whole sample were also compared with published age sex matched normative data (1, 2).

Results: The survey response rate was 62.6% (313 returned). Two hundred and sixty persons reported having to sleep in the daytime and having cataplexy. Twenty-five persons reported having to sleep in the daytime but not having cataplexy. There was no significant difference in the age or sex distribution between the two groups (p = 0.71 and p = 0.67 respectively). There was also no significant difference between any of the SF-36 scale scores of the two groups (p > 0.15 for all scales) or the BDI scores (p = 0.09). The UKAN sample had significantly lower scores for all 8 SF-36 scales than age matched normative data (p < 0.001) indicating a poorer health status.

Conclusions: People who have narcolepsy with or without cataplexy report a poorer functional and emotional status than the normal population. There is no difference in the reported health status or mood between the two narcolepsy groups. This indicates that cataplexy does not have an additional measurable detrimental impact on health related quality of life or mood than that already caused by persistent excessive daytime sleepiness associated with narcolepsy.

References:
(2) Sharples LD, Todd CJ, Caine N, Tait S, Martin A. Measurement properties of the Nottingham Health Profile and Short Form 36 health status measures in a population sample of elderly people: Results from ELPHS. British Journal of Health Psychology 2000: in press.
Narcolepsy, Cataplexy, and Aging

Rogers ER, Silber MH, Krahn LE
(1) The Cleveland Clinic Foundation, (2) Mayo Clinic

Introduction: Classically, narcolepsy is described as a chronic disease consisting of excessive daytime somnolence (EDS) with or without cataplexy. Cataplexy, if present, develops simultaneously with the EDS or follows it. Rarely, cataplexy may precede EDS(1). EDS persists throughout the patient’s life; however, the cataplexy may wane over time(2). There is little information published about narcolepsy and cataplexy in patients over the age of 65 years(3). In this study, we describe the clinical course of cataplexy and EDS in elderly narcoleptics.

Methods: We retrospectively reviewed the histories of patients aged 65 years or older with a diagnosis of narcolepsy with cataplexy evaluated at the Mayo Clinic between 1994 to 1999.

Results: Of 87 patients with EDS and cataplexy, 54 (62.1%) were male and 33 (37.9%) were female. Ages ranged from 65 to 91 years (mean 74). The age of onset of cataplexy (in 53 patients) ranged from 10 to 66 years. Cataplexy preceded EDS in 10 (18.9%) of 53 patients (28 years prior in one patient). Cataplexy and EDS developed simultaneously in 35 (64.5%) patients, and nine could not explain the reason for their relief from cataplexy. Cataplexy preceded EDS in 10 (18.9%) of 53 patients (28 years prior in one patient). Cataplexy and EDS developed simultaneously in 35 (64.5%) patients, and nine could not explain the reason for their relief from cataplexy. Cataplexy preceded EDS in 10 (18.9%) of 53 patients (28 years prior in one patient). Cataplexy and EDS developed simultaneously in 35 (64.5%) patients, and nine could not explain the reason for their relief from cataplexy. Cataplexy preceded EDS in 10 (18.9%) of 53 patients (28 years prior in one patient). Cataplexy and EDS developed simultaneously in 35 (64.5%) patients, and nine could not explain the reason for their relief from cataplexy.

Conclusions: The gender distribution of our patients had an unexpected male bias. Previously, socioeconomic dislocation was cited as a probable explanation for the male preponderance in narcoleptics(1). However, in this elder population one would expect the life expectancy of females to counterbalance this. Cataplexy as an initial symptom of the narcolepsy syndrome has been thought to be rare. Our data show that this may be more common than previously described(1,2). Why one symptom of narcolepsy, excessive daytime somnolence, should persist while cataplexy remits has been described but not convincingly explained. These data suggest that the severity of cataplexy does not necessarily diminish with time. In fact, cataplexy persists or increases in over 50% of patients.

References:

A Pilot Study of Serologic Markers of Autoimmunity in Patients with Narcolepsy

Black JL, Krahn LE, Silber MH
Mayo Clinic-Rochester, MN

Introduction: Narcolepsy is strongly associated with DQB1*0602 but previous attempts to demonstrate its autoimmune etiology have been unsuccessful. This study was designed to test two hypotheses: 1) Narcoleptic patients with cataplexy have more serologic markers of autoimmunity compared to those without cataplexy. 2) HLA DQB1*0602 positive narcoleptic patients have more serologic markers of autoimmunity when compared to those who are negative. Autoantibodies in serum are recognized as humoral markers of neuron-specific and organ-specific autoimmunity were examined. Individuals with neurologic autoimmune diseases have autoantibodies in serum reactive to a variety of epitopes, in addition to the epitopes causing disease.

Methods: Serum was collected from 43 patients for HLA determination and autoantibody testing. The patients (18 years) met the Mayo Narcolepsy Research Criteria for narcolepsy with or without cataplexy. The assays were performed by personnel who were blinded to the diagnosis. All the tests are used in routine practice and are run daily with positive and negative controls. The antibodies tested were N-type and P/Q-type voltage-gated calcium channel, neuronal nicotinic acetylcholine receptor a3 subunit, acetylcholine receptor-binding, striated muscle, type 1 Purkinje cell cytoplasmic, types 1 and 2 antineuronal nuclear, GAD-65, PCA-1, ANNA-1 and ANNA-2, thyroid microsomal, thyroglobulin and amphiphysin. When non-organ-specific autoantibodies (ANA, AMA, and SMA) confound interpretation of neuron-specific antibodies, the sera were absorbed with liver extract and retested.

Results: Twelve of 33 (36%) narcoleptics with cataplexy had one or more autoantibodies compared to 1 of 10 (10%) narcoleptics without cataplexy. (Chi-square, p=0.112). Ten had one positive assay and 3 had two positive assays. No specific pattern of seropositivity was evident. While 36% had one or more antibodies present, 12 tests were performed on each of the 43 patients. Given a 5% false positive rate for each test, the probability that one patient will test positive for one or more antibodies by chance alone is 46%. Thus, we would have expected 20 individuals to have one or more antibodies present. Stratifying by HLA DQB1*0602 status, 9 of 30 (30%) positive patients had one or more autoantibodies compared to 3 of 11 (27%) of the negative patients. (Chi-square, p=0.865).
This study was funded by the Mayo Foundation (with the discretionary funds of the Department of Psychiatry and Psychology and the Piscopo Funds).

560.K

A Comparative Investigation of Sleepiness and Complex Cognitive Function in Narcolepsy and Sleep Deprivation.

Hood BM, Bruck D
Victoria University, Australia

Introduction: Background: Hood and Bruck (1996) found that sleepy narcoleptics demonstrated significant impairment of complex cognitive function that was reversed by a brief nap period. This paper aims to explore whether this observed relationship between sleepiness and performance in narcolepsy is specific to the disorder or simply reflects more generic aspects of the sleepiness and performance interaction. The aims of the current study are therefore (i) To induce a level of sleepiness in normal sleepers that equates with the level of sleepiness previously found in sleepy narcoleptic subjects, (ii) to investigate the comparative effects of narcoleptic and normal sleepiness on complex cognitive function, and, (iii) to compare the recuperative effects of a brief nap on both arousal and cognitive function for sleep deprived and narcoleptic subjects.

Methods: Sixteen subjects participated in the study. Eight subjects undergoing a 32 hour deprivation protocol and eight acting as controls. Following the deprivation protocol subjects completed the PASAT task - a complex cognitive task that measures central information processing capacity. A twenty minute nap was then permitted and subjects were retested under post nap conditions. Comparisons were then made between sleep deprived and narcoleptic subjects (derived from the comparative Hood & Bruck study) on both the manipulations of sleepiness and the impact of sleepiness on complex cognitive performance.

Results: Normal sleepers required a thirty-two hour deprivation protocol to develop a subjective level of sleepiness that equated with that identified by subjects with narcolepsy. In contrast to the comparative analysis with narcoleptic subjects, this induced sleepiness in normals, did not result in any significant decrement in complex performance. Again in contrast to the findings on narcolepsy by Hood and Bruck (1996) a twenty-minute nap for sleep deprived subjects had no recuperative effects on either subjective arousal status or complex cognitive functioning.

Conclusions: Thirty two hours of sleep deprivation was required in non-pathological sleepers to approximate the daily sleepiness reported by narcoleptics. This sleepiness leads to more significant decrements in complex cognitive functioning for narcoleptics than normals. A twenty-minute nap produced more improvement in both arousal and cognitive processing for the narcoleptics than the sleep deprived normals.

References:

561.K

Compliance with Stimulant Treatment Regimens.

Rogers AE, Cantor C, Marcus S
University of Pennsylvania

Introduction: Health care providers cannot assume that their patients with narcolepsy are complying with prescribed treatment regimens. An earlier study documented that over half of the narcoleptic patients studied were taking less stimulant medication or had not taken any medication during a 24-hour monitoring period when they were expected to be on medication (1). Dosage reductions were often substantial, with patients taking less than one-half the amount of medication prescribed. While the findings were instructive, the study relied on rather crude measures of pill-taking behavior (questionnaires, diaries, and medical records). The goal of our current study is to re-evaluate patient compliance using a more exact measure of pill-taking behavior, the Medication Event Monitoring System (MEMS) developed by Aprex (Apria Health-care, Freemont, CA).

Methods: The MEMS consists of MEMS TrackCaps, the MEMS Communicator used to transfer data from TrackCaps to a computer, and software to analyze data recovered from the TrackCaps. Microelectronics built into the pill bottle cap (TrackCap) record the time and date each time the bottle is opened, thus providing data about drug exposure. The
MEMS is considered a more reliable measure of compliance than patient interviews, pill counts, and even serum drug levels. To date, we have analyzed data obtained from the first 24 subjects (19 female, 5 male, 40.9 ± 13.9 yrs) participating in our large multi-site study. All subjects were between 18 and 65 years of age, had a diagnosis of narcolepsy, and were taking stimulant medications. Subjects were excluded from participation if they had a history of sleep apnea, other neurologic disorders, mental illness or alcoholism. MEMS TrackCaps were placed on the patients’ pill bottles three weeks prior to their 24-hour ambulatory polysomnographic recording. At the end of the recording period, the MEMS TrackCaps were removed and the information downloaded into a computer file for analysis.

Results: Subjects had prescriptions for adderal (1), dextroamphetamine (7), methylphenidate (6), modafinil (13), and pemoline (3). On average patients took their stimulant medications as prescribed on 72.1 ± 27.6% of the days that they used the MEMS TrackCaps, took less than prescribed 13.8 ± 17.2% of the time, and took more doses than prescribed 18.6 ± 32.7% of the time. When underdosing occurred, patients were more likely to omit some but not all of their prescribed doses (52 of the 83 days). However, on 31 of the 609 days monitored (5%), patients took no stimulant medications. As shown in the table below, looking at overall compliance rates, obscures the differences between the various medications. These differences, with one exception (% of doses taken) were statistically significant.

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Days Drug Taken Correctly</th>
<th>% Days with Doses Omitted</th>
<th>% Days with Extra Doses</th>
<th>% Doses Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall</td>
<td>86.4</td>
<td>4.5</td>
<td>9.1</td>
<td>104.5%</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>72.2</td>
<td>15.9</td>
<td>11.9</td>
<td>93.6</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>42.4</td>
<td>20.5</td>
<td>35.6</td>
<td>120.0</td>
</tr>
<tr>
<td>Modafinil</td>
<td>80.0</td>
<td>11.1</td>
<td>9.3</td>
<td>100.6</td>
</tr>
<tr>
<td>Pemoline</td>
<td>87.8</td>
<td>9.7</td>
<td>2.4</td>
<td>98.1</td>
</tr>
</tbody>
</table>

Conclusions: Although patients took roughly the correct number of doses of stimulant medications during the monitoring period, they frequently took less medication on some days and more medications than prescribed on others. Only 4 patients (16.6%) took their medications exactly as prescribed throughout the entire monitoring period.

References:

Financial support for this study was provided by a grant (R01 NR04191) from the National Institute of Nursing Research (NIH) and assistance from Cephalon, Inc.

562.K

ICSD 1990 Criteria for Narcolepsy: Interobserver Reliability

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Introduction: Knowledge of interobserver reliability for diagnostic judgement is a prerequisite for the design of multicenter epidemiological studies and clinical trials. The diagnosis of narcolepsy is principally suggested by clinical interview. The classical form characterized by frequent irresistible sleep attacks and cataplexy can be easily recognized; otherwise, when only mild symptoms are present and polygraphic find-ings are not conclusive, diagnostic judgement could vary even among skilled practitioners of sleep medicine. The aim of this study is to estimate the interobserver reliability of diagnosis in suspected narcolepsy among doctors in Italian sleep centers before and after application of ICSD 1990 criteria.

Methods: Ten consecutive patients referred to our sleep center for suspected narcolepsy were included. Four subjects had confirmed narcolepsy (2 with cataplexy), 2 idiopathic hypersomnia, 3 sleep disordered breathing, 1 REM behaviour disorder. Patients underwent video recording of a standardized interview to investigate symptoms required for the diagnosis of narcolepsy according to ICSD 1990 criteria. After a video projection of the interviews, 17 doctors of each of the 17 sleep centers of the Italian Association of Sleep Medicine (7 residents - R - and 10 trainees - T) were invited to classify independently each case as “certain”, “possible” or “excluded” narcolepsy. After discussion of ICSD 1990 criteria and a second video session, the observers again classified the same cases. Finally, a series of 10 simulated cases of narcolepsy without cataplexy (A + D + G ICSD 1990 criteria satisfied) were devised. They had at least a random two of the four polysomnographic parameters required by ICSD 1990 E criterium at pathological levels. The 17 raters were requested to classify each case as “confirmed” or “excluded” narcolepsy. Interobserver reliability of the diagnosis in the 2 case series was calculated in the whole group and in R and T subgroups by means of K statistics (2), and interpreted according to standard classification (3).

Results: In the series of real interviews, before training, the observed agreement on final diagnosis was 77% (73% in R and 81% in T); the reliability was “substantial” among all observers (K=0.61, SE=0.02), “moderate” among R (K=0.54, SE=0.05) and “substantial” among T (K=0.67, SE=0.04). After training, the observed agreement was 97% (97% in R and 96% in T); the reliability was “almost perfect” (K=0.95, SE=0.02), without differences between R and T. In the series of simulated cases, the observed agreement was 72% (72% in R and 70% in T); the reliability was “fair” among all raters (K=0.24, SE=0.03), “fair” among R (K=0.30, SE=0.07) and “slight” among T (K=0.15, SE=0.05).

Conclusions: Among doctors in Italian sleep centers, baseline reliability of diagnostic judgement, on the basis of videotaped standardized clinical interview, is “substantial” when suspected narcoleptic patients are evaluated. A higher reliability can be obtained after application of ICSD 1990 criteria. Otherwise, when diagnosis is based on polysomnographic results, reliability is not satisfactory. Educational training, including discussion of diagnostic clinical criteria and videotaped interview, may be a useful method to improve agreement among physicians. Nevertheless, the ICSD 1990 polysomnographic criteria may need further elucidation when a multicenter study has to be designed.

References:

Research supported by Dompé Biotec spa, Italy
Introduction: Sodium oxybate (sodium gamma-hydroxybutyrate, GHB) has been shown to be effective in the treatment of narcolepsy in both uncontrolled and controlled clinical trials. Previous PSG studies of nocturnally administered oxybate have suggested that GHB may produce its beneficial effects on the daytime symptoms of narcolepsy by generating a more consolidated sleep as evidenced by improved sleep continuity, increased delta sleep and improved REM efficiency. The present open-label clinical study characterized the effects of 4 oral doses of Xyrem®, a 500 mg/mL oral solution of sodium oxybate, on overnight PSG measures in narcoleptic patients.

Methods: A cohort of 25 previously diagnosed narcoleptic patients with cataplexy were accrued at 4 sleep centers. During an initial 4-week period the patients were gradually withdrawn from all anti-cataplectic medications while stimulants for daytime sleepiness were held constant throughout the trial. PSGs were performed at the beginning and the end of this withdrawal-baseline period. Patients were then administered a 4.5g nightly oral dosage of sodium oxybate given as 2.25g at bedtime and again 2.5-4 h later for a period of 4 weeks. Overnight PSGs were again recorded on the first night of 4.5g treatment and at the end of 4 weeks. The dose was then increased at 2 week successive intervals to 6, 7.5 and 9g in divided nightly doses. PSGs were again conducted on the final night of each 2-week dosing interval. The PSGs from all sites were centrally scored in a blinded fashion. For each PSG measure, a 2-way ANOVA was applied among the dosage groups using the PSG recorded at the end of the 4-week washout period as the baseline.

Results: Of the 25 patients who began the study, 21 completed the full 10 weeks and 7 overnight PSGs. Two patients withdrew due to adverse experiences, 1 withdrew consent and 1 was lost to follow-up. Initial analyses of the PSG parameters revealed the following: (1) No dosage regimen altered total sleep time, or the amount of Stage 1 or Stage 2 sleep. (2) The amount of delta (slow wave) sleep increased in a dose-related manner with significant increases associated with the 7.5 and 9g doses. (3) Delta power increased significantly in a dose-related manner for all 4 doses. (4) The number of nocturnal awakenings were reduced significantly with both the 7.5 and 9g doses. (5) As compared to baseline, sleep latency was increased significantly by all 4 doses but remained within the expected range for narcoleptics.

Conclusions: These findings confirm and extend the results of previous studies with respect to the EEG changes produced by sodium oxybate in narcoleptic patients. Sodium oxybate improved the disrupted nocturnal sleep patterns of narcoleptic patients as demonstrated by an increase in delta (slow wave) sleep and a decrease in the frequency of awakenings. This study also revealed a significant dose-related increase in delta power, a finding not reported previously. The clinical significance of the increase in delta power requires further research but may be reflective of a more restorative sleep pattern.

References:

563.K

Dose Response Effects of Sodium Oxybate on Polysomnographic (PSG) Measures in Narcolepsy Patients: Preliminary Findings

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564.K

Effects of Sodium Oxybate on Measures of Daytime Sleepiness in Narcolepsy Patients: Preliminary Evidence of Dose-Related Improvements

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Introduction: In prior clinical trials nocturnally administered sodium oxybate (sodium gamma-hydroxybutyrate, GHB) has been found effective in the treatment of narcolepsy including the symptoms of cataplexy and pathologic daytime sleepiness. In these 3 studies, the drug was given in fixed daily doses of either 50 or 60 mg/kg administered in 2 divided doses at bedtime and 2.5-4 hours later. The present open-label, rising-dose trial characterized the effects of 4 doses of Xyrem(R) oral solution containing 500mg/mL of sodium oxybate, on objective and subjective measures of excessive daytime sleepiness (EDS) in narcoleptic patients. Nightly doses of 4.5, 6, 7.5 and 9g were each evaluated for 2-4 weeks.

Methods: A total of 25 previously diagnosed narcoleptic patients were treated at 4 sleep centers. Stimulants for daytime sleepiness were held constant throughout the study. During an initial 4-week washout period, the patients were gradually withdrawn from all anti-cataplectic medications. Patients were then administered a 4.5g nightly oral dosage of sodium oxybate given in equal divided doses at bedtime and again 2.5-4 h later for a period of 4 weeks. The dose was subsequently increased at 2 week intervals to 6, 7.5 and 9g, in divided nightly doses. Measures of daytime sleepiness included the Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS). The MWT, which quantifies the ability to resist falling asleep, was conducted at the beginning and end of the washout period and again at the end of the 4.5g and 9g treatment periods. The ESS was completed at these same 4 time points and at the end of the 6g and 7.5g treatment periods. For each measure, a 2-way ANOVA was applied among the dosage groups using the data from the end of the 4-week washout period as the baseline.

Results: Of the 25 patients who began the study, 21 completed the full 10 weeks of treatment. Two patients withdrew due to adverse experiences, 1 withdrew consent and 1 was lost to follow-up. Initial analyses revealed the following. The MWT results showed that the average sleep latency increased significantly from 4.5 min at baseline to 8.2 min after 4.5g therapy and 10.6 min after 9g treatment. Sleep onset REM periods were recorded for 86% of patients at baseline: this dropped to 62% after the 4.5g dose and 30% after the 9g dose. Mean ESS total score was 19.8 at baseline [max.=24] and showed a statistically significant dose-related decrease after all 4 doses. The mean (median) decreases in ESS were 2.4(2), 3.8(3), 4.8(4) and 5.8(7) for the 4.5, 6, 7.5 and 9g doses, respectively.

Conclusions: The results of this multicenter trial indicate that sodium oxybate administered at night produces dose-related objective and subjective improvement in excessive daytime sleepiness in patients already taking stable clinical doses of stimulants for EDS. Thus, the significant reduction in EDS as measured by both the MWT and the ESS was in addition to any residual benefit obtained from concomitant stimulant treatment and was comparable in magnitude to that observed with standard stimulant therapy.
CSF Hypocretin Levels in Various Neurological Conditions: Low Levels in Narcolepsy and Guillian-Barre Syndrome

Ripley B, Overeem S, Fujiuki N, Nevsimalova S, Uchino M, Dohi K, Melberg A, Lamers GJ, Mignot E, Nishino S

Introduction: Recent CSF and postmortem brain hypocretin measurements in human narcolepsy suggest that hypocretin deficiency is involved in the pathophysiology of the disease [1,2]. An extended CSF measurement study has demonstrated that abnormal (either low or high) CSF hypocretin levels are predictive for narcolepsy (89.5% of the overall patient population and 94.7% of HLA positive cases). In contrast, all healthy and neurological controls tested have levels that fall within a narrow range (169-376 pg/ml). Thus CSF hypocretin measurement may prove to be a new diagnostic tool for human narcolepsy (see Nishino et al, this issue). Using rats, we have recently demonstrated that hypocretin neurotransmission activity in the hypothalamus is reflected in CSF hypocretin levels (Fujiki et al, this issue). Thus, it is interesting to study whether neurological conditions associated with hypothalamic symptoms may also have abnormal CSF hypocretin levels. We therefore measured hypocretins in the CSF of various neurological patients to identify altered hypocretin levels. The results will also be useful in further evaluating the specificity of low hypocretin levels in narcolepsy.

Methods: CSF was collected from patients with (1) idiopathic narcolepsy (n=36) (2) neurodegenerative disorders (Alzheimer’s [n=24] and others [n=3]), (3) intracranial neoplasms (n=17), (4) multiple sclerosis (n=13) and other demyelinating diseases (n=2), (5) infections (n=32), (6) head trauma (n=4), (7) radiculopathy (n=3) and peripheral polyneuropathy (n=4), (8) inflammatory neuropathy, such as Guillian-Barre syndrome (GBS) (n=8) and chronic, inflammatory demyelinating polyneuropathy (CIDP) (n=13), and (9) subarachnoid hemorrhage (SAH) (n=35, mostly collected from ventricular drains). CSF hypocretin-1 was measured in crude CSF samples (no extraction procedure) (100 µl, duplicate) using a commercially available radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals). Intra-assay variability was 3.8% and the detection limit was 50 pg/ml.

Results: We found a significant correlation between hypocretin levels measured in crude or extracted CSF in a selected sample population (range 160-570 pg/ml). Hypocretin levels in the crude CSF of 34 healthy controls were found to be 397±123 pg/ml (average±SD; range: 231-653 pg/ml). As was seen in measurements from extracted samples, hypocretin levels were undetectable in crude CSF from the majority of narcoleptics (32 out of 36). Hypocretin levels in patients with neurodegenerative disorders were within the control range, except for a case of autosomal dominant cerebellar ataxia with narcolepsy (97 pg/ml) [3]. Levels in patients with multiple sclerosis and allied demyelinating disease, infections (i.e. meningitis and encephalitis) or polyneuropathy were in the control range. Patients with intracranial neoplasms were also in the control range, except for 3 patients with acoustic schwannoma (195±36.0 pg/ml). Patients with head trauma had decreased hypocretin levels (contusion, n=3, 141±11.7 pg/ml and multitrauma, n=1, 162 pg/ml). Hypocretin levels were undetectable in the CSF of 2 patients with GBS, and relatively low levels were observed in 3 other GBS patients (156 pg/ml, 186 pg/ml, and 181 pg/ml) out of a total of 8 patients. Most CIDP patients, however, had normal levels (n=13; 379±116 pg/ml, range: 201-604 pg/ml). Most of the SAH patients had remarkably low levels (97.1±41.2 pg/ml; range: 17.0-234 pg/ml), but the influence of ventricular draining on hypocretin levels is not known at this moment.

Conclusions: The majority of narcoleptic subjects, including one symptomatic case, had extremely low hypocretin levels (less than 100 pg/ml). Although a significant decrease in CSF hypocretin levels was observed in schwannoma patients, head trauma patients, and 5 out of 8 GBS patients (2 of which had undetectable levels), levels in patients with neurological diseases such as Alzheimer’s, MS and CNS infections were within the control range, suggesting that extremely low hypocretin levels are highly specific for narcolepsy. The low levels observed in some GBS patients are interesting, and raise the possibility that a transient autoimmune process could affect hypocretin neurons, since multiple autoantibodies are detected in some GBS patients. GBS is occasionally associated with SIADH, a possible sign of hypothalamic dysfunction. Hypocretin deficient GBS cases may thus represent more global hypothalamic hypofunction, as is expected in some cases of brain trauma and SAH. Further studies exploring low hypocretin levels in GBS and SAH are now underway.

References:

Special thanks to Dr. Yesavage for contributing CSF samples. This work was supported by: NS 27710, NS23724, NS 33797, MH40041 and MH01600.

Sodium Oxybate is an Effective Treatment of Narcolepsy with Cataplexy

Mitter M, Hayduk R, Erman MK

Introduction: Narcolepsy is a chronic, debilitating neurologic disorder caused by the dissociation of sleep and its components. It presents clinically with excessive daytime sleepiness, fragmented nighttime sleep, cataplexy, hypnagogic hallucinations, and sleep paralysis. The REM-related symptoms of cataplexy, hypnagogic hallucinations and sleep paralysis are usually treated with TCAs and SSRIs. The effectiveness of these treatments is frequently limited by undesirable adverse events and tolerance. Sodium oxybate is an investigational drug with demonstrated efficacy for treating REM-related symptoms of narcolepsy, especially cataplexy.

Methods: A randomized, double blind, placebo-controlled, multi-center trial of sodium oxybate was conducted in 136 narcoleptic patients at 18 centers. The trial consisted of 5 phases that began with a screening/washout period of up to 28 days during which all anti-cataplexy drugs were gradually discontinued. The following washout period of 5-28 days allowed time for termination of the clinical effects of prior anti-cata-
plicated, rebound cataplexy, and diary training effects. A subsequent 14-28 day baseline period permitted the assessment of cataplexy attacks. Patients with at least 3 cataplexy attacks per week were eligible to participate. Qualifying patients entered a double-blind treatment period with random assignment to nightly sodium oxybate doses of 3g, 6g, 9g or placebo for up to 4 weeks. Sodium oxybate was administered in equally divided doses at bedtime and 2.5-4 h later. All trial medication was abruptly discontinued at the end of this period and a follow-up evaluation was conducted 3-5 days. Patient daily diaries were used to record the effects of treatment and episodes of cataplexy and all adverse experiences. The change in the number of cataplexy episodes from baseline (last 2 weeks prior to double-blind treatment) to endpoint (last 2 weeks of double-blind treatment) was the primary measure of efficacy.

Results: The percent change in cataplexy attacks per week is shown in Figure 1. Placebo, 3g, 6g, and 9g dose groups showed reductions in the median number of cataplexy attacks of 28%, 40%, 50%, and −55% after 2 weeks treatment and −28%, −49%, −49%, and −69% after 4 weeks treatment, respectively. By endpoint ANCOVA analysis, the 9g dose of sodium oxybate significantly reduced the total number of episodes of cataplexy (p=0.0008) relative to placebo. The 6g dose reduced cataplexy and approached significance (p=0.0529) relative to placebo. Sodium oxybate was well-tolerated at all 3 doses. The most common adverse events were nausea, headache and dizziness, which appeared to be dose related. Cataplexy symptoms returned toward baseline levels following discontinuation of active treatment with no evidence of rebound.

Conclusions: Sodium oxybate exhibited significant benefit for cataplexy symptoms at 6g and 9g doses. It was well-tolerated and showed no evidence of rebound cataplexy following discontinuation. Sodium oxybate appears to be an effective therapy for narcolepsy.

References:

This research was conducted by the U.S. Xyrem(R) Multicenter Study Group with the support of Orphan Medical, Inc., Minnetonka, MN.

567.K
Effects of Reboxetine in Narcolepsy-Cataplexy: Preliminary findings on 14 patients
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Introduction: A dysregulation of rapid eye movement (REM) sleep, reflected in cataplexy, and a markedly increased propensity to REM sleep during daytime naps, are considered the cardinal physiological manifestations of narcolepsy. Several lines of theoretical evidence suggest that noradrenergic mechanisms might be involved in the pathophysiology of the disorder (1). Reboxetine is a new inhibitor of noradrenergic NA-reuptake, that has shown antidepressant properties in numerous studies (2). Moreover, a subtype of depressed patients complaining of anergia, psychomotor retardation and daytime somnolence seem to benefit most from treatment with reboxetine. The objective of this study was to investigate the effects of reboxetine on daytime sleepiness and cataplexy in seven narcoleptic patients by means of an open design.

Methods: Fourteen outpatients (mean age: 36 yrs, SD: 12) meeting criteria for narcolepsy according to the International Classification of Sleep Disorders were included in the study. Diagnostic procedures included history taking, neurological and medical exam, polysomnography, multiple sleep latency test and HLA testing. Design: After completion of diagnostic procedures, patients were treated following an open design for two weeks with 10 mg reboxetine. Reboxetine was administered at gradually increasing dosages reaching 6 mg on day 5 and 10 mg from day 9 on. A sleep study and a multiple sleep latency test were performed thereafter. Patients were rated daily on the Visual Analogue Scale for Subjective Sleepiness, on a weekly basis on the Epworth Sleepiness Scale (ESS), and both at baseline and at the end of the study on the Ullanlinna Narcolepsy Scale (USS) (3) and Beck Depression Inventory (BDI).

Results: All fourteen patients completed the study. Treatment with reboxetine was generally well tolerated. As the adjunct Table shows, a statistical significant improvement of daytime sleepiness was observed both on rating scales as on the MSLT. In addition, a statistically significant reduction in the number of SOREMPs and in the frequency of cataplexy attacks could be found. No changes were shown on the BDI.

Table 1

<table>
<thead>
<tr>
<th>Mean (± S.D.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline Day 7 Day 14 BL-D7 BL-D14</td>
</tr>
<tr>
<td>EPWORTH</td>
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<tr>
<td>BDI</td>
<td>13.14± 9.82</td>
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<tr>
<td>USS</td>
<td>21.85± 7.12</td>
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<tr>
<td>- Cataplexy sub score</td>
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<tr>
<td>MSLT</td>
<td>5.34± 2.43</td>
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<tr>
<td>- Mean sleep latency</td>
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<td>- SOREMPs</td>
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<td>% REM on PSG + MSLT1</td>
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<td>D.1-2</td>
<td>15.5± 7.51</td>
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<td>D.7-8</td>
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<tr>
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</tbody>
</table>

VARS: Visual Analogue Scale (Sleepiness); ESS: Epworth Sleepiness Scale; BDI: Beck Depression Inventory; USS: Ullanlinna Narcolepsy Scale; MSLT: Multiple Sleep Latency Test; SOREMPs: Sleep Onset REM Periods; TST: Total Sleep Time; PSG: Polysomnography; % REM: REM sleep (min) / TST.

Conclusions: Our results suggest therapeutic effects of reboxetine on EDS and cataplexy in patients with narcolepsy. The stimulant activity was not paralleled by improvement in rating scales for depression. These clinical effects are probably related to noradrenergic-mediated REM-sleep suppressing effects of reboxetine. Further studies under controlled conditions are warranted.
References:

568.K
Assessment of Sodium Oxybate for the Long-Term Treatment of Narcolepsy

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Introduction: Sodium oxybate is an investigational drug that has demonstrated efficacy for the treatment of narcolepsy symptoms, including cataplexy. To date, no controlled trials assessing the long-term efficacy of sodium oxybate for cataplexy treatment have been performed. A conventional blinded clinical trial design for long-term efficacy would require patients to withdraw and washout from existing anti-cataplexy medications and then be randomized into prolonged placebo and active treatment groups. An alternative paradigm for assessing long-term efficacy is to remove patients from stable long-term therapy and demonstrate a return of cataplexy. The trial presented herein was designed using this alternative paradigm where the primary measure of efficacy is the return of cataplexy symptoms during a two-week period following the withdrawal of sodium oxybate therapy.

Methods: Fifty-five (55) narcoleptic patients (23 men and 32 women) participated. The patients ranged in age from 16 to 82 years (mean 48 years). Prior to trial entry all of the patients had been taking sodium oxybate, had a history of 5 cataplexy attacks per week prior to receiving any treatment for cataplexy, and were not using antidepressant medications to control cataplexy for 30 days preceding trial entry or during the trial. Stable doses of stimulant medications were permitted. Sodium oxybate (dose range 3 to 9 g/night) was used for 7 to 44 months (mean = 21 months) prior to trial entry. The trial consisted of 3 phases: screening, 2-week single-blind period (baseline), and 2-week double-blind period (endpoint) in which patients were randomized to receive placebo or sodium oxybate. During the conduct of the trial, patients continued on their stable dose of sodium oxybate or equivalent volume of placebo. During both baseline and endpoint each patient recorded the number of cataplexy attacks in a daily diary. The primary efficacy measure was the change in the number of cataplexy attacks per 14-day period from baseline to week 2. There was no significant increase in the number of adverse events in the placebo patients and there were no signs of withdrawal such as insomnia, anxiety, or tremor.

Results: During the double-blind period, 29 patients received placebo and 26 received sodium oxybate at the same dose during the double-blind period. During the baseline period, there was no significant difference in the mean number of cataplexy attacks between treatment groups (9.0 ± 19.3 sodium oxybate group; 15.7 ± 39.9 placebo group). The sodium oxybate group had a mean increase of 3.6 cataplexy attacks compared to an increase of 34.6 for the placebo group (P<0.001). The change in the number of cataplexy attacks seen in the placebo group occurred as a gradual increase from baseline to week 2. There was no significant increase in the number of adverse events in the placebo patients and there were no signs of withdrawal such as insomnia, anxiety, or tremor.

Conclusions: The abrupt removal of patients from sodium oxybate treatment resulted in an increase in cataplexy, which indicates that sodium oxybate is efficacious for the long-term treatment of cataplexy. In addition, abrupt withdrawal of sodium oxybate therapy does not result in increased numbers of adverse events or withdrawal symptoms.

References:

This research was conducted by the U.S. Xyrem(R) Multicenter Study Group with the support of Orphan Medical, Inc., Minnetonka, MN.

569.K
Sodium Oxybate is Safe and Well-tolerated when Used for the Treatment of Narcolepsy

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Sleep Medicine Associates, Nashville, TN

Introduction: Narcolepsy is a chronic disorder consisting of daytime sleepiness, cataplexy, disturbed nocturnal sleep, hypnagogic hallucinations, and sleep paralysis. Sodium oxybate has been shown to decrease the incidence and severity of these symptoms. A double-blind, placebo-controlled trial followed by an open-label extension trial, was conducted to determine the safety and efficacy of sodium oxybate in narcolepsy patients at fixed, randomized doses and after titration to optimal clinical effect.

Methods: A randomized, double blind, placebo-controlled, multi-center trial of 3 doses of sodium oxybate was conducted in documented narcoleptic patients. The trial consisted of 5 phases beginning with a screening/withdrawal period of up to 28 days during which all anti-cataplexy drugs were gradually discontinued. Stimulant medications were continued at stable doses. A washout period of 5-28 days allowed for termination of the clinical effects of prior anti-cataplexic medication, rebound cataplexy, and diary training effects. A subsequent baseline period of 14-21 days enabled an assessment of cataplexy attacks. Patients with at least 3 cataplexy attacks per week during baseline were eligible to participate. Qualifying patients entered a double-blind treatment period with random assignment to 3g, 6g or 9g per day or placebo for up to 4 weeks. Sodium oxybate was administered in equal divided doses at bedtime and 2.5-4 h later. All trial medication was abruptly discontinued at the end of this period and a follow-up evaluation was conducted 3-5 days later to assess the return of symptoms. In the open-label phase, patients were started at 6g and then titrated to optimal clinical effect within the range of 3 to 9g with dose changes at 2-4 week intervals.

Results: 136 narcolepsy patients enrolled from 18 participating sleep centers in the double-blind trial; 118 of these patients enrolled in the open-label phase and 80 completed it. Sodium oxybate improved the...
symptoms of cataplexy, daytime sleepiness, nighttime awakenings, and the overall severity of illness in the 4-week double-blind trial. In the open-label trial, clinical improvement optimized approximately 3 months after the beginning of the double-blind trial and continued throughout the 12-month trial. Sodium oxybate was well tolerated. Adverse events reported by individual patients (double-blind, open-label) included dizziness (32, 31), headache (26, 39), nausea (21, 33), pain (16, 30), viral infection (9, 32), somnolence (0, 23), incontinence (7, 10), and vomiting (6, 8). Nausea, vomiting, dizziness and incontinence achieved significance and occurred in a dose dependent manner in the double-blind but not the open-label trial. These events were considered to be mild to moderate. Ten and 11 patients discontinued the double-blind and open-label trials, respectively, due to adverse events. One and 3 patients in the double-blind and open-label trials, respectively, experienced serious adverse events. Only two of these events were considered related to study medication. Of note, patients that discontinued study medication reported no evidence of rebound cataplexy.

Conclusions: Consistent with other reports, these trials demonstrate sodium oxybate to be a well-tolerated medication that improves the symptoms of narcolepsy.

References:

This research was conducted by the U.S. Xyrem(R) Multicenter Study Group with the support of Orphan Medical, Inc., Minnetonka, MN.

570.K

Sodium Oxybate Therapy Significantly Improves the Excessive Daytime Sleepiness Associated with Narcolepsy

Feldman NT
St. Petersburg Sleep Disorders Center, St. Petersburg, FL

Introduction: The clinical manifestations of narcolepsy include excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, sleep paralysis and fragmented nocturnal sleep. Because nightly doses of sodium oxybate have been demonstrated to decrease the incidence and severity of narcolepsy symptoms,1 the present clinical studies, a double-blind placebo-controlled trial followed by an open-label extension trial, examined the efficacy of sodium oxybate in the treatment of EDS. In addition, investigators assessed changes in the numbers of inadvertent naps/sleep attacks and changes in overall severity of illness.

Methods: Patients were tapered from hypnotic or antidepressant medications, however fixed doses of stimulants were permitted throughout both trials. Patients experiencing at least 3 cataplexy attacks each week during a 4-week baseline period were enrolled. In double-blind fashion, patients were randomly assigned 3 g, 6 g, 9 g sodium oxybate or placebo taken in equal divided doses immediately upon retiring to bed and 2.5–4 hours later. Patients remained on their dose of sodium oxybate or placebo for 4 weeks. Patients completing the trial were eligible to enter a 12-month open-label extension trial. Patients were then started on 6 g sodium oxybate taken nightly in equal divided doses at bedtime and 2.5–4 hours later. The dose was titrated to optimal clinical effect within the range of 3–9 g. Dosing adjustments were made at 2–4 week intervals. Once established, each patient remained on that dose until study conclusion. Cataplexy and other symptoms were recorded daily in patient diaries. EDS was measured using the Epworth Sleepiness Scale (ESS). Investigators measured overall improvements in illness severity using the Clinical Global Impression of Change (CGI-C).

Results: One hundred thirty-six narcoleptic patients were enrolled at 18 sleep centers. During the double-blind phase, the median ESS Scores decreased for each dose, becoming significant at 9 g (p=0.0001). Similarly, the median number of inadvertent naps/sleep attacks was decreased for each dose becoming significant at 6 g (p<0.05) and 9 g (p<0.05). These data are presented in Figures 1 & 2. In addition, 32%, 47%, 52%, and 80% of patients in the placebo, 3g, 6g, and 9g treatment groups, respectively, had either much improved or very much improved CGI-C measures, which was significant at 9g (p<0.05). In the following open-label study, ESS also improved significantly at 3 and 6 g doses (p<0.001).

Figure 1

Figure 2

Conclusions: Although these narcoleptic patients were being concurrently treated with stimulant medications, nighttime doses of sodium oxybate produced significant improvements in daytime sleepiness, inadvertent daytime naps/sleep attacks and the overall severity of illness. At 4 weeks, statistically significant improvement in EDS, number of inadvertent sleep episodes and CGI-C occurred primarily at the 9 g dose. The results of the open-label study suggest that, at lower doses, more than 4 weeks of therapy may be necessary to achieve therapeutic effects. Sodium oxybate appears to be effective in treating excessive daytime sleepiness associated with narcolepsy.

References:

This research was conducted by the U.S. Xyrem(R) Multicenter Study Group with the support of Orphan Medical, Inc., Minnetonka, MN.
Sodium Oxybate Therapy Improves the Quality of Life of Narcoleptic Patients

Hayduk R, Mitler M
The Scripps Research Institute, LaJolla, CA

Introduction: Narcolepsy is a chronic neurological disorder characterized by symptoms of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and fragmented nighttime sleep. It is generally accepted that these symptoms have a negative impact on the quality of life (QOL) in these patients. While a recent study indicates that alleviating the daytime sleepiness associated with narcolepsy has a significant positive effect on patient QOL, the effect of other drug therapies in these patients has not been systematically examined. The impact of treating narcoleptic patients with sodium oxybate on patient QOL was evaluated with the SF-36® Survey questionnaire, which was administered in conjunction with a 6-month open-label trial of sodium oxybate. SF-36 is a well-validated and widely used questionnaire. It provides scores for 8 different scales, which correspond to various facets of patient’s QOL. The Summary Scores of these 8 scales reflect general physical and mental health.

Methods: The SF-36 Survey questionnaire was administered to narcoleptic patients who met study criteria at baseline, prior to receiving sodium oxybate, and after 6 months of sodium oxybate therapy. Sodium oxybate was taken nightly in equal divided doses, at bedtime and 2.5–4 hours later, starting with a nightly dose of 6 g. The dose was titrated to optimal clinical effect within the range of 3–9 g, with dose changes occurring at 2–4 week intervals. The optimal dose of sodium oxybate was maintained for the duration of the study. Tricyclic antidepressant and serotonin-selective reuptake inhibiting medications were discontinued after a stable dose of sodium oxybate was established. Patients were permitted to remain on stable doses of stimulant medications. SF-36 questionnaires were scored centrally. Scoring the SF-36 survey questions resulted in 8 Scale Scores. These scores were expressed as Norm Based Scores where the mean and standard deviation of the general population are 50 and 10, respectively. The difference in before and after scores was analyzed using student’s two-tailed t-test with significance established at $p < 0.05$.

Results: The nightly administration of sodium oxybate significantly decreased the incidence of cataplexy. A statistically significant improvement was seen in every SF-36 Scale except Bodily Pain. The Physical and Mental Summary Scores also revealed a significant improvement in overall patient QOL. These data are summarized in Table 1.

<table>
<thead>
<tr>
<th>SF-36 SCALE SCORES (N=163-165)</th>
<th>Pre-treatment Mean Score (SD)</th>
<th>Post-treatment Mean Score (SD)</th>
<th>Signif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>46.37 (10.36)</td>
<td>48.67 (9.12)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Role Limitations – Physical</td>
<td>57.15 (11.04)</td>
<td>47.10 (12.32)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>46.59 (10.52)</td>
<td>47.87 (10.28)</td>
<td>$p=0.008$</td>
</tr>
<tr>
<td>General health</td>
<td>45.27 (10.81)</td>
<td>47.47 (10.43)</td>
<td>$p&lt;0.005$</td>
</tr>
<tr>
<td>Vitality</td>
<td>55.59 (9.82)</td>
<td>42.14 (11.35)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Social Function</td>
<td>37.05 (12.15)</td>
<td>32.07 (12.27)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Role Limitations – Emotional</td>
<td>42.57 (12.96)</td>
<td>46.62 (11.95)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Mental Health</td>
<td>43.70 (11.32)</td>
<td>47.82 (10.40)</td>
<td>$p&lt;0.05$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUMMARY SCORES (N=163-165)</th>
<th>Pre-treatment Mean Score (SD)</th>
<th>Post-treatment Mean Score (SD)</th>
<th>Signif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>44.26 (9.57)</td>
<td>46.06 (9.74)</td>
<td>$p&lt;0.05$</td>
</tr>
<tr>
<td>Mental</td>
<td>59.55 (11.96)</td>
<td>44.31 (12.52)</td>
<td>$p&lt;0.05$</td>
</tr>
</tbody>
</table>

Conclusions: A significant improvement in QOL was observed in narcoleptic patients treated with sodium oxybate. This improvement was associated with the significant reduction of cataplexy and other symptoms of narcolepsy in these patients.

References:

Research supported by Orphan Medical, Inc., Minnetonka, MN.

How Common Is The “Classical” Presentation of Narcolepsy in Clinical Practice?

Mehta RM, Chodri T, Mattoo A, Albertario CL, Weinstein MD, Groth ML
Winthrop Sleep Disorders Center

Introduction: The diagnostic criteria for narcolepsy are controversial. The presence of unequivocal cataplexy, observed by a physician, in a patient with excessive daytime somnolence (EDS) is pathognomonic for this disorder (1). Auxiliary symptoms, such as sleep paralysis, hypnagogic hallucinations, automatic behavior and disturbed nocturnal sleep are not unique to this disorder and are present in 25-80% of patients with narcolepsy. Polysomnographic (PSG) parameters for the diagnosis of narcolepsy include short sleep and REM latencies during PSG, increased Stage 1 sleep, and typical abnormalities during Multi-Sleep-Latency-Testing (MSLT): short sleep latency (SL), typically < 5 minutes and 2 or more sleep onset REM periods (SOREM’s). We observed that many patients treated for narcolepsy at our center had atypical presentations and that the combination of EDS and cataplexy was infrequent. We therefore conducted a study to characterize the clinical features and PSG findings of all patients diagnosed with narcolepsy at our institution.

Methods: We retrospectively reviewed all available charts and PSG/MSLT data of patients diagnosed and treated with narcolepsy at our center from January’87 to December’00. All patients had had a full clinical evaluation by one of our sleep physicians and overnight PSG followed by MSLT (33/34 patients, 97%). Demographic data, presenting symptoms, clinical findings and PSG parameters were recorded. Complete data were available for 34 patients.

Results: Nineteen (55.9%) of the patients were males. Mean age was 37.4 years (range 17-76). Ten (29.4%) of the patients were >50 years of age. Mean duration of symptoms prior to diagnosis was 14.5 years (range 4-59). The most common presenting symptom was EDS, seen in 94% of patients, and was the only complaint in 29.4% of patients. The average Epworth Sleepiness Scale (ESS) score was 17.7. Cataplexy was described by only 9 patients (26.5%) at the time of presentation and ultimately developed in 50%. Of the patients with cataplexy, 59% were female. Sleep paralysis was present in 38.2%; hypnagogic hallucinations in 25.6% and parasomnias in 20.6%. Four patients (11.7%) reported frequent naps of 1-2 hour duration. The mean SL was 14.6 minutes and 29.4% of the patients had a PSG REM latency < 20 minutes. MSLT SL averaged 3.34 minutes (range 0.5-7.5) with 3 SOREM’s. Four patients had a concomitant diagnosis of OSA that was treated prior to the diagnosis of narcolepsy; two of these patients described unequivocal cataplexy. All patients have reported improvement in EDS with the use of...
Conclusions: We conclude that the spectrum of narcolepsy in clinical practice is varied and that the classical finding of EDS with cataplexy is present less frequently than previously described, having been seen in only 50% of the patients in our series. A high index of clinical suspicion is required to establish this diagnosis in patients with unexplained EDS. In the absence of cataplexy, a distinction between classical narcolepsy/cataplexy syndrome and its variants was not clinically relevant, as treatment modalities were the same for all patients.

References:

573.K

Experiences that Trigger Cataplexy

Goada A, Krahn LE, Slocumb N, Lymp J, Moore W, Silber MH
Sleep Disorders Center, Mayo Clinic

Introduction: Cataplexy is one of the cardinal symptoms of narcolepsy occurring in approximately 75% of patients. The clinical diagnosis of narcolepsy often hinges on whether a patient has events suggestive of cataplexy. Cataplexy is rarely witnessed and difficult to identify in a clinical interview by a clinician without significant experience with this entity. Standardized questionnaires are critically important to detect probable cataplexy and identify the triggers. A cataplexy questionnaire was published that confirmed the role of laughter and anger as triggers that distinguished cataplexy from other types of muscle weakness (1). The control group consisted of sleep disorder clinic patients without specified diagnosis and not suspected to have “clear cut” cataplexy. The objectives of this study are to verify previous research regarding potential cataplexy triggers and to examine the risk of cataplexy during selected activities including driving (2,3).

Methods: The Stanford cataplexy questionnaire was modified by rewording several questions and adding items related to driving, television, computer games, hunting, fishing, and amusement park rides. The Mayo Narcolepsy Diagnostic Criteria was used to determine that all patients had definite narcolepsy (sleepiness, cataplexy, mean initial sleep latency on MSLT<8 minutes, 2 or more SOREMS, and AHI<10). This narcolepsy classification has been shown to have an interrater reliability of 0.98. Fifty-five patients with narcolepsy-cataplexy completed the modified cataplexy questionnaire as well as 47 obstructive sleep apnea controls (laboratory confirmed). Odds ratios were used to summarize associations. Chi-square statistics were used to determine statistical significance of associations between each question and clear-cut cataplexy.

Results: Table 1 shows the questionnaire data with the emotional triggers in descending order of frequency. Table 2 includes data related to the additional items added to the Stanford questionnaire. 29 out of 35 narcoleptic patients reported “sudden loss of muscle control” while driving compared to 4 out of 45 OSA controls. This represented a twelve fold increased odds of having muscle weakness while driving for narcoleptic patients. (chi-square statistic on 1 degree of freedom, p<0.05 if chisq>3.84, for tables 1 and 2).

Table 1

<table>
<thead>
<tr>
<th>Precipitants</th>
<th>Narcolepsy</th>
<th>Controls</th>
<th>OR</th>
<th>CHISQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV or movies</td>
<td>52</td>
<td>40</td>
<td>1.09</td>
<td>28.3</td>
</tr>
<tr>
<td>Computer or arcade games</td>
<td>22</td>
<td>9</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Driving</td>
<td>53</td>
<td>29</td>
<td>4.2</td>
<td>22.9</td>
</tr>
<tr>
<td>Hunting</td>
<td>18</td>
<td>9</td>
<td>3.7</td>
<td>7.9</td>
</tr>
<tr>
<td>Fishing</td>
<td>30</td>
<td>14</td>
<td>2.1</td>
<td>14.1</td>
</tr>
<tr>
<td>Amusement park rides</td>
<td>35</td>
<td>17</td>
<td>1.7</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Conclusions: This study confirms the observation that laughter clearly was the most important trigger for differentiating cataplexy from other types of muscle weakness (1). In our study excitement and surprise were more specifically associated with cataplexy than anger. The occurrence of cataplexy while driving represents an important safety issue and reinforces the need to ask narcolepsy patients about cataplexy triggered by surprise, laughter etc while driving. The association of cataplexy with television shows indicates the possibility of potentially incorporating this modality into a provocative objective cataplexy test.

References:

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Chronic Administration of Sodium Oxybate Produces Significant and Long-Term Improvements in Narcolepsy Symptoms

Hagaman MH
Sleep Medicine Associates, Nashville, TN

Introduction: Narcolepsy is a chronic disorder consisting of the following symptoms: excessive daytime sleepiness (EDS), cataplexy, disturbed nocturnal sleep, hypnagogic hallucinations and sleep paralysis. Until recently, no medication has effectively controlled this myriad of symptoms. Sodium oxybate has been shown to decrease the incidence and severity of these symptoms (1). A double-blind placebo-controlled trial, followed by an open-label extension trial, was conducted to determine the safety and efficacy of sodium oxybate in narcolepsy patients at fixed, randomized doses and after titration to optimal clinical effect.

Methods: Prior to beginning the study, patients were tapered from hypnotic or antidepressant medications. Of note, fixed doses of stimulants
were permitted throughout both trials. During a 14 to 21-day baseline period, narcolepsy-related symptoms were recorded and patients who experienced at least 3 cataplectic attacks per week were enrolled. In double-blind fashion, patients were randomly assigned to 3 g, 6 g, 9 g sodium oxybate or placebo groups. One-half of the dose was administered at bedtime and the remainder 2.5-4 hours later. Patients remained on their dose of sodium oxybate or placebo for up to 4 weeks. Patients who completed the trial were eligible to enter an open-label extension trial after a 3-5 day washout period. During the open-label phase, patients were started on a nightly 6 g dose and then titrated to optimal clinical effect within the range of 3-9 g with dose changes made at 2-4 week intervals. Once an optimal dose was established, each patient remained on that dose until the study was concluded. Cataplexy and other symptoms were recorded daily in patient diaries. EDS was measured using the Epworth Sleepiness Scale (ESS). The Clinical Global Impression of Change (CGI-c) was utilized to measure changes in overall severity of illness.

**Results:** Initially, 136 narcolepsy patients were enrolled from 18 participating sleep centers in the double-blind trial; 118 of these patients entered the open-label phase and 80 completed it. During the double-blind phase, the 9 g dose significantly reduced the episodes of weekly cataplexy, inadvertent daytime naps/sleep attacks and nighttime awakenings (p < 0.05). ESS and CGI-c scores were also significantly improved (p < 0.05). The 6 g dose substantially reduced the incidence of cataplexy, and significantly decreased inadvertent daytime naps/sleep attacks (p < 0.05). In the open-label study, these clinical improvements became maximal for EDS and cataplexy attacks after 2 and 3 months, respectively, from the beginning of the double-blind trial (for each, p < 0.05) and were maintained through the 12-month study. In addition, nocturnal awakenings, hypnagogic hallucinations and sleep paralysis all showed continuous improvement trends over 12 months of stable dosing.

**Conclusions:** Sodium oxybate effectively reduces the episodes of cataplexy, EDS and nocturnal awakenings. After significant improvements occurred, there were no signs of tolerance over a 12-month period. Sodium oxybate may be an effective and safe medication in the treatment of narcolepsy.

**References:**

This research was conducted by the U.S. Xyrem(R) Multicenter Study Group with the support of Orphan Medical, Inc., Minnetonka, MN.

575.K

**The Narcolepsy Diagnosis: Comparison Between the Sleep-EVAL System and Clinicians**

**Black J, Ohayon M, Okun M, Guilleminault C, Mignot E, Zarcone V**

Sleep Disorders Center, Stanford University

**Introduction:** Narcolepsy is a disabling sleep disorder manifesting excessive daytime sleepiness, and is characterized by an imperative need to sleep suddenly and for brief periods. This disorder affects from 20 to 67 individuals per 100,000. This study aims to determine the validity of the Sleep-EVAL system, a diagnostic tool for evaluating sleep disorders in the general population, in discerning the clinical complexity of narcolepsy.

**Methods:** Ninety-six narcoleptic individuals and their family members (father, mother, brothers and sisters) were interviewed by telephone using the Sleep-EVAL system. First, the narcoleptic subject was contacted and s/he provided information regarding his/her family members. Almost all individuals (96%) contacted were willing to participate in the study. A control group was also assessed. This group consisted of unrelated individuals (friend or spouse) to the narcoleptic subject. Information collected by the system included 1) a complete description of narcolepsy symptoms (daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, automatic behavior and disturb nocturnal sleep), 2) daytime functioning, 3) sleep habits, and 4) sleep and psychiatric disorders according to the DSM-IV and ICSD classifications. Validations were performed between the Sleep-EVAL diagnosis and 1) the first diagnosis given by the usual physician of the subject; and 2) the consensus diagnosis of four sleep specialists reviewing each clinical observation. These observations were obtained from each participant during the Sleep-EVAL interview. The resulting clinical vignettes were reviewed by the four sleep specialists who highlighted the main symptoms underlying each of their three diagnoses. A diagnostic consensus was established when three of the four specialists gave the same diagnosis. This diagnostic consensus was then compared to that provided by the Sleep-EVAL system.

**Results:** The final sample included 518 subjects: 96 narcoleptics (61 women and 35 men), 89 fathers, 89 mothers, 91 sisters, 68 brothers and 85 control subjects (43 women and 42 men). The mean age for the narcoleptic subjects was 30.4±10.3 years. Episodes of cataplexy were reported by 88 subjects (80 were narcoleptic individuals). The most frequent reported cataplexy symptom was muscle weakness affecting the hands and/or the arms. Complete loss of muscle tone (paralysis) was almost exclusively reported by narcoleptic subjects. Based on the information collected during the interview, the Sleep-EVAL system adequately recognized 91 narcoleptic subjects (kappa 0.96). Five narcoleptics did not report symptoms associated with the narcoleptic tetrad (cataplexy, sleep paralysis, hypnagogic & hypnopompic hallucinations, excessive daytime sleepiness). The conclusions from the four sleep specialists are still under process and will be provided.

**Conclusions:** Our aim is to reliably identify narcoleptic individuals based on self-report information. The results of the first part of this study show that Sleep-EVAL performs adequately. However, the results of the second part will allow us to draw a more definitive conclusion.

**References:**
(1) Ohayon MM. Improving decision making processes with the fuzzy logic approach in the epidemiology of sleep disorders. J Psychosom Res 1999;47:297-311.

576.K

**The Comparability of the Stanford Sleep Inventory and the Sleep-EVAL System in Narcolepsy Diagnosis**

**Okun ML, Ohayon MM, Mignot E**

Stanford University

**Introduction:** Traditional tools to recognize narcolepsy in the general population are scant. The Stanford Sleep Inventory (SSI) was developed at the Stanford Sleep Disorders Clinic. The SSI is a self-reporting, paper and pencil questionnaire that asks about symptoms that comprise the narcolepsy syndrome and other sleep disorders with special emphasis on cataplexy. Data from the SSI, clinical files, results of PSG, MSLT (if available) were used by the Center of Narcolepsy to establish a final diagnosis of narcolepsy. The Sleep-EVAL System is a computerized diagnostic tool based on a collection of sleep and psychiatric symptomatology. Its goal is to establish a diagnosis, which is continually refined throughout the interview. This allows improvement of the decision-making process of rare syndromes and their manifestations in the general population. This study presents the results of a comparison between clin-
ical assessment of narcolepsy and the Sleep-EVAL system for narcoleptics, their family members and control subjects.

**Methods:** A sample of 96 narcoleptic individuals (61 women and 35 men, mean age of 30.4±10.3 years) and their family members: 89 fathers, 89 mothers, 91 sisters, 68 brothers, were interviewed by telephone using the Sleep-EVAL system. A control group of 85 unrelated subjects (friend or spouse: 43 women and 42 men, mean age of 32.4±11.3 years) was also interviewed. The information to call family members and control subjects was provided by the narcoleptic individual upon first telephone contact. Almost all of these individuals (96%) accepted to participate in the study. Information collected by the Sleep-EVAL System included 1) a complete description of narcolepsy symptoms (daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis); 2) daytime functioning; 3) sleep habits; and 4) sleep and mental disorders diagnoses according to the DSM-IV and ICSD classifications. A computerized version of the Stanford Sleep Inventory sections assessing narcolepsy-related symptoms was also administered.

**Results:** The Sleep-EVAL System correctly identified 95% (91/96) of narcoleptic subjects as compared to 74% for the SSI. None of the control subjects were identified as narcoleptics by the SLEEP-EVAL system. Results from family members will be presented. The differences in results are mainly due to a better recognition of other sleep disorders by the sleep-EVAL System. In addition, its ability to make differential diagnoses during the process of the interview itself allows elimination of ambiguous diagnoses not relevant to the subject.

**Conclusions:** The use of a computerized diagnostic tool such as Sleep-EVAL, provides a method for non-sleep specialists to diagnose narcolepsy in the context of family studies. It is able to achieve a diagnosis using fuzzy answers (e.g., always, often, sometimes, rarely, never) with results superior to those obtained with a paper-pencil questionnaire.

**References:**
(1) Ohayon MM. Improving decision making processes with the fuzzy logic approach in the epidemiology of sleep disorders. J Psychosom Res. 1999; 47:297-311.

577.K

Long-term (136 Weeks) Safety and Efficacy of Modafinil for the Treatment of Excessive Daytime Sleepiness Associated With Narcolepsy

*Hirshkowitz M, Schwartz J, Corser B, Sahota P*

(1) VA Medical Center, Houston, TX, (2) Integris Sleep Disorders Centers of Oklahoma, Oklahoma City, OK, (3) Community Research Management Assoc., Cincinnati, OH, (4) University of Missouri, Columbia, MO

**Introduction:** The purpose of this study was to assess the safety and efficacy of modafinil (PROVIGIL) during long-term treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy. Modafinil has been available in the US for nearly 2 years, and has been commercially available in Europe for over 6 years. Since its introduction in the US, modafinil has become the drug of choice for patients with excessive daytime sleepiness, due to its unique efficacy and safety profile. Modafinil was effective and well tolerated in two large-scale clinical trials in 558 patients. Continued long-term efficacy and safety from subsequent open-label trials have previously been demonstrated for up to 40 and 88 weeks. We report here safety and efficacy data in patients taking modafinil for up to 136 weeks (>2.5 years).

**Methods:** 86% of patients (478/558) entered the 40-week, open-label phase of treatment after undergoing a 2-week washout period after the double-blind trials. Patients received modafinil 200 or 400 mg/day. 53% of patients (254) from the double-blind trials were still receiving modafinil during Weeks 88-136. Efficacy of modafinil for EDS was assessed using the patient-rated Epworth Sleepiness Scale (ESS). Safety was assessed by recording adverse events (AEs).

**Results:** A total of 214 patients completed 136 weeks of open-label treatment with modafinil. The most common treatment-related AEs for Weeks 0-40 were headache (13%), nervousness (8%), and nausea (5%) (Table 1). For Weeks 40-88 and Weeks 88-136, the most common treatment-related AEs were headache (9% and 7%, respectively) and dry mouth (5% and 6%, respectively). During Weeks 0-40, 9% of patients discontinued treatment because of AEs compared with 2% during Weeks 40-88 and 4% during Weeks 88-136. Over the 136-week period, 76 patients (16%) discontinued treatment because of insufficient efficacy, which included only 22 patients (5%) who discontinued during the last 96 weeks of treatment. The mean ESS score at Week 0 after the washout period was 16.5 (Figure 1). After 2 weeks of treatment, the mean ESS score decreased to 12.4 (P<0.001). Mean ESS scores ranged from 11.8 to 12.9 for Weeks 8-136. During the 136-week period, the majority of patients (range 74% to 83%) were receiving 400-mg maintenance doses of modafinil, with no significant increase in the percentage of patients taking 400-mg doses as time progressed.

**Table 1**

<table>
<thead>
<tr>
<th>Percent of Patients Experiencing Adverse Events (AEs ≥2.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double Blind</td>
</tr>
<tr>
<td>Treatment-Related AE</td>
</tr>
<tr>
<td>N =</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nervousness</td>
</tr>
<tr>
<td>Nausea</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Dry mouth</td>
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<tr>
<td>Somnolence</td>
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<tr>
<td>Cataplexy</td>
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<tr>
<td>Insomnia</td>
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<td>Diarrhea</td>
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<td>Anorexia</td>
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<tr>
<td>Amblyopia</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Dizziness</td>
</tr>
</tbody>
</table>

**Conclusions:** Long-term modafinil treatment in narcolepsy patients with excessive daytime sleepiness appears to be very well tolerated after more than 2.5 years. Side effects with modafinil were mild to moderate
A trial of modafinil for the treatment of pathological somnolence in narcolepsy. 

**References:**


**Supported by Cephalon Inc., West Chester, PA**

**578.K**

**Hypocretin (Orexin) Levels in Human Lumbar CSF in different Age Groups**


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**Introduction:** Hypocretins / Orexins are newly discovered hypothalamic peptides. These peptides have aroused interest among sleep researchers because two recent reports disclosed a dysfunction of hypocretin neurotransmission in animal models of narcolepsy (1). Subsequently, it was found that impaired hypocretin neurotransmission is also involved in human narcolepsy (2). Extensive studies in human narcolepsy suggest that CSF hypocretin measures could be used as a diagnostic tool for narcolepsy or other neurological diseases (Nishino et al and Kanbayashi et al in this issue). Although the levels in healthy adults fall in a relatively narrow range (250 - 280 pg/ml) (2), whether CSF hypocretin-1 levels fluctuate due to various conditions, such as age or gender, is not well known. In order to investigate the developmental change of CSF hypocretin concentrations, we measured CSF hypocretin levels across an age range from infants to elderly people (two month to 79 years old).

**Methods:** Since it was not easy to obtain CSF samples from healthy controls, we used samples of CSF samples previously collected for diagnostic purposes. One hundred nineteen patients were included in this study, with 68 male and 51 females (Table 1). These patients were admitted to several hospitals in Akita City. The patients were diagnosed by clinical inspection, radiological and clinical examinations. The CSF samples were obtained by lumbar puncture for routine diagnostic purpose. Either patients or families gave informed consent for the lumbar puncture. CSF samples were kept in a -80°C refrigerator. CSF hypocretin was measured using radioimmunoassay kits (Phoenix Pharmaceuticals, Mountain View, CA) as previously reported (2). All results are reported as the mean and standard deviation (SD). Comparisons of generations and genders were made by using one way and two way ANOVA. Since samples from patients with narcolepsy (2) and Guillain Barre Syndrome (Ripley et al in this issue, Kanbayashi et al in this issue) showed significantly lower hypocretin 1 levels, these samples were excluded from the statistical analysis.

**Results:** The mean CSF hypocretin levels of each generation are shown in Table 1. In our sample population, there was no significant difference overall between females (299 ± 60 pg/ml) and males (286 ± 54 pg/ml), nor within any age group (data not shown). We also did not observe any significant differences among age groups (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Mean+/-SD</th>
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<tr>
<td>5-9</td>
<td>13</td>
<td>276 +/-72</td>
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<tr>
<td>10-14</td>
<td>11</td>
<td>287 +/-60</td>
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<tr>
<td>15-20</td>
<td>8</td>
<td>287 +/-60</td>
</tr>
<tr>
<td>20-29</td>
<td>11</td>
<td>304 +/-55</td>
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</tbody>
</table>

**Conclusions:** Yamamoto reported in a rat study that expression of the prepro-hypocretin gene was weakly detected at postnatal day 0 and increased gradually from neonatal and infantile periods (3). In the juvenile period, prepro-hypocretin gene expression markedly increased. After this period, there were no significant changes in the expression between pubertal and adult period. In the current study, we have samples from 3 infants (two, 3 and 8 month of age). However, CSF hypocretin levels are consistently detected in these infants. Although our samples constitute a heterogeneous group of neurological conditions, hypocretin levels are not different in respect to gender or generations. Thus, the undetectable CSF hypocretin levels seen in narcolepsy are an abnormal finding at any age. It is therefore interesting to know when the decline in CSF hypocretin levels occurs in patients with narcolepsy, as this is critical information in further understanding the pathophysiology of the disease.

**References:**


This research supported by a grant from the Japanese Ministry of Health and Welfare, and Special Coordination Funds for Promoting Science and Technology from the Science and Technology Agency.

**579.K**

**Hypocretin / Orexin Concentrations in CSF Are Low in Patients with Guillain Barre Syndrome**


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**Introduction:** Hypocretins /orexins are recently discovered hypothalamic peptides that are associated with feeding, energy homeostasis and the neuroendocrine system (1). These peptides have aroused interest in light of two recent reports linking dysfunction of the hypocretin peptide/receptor system to animal models of narcolepsy (1). In 2000, Nishino reported that hypocretin 1 in the cerebrospinal fluid (CSF) was significantly low in patients with narcolepsy (2). Human narcolepsy has been shown to be closely associated with a specific HLA (3). Since most
diseases associated with a specific HLA are autoimmune in nature, the finding suggests that autoimmunity is involved in the pathophysiology of narcolepsy. However, at present, all attempts to demonstrate that human narcolepsy is an autoimmune disease have failed. Thus, it is important to know whether hypocretin changes are found in any definite neuroimmunological diseases (NID).

**Methods:** CSF samples were obtained from Japanese patients with 17 NID (ten Guillain Barre Syndrome [GBS], 7 Multiple Sclerosis [MS], and 16 non-NID (Parkinson disease [n=6], cerebral infarction [n=5], and epilepsy [n=5]). The diagnosis was made by neurologists based on the clinical inspection, radiological, laboratory testings and systematic clinical examinations. Patients gave informed consent for the lumbar puncture. CSF levels of hypocretin 1 were measured using RIA kits (Phoenix Pharmaceuticals, Mountain View, CA) as previously reported (2). Statistical analysis was made by using one way ANOVA and Fisher’s exact probability test.

**Results:** CSF hypocretin 1 levels did not differ between the non-NID patients (281 ± 42 pg/ml, [mean ±SD], n=16, Table1) and normal controls (2). Hypocretin 1 in MS patients (261 ± 61 pg/ml, n=7) did not differ from those in non-NID patients and are in the control range. On the other hand, GBS patients had significantly lower hypocretin 1 levels (214 ± 70 pg/ml, n=10) than non NID patients (p<0.005, Fisher’s PLSD ). The standard deviation of hypocretin levels in GBS is large, and levels are in the normal range for some patients. However, levels in 4 out of 10 subjects are lower than 200 pg/ml, in contrast to MS and non NID, only 1 out of 23 patients had levels below 200 pg/ml in these patients (p< 0.02, Fisher’s exact probability test, Fig1).

**Figure 1**

Conclusions: GBS is an acute, immune-mediated polynuropathy characterized by rapidly progressive muscle weakness. An elevation in the CSF protein content with normal cell count is one of the characteristics of the disease, and antibodies to gangliosides are seen in sera and CSF of about one-fourth of patients. In the samples of GBS patients in this study, there was no clear relation between the CSF hypocretin levels and CSF protein levels, the severity of disease, period from the disease onset to lumbar puncture and the duration of the sample storage. The decreased level of hypocretin 1 in patients with GBS was also observed in a separate experiment (Ripley et al in this issue). The meaning of these results should be considered in further studies.

**References:**

This research supported by a grant from the Japanese Ministry of Health and Welfare, and Special Coordination Funds for Promoting Science and Technology from the Science and Technology Agency.

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**580.L.**

**Polysomnographic Verification of the Hypnotic Effect of Dormican**

You G, Zhang K, Zhu S

Department of Neurology, Tangdu Hospital

**Introduction:** Verification of the hypnotic effects of dormican were performed by polysomnographic studies and compared with patients’ subjective sleep quality estimation. In addition, the parts of the sleep structure it acts upon and the side effects shown on PSG were also investigated.

**Methods:** Thirty patients (male 13, female 17, 18-67yrs) with a duration of illness 55.2±75.49 months were studied. The PSG records of each patient on the 10th night after a daily administration of 7.5mg dormican per night were compared with those of the night before drug application (with a night for adaptation before). Sleep latency (SL), number of awakening per night (AW) and total sleep time (TST) were recorded by patients in the same night.

**Results:** 1. Sleep structure changes: (1) The average SL, AW and sleep efficiency improved significantly in patients with abnormal parameters, e.g., from 69.00±60.99 to 14.79±14.87min (P=0.003), 16.60±4.43 to 9.90±4.28 (P=0.003) and 53.1±21.60% to 75.77±11.09% (P=0.000), respectively. (2) No significant changes of deep sleep ratio and morning awakening time were found in all patients. (3) REM sleep improved prominently. For example, SL of 9 patients normalized in 29 abnormal ones with another 2 patients who were proved later to be depressed because of too short SL. The average SL value of these 29 patients drops from 199.25±71.61 to 126.86±56.02 min (P=0.000). The number and ratio of REM sleep increased from 1.65±0.61 to 3.06±1.03 (P=0.000) and 11.54±5.12% to 15.80±5.61% (P=0.005), respectively, in the abnormal group.

2. Subjective-objective comparisons: The coincidence rates of SL and TST before and after drug administration were 40% and 40% as well as 53.3% and 46.7%, respectively. That is, about half of the patients exaggerated the difficulties for sleep-onset and insufficiency of TST even after taking hypnotics. However, the self-estimated AW was comparatively accurate with a coincidence rate of 96.3% and 78.5%, respectively, and even the subjective AW was less than the actual AW (>5 min) recorded by PSG in 50-73% patients. In 7 cases of mild obstructive sleep apnea syndrome (AHI=5.5-26.8), no significant aggravation of apnea occurred. No important cardio-vascular and EEG abnormalities were found.

**Conclusions:** 1. Dormican is an effective and safe short-term hypnotics. However, like all the benzodiazapines, it has no effects of promoting deep sleep. 2. The prominent beneficial action on REM sleep is caused by the improvement of sleep fragmentation, which interferes with the genesis of REM sleep and thus can be utilized for the diagnosis of depressive insomniacs because accurate REM SL may be obtained. 3. Because of the frequent exaggeration of sleep difficulties by the chronic insomniacs, hypnotics over-dose should be avoided.

**References:**

Research supported by Shanghai Roche Pharmaceuticals Ltd.
Assessment of Patients Preferences Between Two Hypnotics, Zolpidem (10mg) vs. Zaleplon (10mg)

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Methods: Twelve general practitioners recruited 53 untreated patients complaining of insomnia characterised by difficulties in falling asleep. No hypnotics or psychotropics were allowed during the seven days before inclusion. Both drugs, zolpidem and zaleplon, were consecutively given at bedtime for 2 nights (Night 1, N1 and Night 2, N2). After each dosing, patients were asked to complete a sleep questionnaire (LSEQ) and a visual analog scale (VAS) to assess the quality of life during both daytime. After the second study night, patient self-assessed preference was established by a quality-of-sleep scale and a drug-preference scale (forced choice). Data analysis about this preference was carried out using the Chi square test, with a statistical significance level fixed at 5%. ANOVA analysis was performed.

Results: The results are the following: in intention to treat (ITT), 53 patients (mean age 52.2 years old; 51% male) were analysed; 62.3% favored zolpidem versus 37.7% for zaleplon (p=0.08). Two items of the LSEQ are in favor of zolpidem respectively: quality of sleep (p<0.0001), quality of the onset of sleep (p=0.03). On the VAS, the subjective appreciation of sleep quality is in favor of zolpidem (p<0.0001): Diurnal awareness and quality of life were very good in both groups with statistical significant difference. The total duration of sleep was 8.3h for zolpidem and 8h for zaleplon (NS). As two patients were excluded (protocol violation), the per protocol analysis lead to similar results. Safety was similar between the two drugs.

Conclusions: In conclusion, insomniac patients preferred the night treated with zolpidem on both nocturnal and diurnal assessments, whether on N1 or N2.

References:

Efficacy and Safety of Discontinuous Zolpidem Treatment - An Exploratory Polysomnographic Study

Cluydts R, Heyde K, De Volder F
(1) Dept. of Psychology, University of Brussels, (2) Sleep-Wake Disorders Center, University Hospital Antwerp, Belgium

Introduction: Today, three non-benzodiazepine hypnotics are available on the market: zopiclone, zolpidem and zaleplon. The physician’s choice between these three drugs is based as much on the insomnia characteristics as on the drugs’ pharmacokinetic properties. In order to help in making this choice we propose an additional argument based on the patient’s preference for a given drug. This was assessed by a double-blind, cross-over, randomised study comparing two consecutive nights after dosing with two different drugs: zolpidem (10mg) and zaleplon (10mg).

Methods: Twelve insomniac patients without significant medical or psychiatric disorders were enrolled in this single-centre, single-blind study. The study commenced in the sleep laboratory with one adaptation night, one night on placebo for baseline PSG and one night on zolpidem, the first of 10 nights alternating zolpidem and placebo treatment. Patients then continued treatment at home, having been given a blister card containing ten tablets and told that these comprised active and inactive treatments in random order, returning to the laboratory for the last four nights. Eight-hour PSG recordings were computer-scored using the Rechtschaffen-Kales criteria, then visually corrected, after blinding, by an experienced technician not otherwise involved in the study. Subjective sleep quality was assessed by questionnaire and next-day psychomotor performance by four-choice reaction test.

Results: A clear and consistent variation in sleep parameters was seen between zolpidem and placebo nights throughout treatment. Objectively measured sleep onset latency and total sleep time improved with zolpidem, without going beyond the baseline value on the intervening placebo nights (Table 1). Subjective assessments of sleep onset latency and sleep quality tended to follow the same pattern as previously reported (3). The alternating schedule was well tolerated. The proportions of sleep stages 1, 2, 3 and 4 and the relative proportion of REM sleep were not significantly affected by zolpidem relative to baseline and varied little between zolpidem and placebo nights. Next-morning psychomotor performance remained constant throughout the study.

Table 1
Sleep onset latency (S.O.L) and total sleep time (T.S.T) with zolpidem (ZOL) and placebo (PLA)

<table>
<thead>
<tr>
<th></th>
<th>Baseline PLA</th>
<th>N1-ZOL</th>
<th>N3-ZOL</th>
<th>N5-ZOL</th>
<th>N7-ZOL</th>
<th>N9-ZOL</th>
<th>N10-PLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.O.L. (min)</td>
<td>36.79</td>
<td>28.25</td>
<td>43.96</td>
<td>49.96</td>
<td>29.33</td>
<td>43.29</td>
<td></td>
</tr>
<tr>
<td>T.S.T. (min)</td>
<td>382.00</td>
<td>425.88</td>
<td>406.17</td>
<td>388.08</td>
<td>426.17</td>
<td>398.38</td>
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</table>

Conclusions: The results of this exploratory study demonstrate the feasibility of discontinuous treatment with zolpidem even under drastic conditions of nightly alternation between zolpidem and placebo. The “start-stop” schedule was well tolerated by the patients and did not affect next morning psychomotor performance. Both objective PSG measurements and subjective evaluation of sleep quality indicated a minimal risk of rebound insomnia.

References:
(2) Walsh JK, Roth T, Jamieson A, Schweitzer PK, Scharf MB, Ware JC,
A Comparative, Double-blind Study of Two Non-benzodiazepine Hypnotics, Zolpidem and Zopiclone, in Patients with Chronic Primary Insomnia


Methods: The patients enrolled in this double-blind, double-dummy study were randomised to receive daily either 10 mg zolpidem or 7.5 mg zopiclone, with the corresponding placebo dummy, for a total of 14 days, after a washout period of up to one week for previously medicated patients. A post-treatment follow-up extending up to one week was included to assess rebound insomnia. The study was designed to test the equivalence of zolpidem and zopiclone with regard to the primary endpoint: the investigator’s rating of global improvement of sleep disorders (modified CGI-2). The criterion of equivalence was 90% CI limits of the rating difference ≤10%.

Results: Results: Altogether 479 patients were randomised in 95 centres throughout Japan (zolpidem: 231, zopiclone: 248), of whom 428 were evaluable for efficacy (zolpidem: 209, zopiclone: 219). Thirty-two patients receiving zolpidem (13.9%) and 45 receiving zopiclone (18.2%) withdrew from the study prematurely. After treatment, 18.7% of the patients in the zolpidem group were rated as “markedly improved” versus 16.4% of those in the zopiclone group. Altogether 67.9% of patients receiving zolpidem were rated as at least “moderately improved” versus 61.6% of those receiving zopiclone. The 90% CI limits of this rating difference were [-1.7%, 14.3%], indicating that zolpidem was at least as effective as zopiclone. Sleep onset latency was improved in more patients with zolpidem (85.8% versus 77.5%, p=0.041). Moreover, rebound insomnia, in terms of exacerbated sleep latency relative to baseline, was less frequent in the zolpidem group (4.5% of patients versus 15.4%, p=0.005). Fewer patients receiving zolpidem reported adverse events (31.3% versus 45.3%, p=0.004) and abnormal post-treatment laboratory results were also less frequent (4.3% of patients versus 10.3%, p=0.028). The pattern of adverse events was similar, except for bitter taste, representing only 5.8% of drug-related adverse events with zolpidem versus 39.9% with zopiclone. Adverse events prompted the premature withdrawal of fourteen patients in the zolpidem group (6.6%) and 20 patients in the zopiclone group (8.9%).

Conclusions: Zolpidem was at least as effective as zopiclone in achieving overall sleep improvement in patients with chronic primary insomnia and improved sleep latency relative to baseline in more patients. At the same time, zolpidem was better tolerated and induced significantly less rebound insomnia with regard to sleep onset latency after abrupt treatment discontinuation. The good efficacy and safety of zolpidem observed in this study are consistent with previously published data for patients and healthy volunteers (1.2).

References:

Introduction: Surveys in Japan have indicated that around 12% of the population suffer from chronic insomnia. Newer, non-benzodiazepine hypnotics have been shown to be as effective as benzodiazepines and safer in treating this disorder. The purpose of this study was to compare the efficacy and safety of two non-benzodiazepine hypnotics, zolpidem and zopiclone, in patients with chronic primary insomnia.

Methods: The patients suffering of a sleep disorder other than insomnia are excluded. Furthermore, exclusion criteria also include suffering of a medical disorder interfering with sleep or a major psychopathology as well as using a medication disrupting sleep architecture. The insomnia duration (INS and INSBZ) was of 25.8 years (SD = 15.7), the duration of BZD use (INSBZ) was 13.5 years (SD = 10.0) and the frequency of BZD use (INSBZ) was 6.6 nights/week (SD = 1.1). Objectively, sleep is assessed through polysomnographic recordings (PSG) while measures from the sleep diary reflect the subjective quality of sleep. Neuropsychological measures assessing attention, concentration, memory, executive functions and reaction time constitute the objective evaluation of performance. Participants also estimate the subjective perception of performance after the Neuropsychological testing.

Results: A correlational study reveals that cognitive performance and quality of sleep are associated, but differently among the three groups, for both subjective and objective measures. There are positive relations between sleep quality and cognitive performance, for objective as well as subjective measures (r = .44 to r = .85; a = .05; Table 1). In that regard, insomniacs have more difficulty to accurately estimate their cognitive performance than good sleepers. On the other hand, BZD users and drug-free insomniacs appear more accurate in their estimations of sleep than good sleepers.
Table 1

<table>
<thead>
<tr>
<th>Objective measures of sleep and performance</th>
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<tbody>
<tr>
<td>SOL</td>
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<tr>
<td>--------------------------------------------</td>
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<tr>
<td>Good Sleepers</td>
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<tr>
<td>VVM</td>
</tr>
<tr>
<td>PS</td>
</tr>
<tr>
<td>AC</td>
</tr>
<tr>
<td>EF</td>
</tr>
<tr>
<td>Insomniacs without medication</td>
</tr>
<tr>
<td>VVM</td>
</tr>
<tr>
<td>PS</td>
</tr>
<tr>
<td>AC</td>
</tr>
<tr>
<td>EF</td>
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<tr>
<td>Benzodiazepine Users</td>
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<tr>
<td>VVM</td>
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<tr>
<td>PS</td>
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<tr>
<td>AC</td>
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<td>EF</td>
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Note. VVM = Visual/verbal memory; PS = Psychomotor speed; AC = attention/ executive functions; EF = Reaction Time; Digit span (backward); PS = Purdue.

Conclusions: Although high cortical arousal in insomniacs might contribute to their misperceptions about performance, it could also enhance their ability to perceive slight variations in sleep depth. Insomniacs may also spend more energy to maintain a good performance despite a poor sleep quality. Furthermore, benzodiazepine intake, even if chronic, might also alter performance perceptions.

Research supported by Fonds de la recherche en santé du Québec

Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW

Quantitative Criteria for Insomnia

Introduction: Diagnostic manuals (ICSD, DSM-IV) avoid setting quantitative criteria for insomnia. This creates interpretation problems when comparing treatment efficacy across clinical trials and epidemiological surveys, because insomnia criteria vary widely. This paper surveyed psychology clinical trials to determine modal insomnia criteria, evaluated these criteria through sensitivity-specificity analyses, and produced a recommendation for quantitative criteria.

Methods: We found 61 clinical trials for insomnia during the period 1980 to 1999, and we tabulated their insomnia admission criteria with respect to frequency, severity, and duration. We then tested a series of these criteria on a randomized sample of 772 volunteers. We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Volunteers completed 14 sleep diaries.

Results: Frequency varied between 1 and 4 nights/week, but ≥ 3 nights/week was adopted in 55% of the studies, and this was 2.1/2 times more common than the next most common frequency criterion. Duration varied between 1 month and 5 years. 61% of studies adopted a 6-month criterion, and this was 3.1/2 times more common than the next most common duration criterion. Three modes emerged for severity as measured by wake time at sleep onset or during the night: ≥ 30 minutes, ≥ 30 minutes, or ≥ 60 minutes. We also computed the mean severity across studies and this was about ≥ 40 minutes. We combined the criteria of 3 nights/week and 6 months duration with each of the severity criteria, and then applied these four criteria sets to our sample. Individuals were classified as having insomnia if they reported an insomnia complaint having lasted at least 6 months. Sensitivity descended from 82.2% to 44.1% as the severity criteria graduated from ≥ 30 minutes to ≥ 60 minutes. Specificity ascended from 61.3% to 89.6% over this same range of severity criteria. Further, we calculated the error rate as the sum of false positives and false negatives divided by the full sample size. ≥ 30 minutes produced the worst error rate, 32.0%. The other three criteria varied within the narrow range of 25.0% to 26.0%. In selecting a severity criterion, we applied three standards: (a) minimizing the error rate, (b) exhibiting the best balance of sensitivity and specificity, and (c) a criterion that would gain the broadest acceptance among researchers. ≥ 30 minutes was selected because it had one of the lowest error rates, produced the smallest discrepancy between sensitivity and specificity, and registered the strongest mode of use in the published studies. ≥ 40 minutes was a close second. Strong arguments could be made for rejecting ≥ 30 minutes and ≥ 60 minutes.

Conclusions: We recommend the following quantitative criteria for insomnia in research studies: (1) frequency ≥ 3 nights/week, (2) duration ≥ 6 months, and (3) severity > 30 minutes latency or wake time. Health providers may find these standards useful, but this recommendation is not intended to encumber the clinical judgement of providers.

Research supported by National Institute on Aging grants AG12136 and AG14738.

587.L

Clock Monitoring in the Maintenance of Insomnia

Harvey AG, Schmidt DA

University of Oxford

Introduction: Attentional bias toward threat-related material has been implicated as a trigger to threat perception and excessive negatively toned cognitive activity across a range of psychological disorders (Williams et al., 1997). In the context of insomnia, clinical observation (Morin, 1993) has implicated clock watching during the pre-sleep period as a trigger for excessive negatively toned pre-sleep cognitive activity. The present study was designed to index the effect of clock watching during the pre-sleep period on sleep-onset latency and worry about not getting enough sleep. There were three predictions: (1) that participants instructed to monitor the clock would take longer to get to sleep than participants instructed not to monitor the clock, (2) on the basis that one mechanism by which clock monitoring may be detrimental to sleep onset is that it triggers worry, we expected that participants instructed to monitor the clock would report that worrying about how long it was taking them to fall asleep interfered with getting to sleep more than participants instructed not to monitor the clock, and (3) on the basis of previous findings showing that a simple cognitive manipulation can induce a ‘state’ of insomnia in good sleepers we reasoned that hypotheses 1 and 2 would hold for both good sleepers and insomniacs.

Methods: Sixty adults participated; 30 good sleepers and 30 insomniacs. Good sleepers and insomniacs were randomly allocated to one of two experimental conditions. In the first, participants were instructed to monitor the clock during the pre-sleep period. In the second, participants were instructed not to monitor the clock during the pre-sleep period. Sleep onset latency was measured by self-report and actigraphy. Worry was measured by self-rating. Manipulation checks were included to check compliance with task instructions, plausibility of the rationale, and expectation that the task would aid falling asleep.

Results: The results indicated that participants instructed to monitor the clock experienced longer sleep onset latency (subjective rating p < .001, actigraphy p < .01) and more worry (p < .01) about falling asleep compared to participants instructed not to monitor the clock. These findings were observed across diagnostic status. Interestingly, instructions to monitor the clock lead participants to overestimate sleep onset latency relative to instructions not to monitor the clock (p < .01). This finding
may be explicable with reference to two factors. First, previous research indicates that time seems longer as the number of units of information processed per unit of time is increased. Monitoring the clock involves processing more units of information than not monitoring the clock. Second, detailed analysis of the actigraphic data revealed that in the first 60 minutes after sleep onset those instructed to monitor the clock had more awakenings than those instructed not to monitor (p < 0.001). It is possible that these awakenings may have been perceived by the participant as continuous wakefulness (Knab & Engel, 1988).

Conclusions: Consistent with the predictions, the present study demonstrated that monitoring the clock lead to longer sleep onset latency and more worry about not getting to sleep compared to not monitoring the clock. Interestingly, clock monitoring was associated with less inaccurate perception of sleep onset latency. These findings are consistent with previous clinical observations and support the hypothesis that clock checking may be involved in the maintenance of insomnia.

References:

588.L

Attentional Processes in Insomnia: The Role of Monitoring the Environment and the Body for Sleep Related Cues

Neitzert Semler C, Harvey AG
University of Oxford

Introduction: Previous research has implicated heightened attention focus and monitoring of body sensations in the maintenance of a range of psychological disorders (Barsky, Wyshak, & Klerman, 1990; Ehlers & Breuer, 1995). Monitoring processes have also been highlighted as of potential importance in the maintenance of insomnia (Harvey, 2000). The present study was undertaken to investigate the following six types of monitoring among insomniacs and good sleepers: (1) monitoring of physical state/body sensations during the pre-sleep period for bodily signs consistent with falling asleep (e.g., slowed heart rate, loss of muscle tone, physical signs of “drifting off”), (2) monitoring of the environment during the pre-sleep period for signs of not falling asleep (e.g., being able to hear a dog barking and for noises outside and inside the house), (3) monitoring of the clock during the pre-sleep period to see how long it is taking to fall asleep, (4) monitoring of physical state/body sensations on waking for signs of poor sleep (e.g., sore head, achy and heavy eyes), (5) monitoring of physical state/body sensations during the day following a bad night of sleep for signs of fatigue (e.g., heavy legs, sore shoulders), and (6) monitoring of the clock on waking to determine how many hours of sleep were obtained.

Methods: Eighty participants between 18 and 35 years of age (40 good sleepers and 40 insomniacs) completed an extensive semi-structured interview assessing for the presence, nature and consequence of each of the six types of monitoring. Measures included an assessment of the frequency of each type of monitoring, along with associated thoughts, emotions, and safety behaviors.

Results: The results indicated that insomniacs attended to time and noise in their environment more frequently than good sleepers during pre-sleep and reported more frequent attention to their bodily sensations on waking compared to good sleepers. Insomniacs reported more negative thoughts, more negative emotion and greater use of safety behaviors as a consequence of monitoring. A path analysis indicated that frequency of attending to cues related to sleep was positively related to negative thoughts, and that negative thoughts in turn were positively related to both negative emotion and safety behaviors.

Conclusions: These findings suggest that heightened attention to and monitoring of body state and the environment for sleep-related cues during the pre-sleep period, on waking and during the day following a poor night of sleep may perpetuate insomnia.

References:

589.L

Expanded Symptom Recognition in Severe Insomnia

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Introduction: While sleep parameters are often used in quantifying insomnia, additional symptoms contribute to its severity. To characterize these, this study examined symptom number, severity, type, and diagnostic association in severe insomnia patients.

Methods: Chart data were reviewed from 94 (40 male, 54 female; mean age = 46 ± 14 S.D.) clinically-referred patients with a chief complaint of insomnia and diagnosed with DSM-IV Primary Insomnia, or Insomnia related to another disorder. Data included ICD diagnoses; clinician-reported symptoms; patient-endorsed items from the Survey of Sleep (SOS), a sleep history questionnaire; Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS); and Beck Depression Index (BDI). Primary diagnoses were categorized into four subgroups: primary insomnia (PI)(N=50), depression-related(DR)(31), anxiety-related(AR)(6), and other(O)(7). Selected ANOVAs were used in an exploratory manner to explore symptom differences between subgroups.

Results: The seven clinicians reported an average 13 symptoms per patient. Patients reported an average of 19 symptoms including long sleep latency (53 min. ± 52 S.D.), and short sleep hours (5.0 ± 1.7). Of SOS completers (N=83), 79% endorsed their problems as severe and occurring daily, and 83% with insomnia longer than one year. Those within the DR subgroup, controlling for sex, had a higher SOS total symptom count than the PI subgroup (p < 0.007), but not for clinician-reported symptom totals. Only 14% endorsed sleeping better away from home. While 55% endorsed taking some naps, only 12% did so daily. The PSQI total score mean (13.2 ± 3.4 S.D.) reflected very poor sleep quality. While ESS scores (4.7 ± 4.6 S.D.) indicated low tendency to doze, 36% endorsed a moderate or severe daytime sleepiness feeling on the SOS. Even within the DR subgroup, the BDI ratings generally were not severe (15.6 ± 9). The 20 most frequent symptom types mentioned by clinicians (Table 1) and endorsed on the SOS (Table 2) included significant daytime symptoms or disabilities (11 and 7, respectively). In general, individual symptom occurrence percentages did not vary appreciably by subgroup from either clinician reports or patient endorsements. Table 1 suggests the domains of sleep, energy/alertness, and mood/cognitive variables; whereas that of Table 2 suggests those of sleep, sleep/wake transition problems, and impaired daytime function.
Table 1

<table>
<thead>
<tr>
<th>Clinician-Reported Symptoms</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Sleep Latency</td>
<td>61</td>
<td>65%</td>
</tr>
<tr>
<td>Daytime Fatigue</td>
<td>61</td>
<td>65%</td>
</tr>
<tr>
<td>Numerous Wakenings</td>
<td>56</td>
<td>60%</td>
</tr>
<tr>
<td>Difficulty Returning to Sleep</td>
<td>53</td>
<td>56%</td>
</tr>
<tr>
<td>Depression</td>
<td>50</td>
<td>53%</td>
</tr>
<tr>
<td>Difficulty with concentration</td>
<td>45</td>
<td>48%</td>
</tr>
<tr>
<td>Uses a sleeping pill frequently</td>
<td>43</td>
<td>46%</td>
</tr>
<tr>
<td>General Worry</td>
<td>42</td>
<td>45%</td>
</tr>
<tr>
<td>Insufficient sleep hours</td>
<td>40</td>
<td>43%</td>
</tr>
<tr>
<td>Loss of Energy</td>
<td>40</td>
<td>43%</td>
</tr>
<tr>
<td>Nighttime Restlessness</td>
<td>39</td>
<td>41%</td>
</tr>
<tr>
<td>Irritability</td>
<td>37</td>
<td>39%</td>
</tr>
<tr>
<td>Feels Tense</td>
<td>34</td>
<td>36%</td>
</tr>
<tr>
<td>Awakes Too Early</td>
<td>33</td>
<td>35%</td>
</tr>
<tr>
<td>General Anxiety</td>
<td>33</td>
<td>35%</td>
</tr>
<tr>
<td>Low Motivation</td>
<td>33</td>
<td>35%</td>
</tr>
<tr>
<td>Has Light Sleep</td>
<td>30</td>
<td>32%</td>
</tr>
<tr>
<td>Mind Can’t Stop at Bedtime</td>
<td>29</td>
<td>31%</td>
</tr>
<tr>
<td>Has daytime sleepiness</td>
<td>29</td>
<td>31%</td>
</tr>
<tr>
<td>Loss of Task Productivity</td>
<td>29</td>
<td>31%</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Responses from the SOS</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some aspect of daytime function suffers</td>
<td>72</td>
<td>89%</td>
</tr>
<tr>
<td>Difficulty staying asleep</td>
<td>66</td>
<td>82%</td>
</tr>
<tr>
<td>Functional interference with work, or others</td>
<td>66</td>
<td>82%</td>
</tr>
<tr>
<td>Awake for no particular reason</td>
<td>62</td>
<td>75%</td>
</tr>
<tr>
<td>Awakening early and unable to fall back asleep</td>
<td>60</td>
<td>73%</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>59</td>
<td>71%</td>
</tr>
<tr>
<td>Anxious, tense, or worrying at bedtime</td>
<td>59</td>
<td>71%</td>
</tr>
<tr>
<td>Frequent tossing and turning</td>
<td>59</td>
<td>71%</td>
</tr>
<tr>
<td>Low energy in morning</td>
<td>59</td>
<td>71%</td>
</tr>
<tr>
<td>Moderate or severe daytime fatigue</td>
<td>54</td>
<td>66%</td>
</tr>
<tr>
<td>Need to urinate at night</td>
<td>49</td>
<td>59%</td>
</tr>
<tr>
<td>Sleepy in morning</td>
<td>49</td>
<td>59%</td>
</tr>
<tr>
<td>Difficulty awakening and becoming alert in the morning</td>
<td>42</td>
<td>51%</td>
</tr>
<tr>
<td>Feeling physically tense at bedtime</td>
<td>42</td>
<td>51%</td>
</tr>
<tr>
<td>Irritable in morning</td>
<td>38</td>
<td>46%</td>
</tr>
<tr>
<td>Awakened by noises</td>
<td>37</td>
<td>45%</td>
</tr>
<tr>
<td>Regularly awakens at any particular time of night</td>
<td>36</td>
<td>43%</td>
</tr>
<tr>
<td>Large body jolts as you are falling asleep</td>
<td>35</td>
<td>42%</td>
</tr>
<tr>
<td>Feeling too hot or too cold</td>
<td>35</td>
<td>42%</td>
</tr>
<tr>
<td>Awakened by bedpartner’s movements/sounds</td>
<td>35</td>
<td>42%</td>
</tr>
</tbody>
</table>

Conclusions: In addition to sleep itself, severe insomnia affected self-perceived daytime functioning significantly, according to the patients' charts reviewed in this study. The low likelihood of dozing despite feelings of sleepiness may be one peculiar expression of a daytime impact from insomnia. While clinicians and patients might judge different aspects of insomnia to be more salient, the present study’s methodology is limited in establishing this. The experience of severe insomnia needs further clarification. Nonetheless it does appear simplistic to assert that insomnia diagnoses are simply depressive or anxiety disorders in another guise. Furthermore, while instruments for measuring quality of life in insomnia are increasingly available, quantifying the severity of insomnia should include several of the variables and/or domains highlighted in this chart review.

Research supported by AG00972, AG15138, MH30915, MH16804

590.L

Effects of a Single Dose of Zolpidem (5 mg), Zopiclone (3.75 mg) and Lorazepam (1 mg) on Postural Sway and Memory Functions in Elderly Subjects

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Introduction: Balance disturbances and falls, more frequent in elderly subjects, may be increased by hypnotics, particularly benzodiazepines.

The primary objective of this study was to evaluate in healthy elderly subjects the effects of body sway and memory of two non-benzodiazepine hypnotics, zolpidem and zopiclone (1/2 in the elderly 3h and 7h, respectively), compared with the benzodiazepine lorazepam (1/2 10h)and placebo.

Methods: The single-centre, randomised, double-blind, placebo-controlled, latin-square crossover study comprised four 12-hour treatment periods, separated by ≥ 8-day washouts. In each period, patients received a single dose of zolpidem (5mg), zopiclone (3.75mg), lorazepam (1mg) or placebo at about 11 p.m. Body sway (CSP), Simple Reaction Time (SRT), drowsiness (visual analogue scale: VAS), Critical Tracking Test (CTT) and Sternberg 2-6 digit reaction time were assessed pre- and post-dose, the first three parameters throughout the night. A Learning Task (LMT) and Leeds Sleep Evaluation Questionnaire (LSEQ) were administered the morning after drug administration.

Results: Forty-nine consenting patients over 65 years old were enrolled, of whom 48 were evaluable. One patient withdrew due to non-stabilised hypertension unrelated to study treatment. The results of Per-Protocol analysis are described below (in comparison to placebo unless otherwise indicated). All times are post-dose. All three hypnotics initially increased body sway area eyes open, but this effect disappeared after 5h with zolpidem versus 8h with lorazepam and zopiclone (Table 1). Zolpidem and lorazepam induced sedation (VAS) only up to 5h (p=0.0415, p=0.0175), whereas with zopiclone sedation persisted up to 8h (p=0.0155). Lorazepam decreased LMT delayed recall relative to placebo and zolpidem (p=0.0140, 0.0118), and both lorazepam and zopiclone increased 6-digit Sternberg Mean Reaction Time (p=0.0042, p=0.0068). LSEQ items “Getting to Sleep” and “Quality of Sleep” were improved with zolpidem (p=0.0003, p=0.0153), zopiclone (p=0.0001, p=0.0001). Overall clinical safety of all hypnotics was good.

Table 1

<table>
<thead>
<tr>
<th>Body sway area eyes open Day 1 (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time post-dose</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>0 h</td>
</tr>
<tr>
<td>4 h</td>
</tr>
<tr>
<td>8 h</td>
</tr>
<tr>
<td>12 h</td>
</tr>
<tr>
<td>24 h</td>
</tr>
</tbody>
</table>

1 p<0.01 vs. placebo  * p<0.05 vs. placebo

Conclusions: In elderly subjects, zolpidem did not induce increased body sway area eyes open or sedation beyond 5h post-dose, diminishing the risk of falls. It had minimal effect on next-day memory functions. These results are consistent with the short elimination half-life of zolpidem and its safety profile in the elderly (1) and with observations in young healthy volunteers (2).

References:
Sequential Treatment for Chronic Insomnia: A Pilot Study

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Introduction: Recent studies of the relative efficacy of behavioural and pharmacological therapies have yielded mixed results as to whether it is preferable to use single or combined approaches when treating insomnia. Although a combined approach is preferable to drug therapy alone, the evidence is still equivocal regarding whether combined behavioural and drug treatments produce superior outcome to behavioural treatment alone. The few studies examining this issue have implemented treatments in a concurrent fashion. It is plausible that a sequential approach might yield superior outcome to concurrent implementation of behavioural and drug therapies. The aim of this pilot study was to explore the efficacy of sequential treatments consisting of cognitive-behavioural therapy (CBT) and pharmacotherapy (zopiclone) for chronic insomnia.

Methods: The sample consisted of six participants (mean age 47.5 years old) meeting diagnostic criteria for primary and chronic insomnia (mean duration of 15.5 years). Each participant completed a multistep assessment including a structured clinical interview (SCID-IV), a sleep evaluation, and a medical examination. Participants completed daily sleep diaries from baseline to posttreatment and during two weeks at a three-month follow-up. A multiple-baseline design was used and participants were randomly assigned to one of three treatment sequences that lasted ten weeks each (see figure 1): (a) medication (zopiclone) for the first five weeks, followed by CBT for the last five weeks, (b) concurrent medication and CBT for the 10-week treatment period, and (c) medication for the first five weeks, followed by a supervised withdrawal and CBT initiated during week 4. There were two participants in each condition. The main outcome variables (e.g., sleep efficiency, sleep onset latency, total wake time) were derived from the sleep diary and were examined with time series analyses.

Results: Results of the auto-regression analysis indicate that five of the six participants had an excellent treatment response from baseline to posttreatment. Furthermore, during the first five weeks of treatment, all participants reduced significantly their sleep onset latency. Participants in conditions B and C had a significant improvement on sleep efficiency and total wake time during the initial intervention phase. During the last five weeks of treatment, all participants maintained their therapeutic gains. In addition, participants in condition A improved significantly on sleep efficiency and total wake time measures. Finally, sleep improvements were well sustained for 4 out of 5 participants that completed the three months follow-up assessment period.

Conclusions: These preliminary results suggest that a sequential treatment is effective for chronic insomnia. Each sequence examined showed clinically meaningful improvement on sleep onset latency. Additional participants are currently enrolled to examine the relative efficacy of the different treatment sequences.

Research supported by FRSQ-FCAR-sante

Home-Based Nightcap Measures Insomniacs’ Sleep Onset Latency (SOL) Unobtrusively

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Introduction: In the few insomnia studies that have used objective assessment of sleep, laboratory PSG has typically been employed. Besides the drawback of high cost, laboratory PSG is subject to strong situational influences (e.g., the first night effect, disruption of normal sleep behavior), making adaptation problematic. Additionally, insomnia is often setting-specific so that sleep lab evaluations may fail to observe insomnia as it occurs at home. In fact, there may be a reversal of the first night effect in the sleep lab for insomniacs due to poor generalization of conditioned elements to the laboratory. The Nightcap (NC) is a small, portable sleep monitor system that is capable of monitoring sleep states without the disruptive influence of the laboratory and recording electrodes. It reliably distinguishes wake, NREM, and REM using eyelid and head movement data when compared to traditional PSG.

Methods: We employed the NC as an objective measure of sleep in a randomized clinical trial comparing pharmacological and behavioral therapy for sleep-onset insomnia. We examined whether the NC would show first-night effects on sleep-onset latency (SOL) and whether sleep on NC nights would differ from sleep on non-NC nights. The first fifty sleep-onset insomniacs (34 females and 16 males, mean age 47.6, who were free of hypnotics and screened for underlying sleep disorders and major psychiatric disorders) who completed three home-based Nightcap recording nights prior to initiating treatment for insomnia were included in the analysis. Our analysis focused on pretreatment data.

Results: Neither objective SOL (mean= 46.6 min) nor subjective SOL (mean= 86.6 min) showed significant differences across all three nights (objective SOL was defined as the time to the first 15 minutes of uninterrupted NREM sleep as measured by the NC’s scoring algorithm); therefore, there were no significant first night effects for SOL. When comparing subjective SOL on NC nights to eleven non-NC nights for each subject (mean SOL= 73.9), no significant differences were observed (because subjective SOL was stable across all 11 non-NC nights, we used the mean of the 11 nights).

Conclusions: These results suggest that sleep on NC nights is representative of a typical night’s sleep for insomniacs and captured their sleep naturally. The NC’s combination of portability, low cost, and minimal intrusiveness makes it ideal for studies of insomniacs’ sleep in the home environment. The high compliance rate that we observed suggests that the NC is user-friendly because it is easy to use and relatively unobtrusive.

References:

Supported by NIH R29 HL 59387, NIDA 1RO1DA1174401A1, NIH MH 48832
Home-Based Nightcap Documents Distorted Sleep Latency Estimates In Insomniacs

Jacobs GD,1,2 Stickgold R,3 Hobson JA,3 Pace-Schott EF3
(1) Sleep Disorders Center, Beth Israel Deaconess Medical Center, Boston, MA, (2) The Mind/Body Medical Institute, Harvard Medical School, Boston, MA, (3) Laboratory of Neurophysiology, Harvard Medical School, Boston, MA

Introduction: Previous research demonstrates that, in the laboratory, insomniacs overestimate sleep-onset latency (SOL) compared to PSG.1 Because insomnia is often setting-specific and the lab is subject to strong situational influences2, the lab may confound insomniacs’ estimates of SOL.

Methods: We employed the Nightcap (NC) as an objective home-based measure of sleep in a randomized clinical trial comparing pharmacological and behavioral therapy for sleep-onset insomnia. The NC is a small, portable sleep monitor system that is capable of monitoring sleep states without the confounding influence of the laboratory. It reliably distinguishes wake, NREM, and REM using eyelid and head movement data when compared to traditional PSG.3 In this study, we examined the congruence between insomniacs’ subjective SOL and NC-derived SOL (NC SOL was defined as the time to the first 15 minutes of uninterrupted NREM sleep as measured by the NC’s scoring algorithm4) at home. The first fifty-three sleep-onset insomniacs (36 females and 17 males, mean age= 47.7) who were free of hypnotics and screened for underlying sleep disorders and major psychiatric disorders) who completed three home-based nightcap recording nights prior to initiating treatment for insomnia were included in the analysis. Our analysis focused on pretreatment data.

Results: Across three NC nights, insomniacs significantly (p<.01) overestimated SOL compared to objective SOL (mean subjective SOL = 86.6 min, mean objective SOL = 46.9 min). In a subset of 27 insomniacs who reported sleep-latencies of at least two hours (approx. half a standard deviation from the mean SOL of 86.6 min), an analysis of 50 NC recording nights indicated a significant (p<.05) negative correlation between subjective and objective SOL; the greater the subjective SOL, the shorter the objective SOL. In this group, subjective sleep latencies not only significantly exceeded objective SOL; they significantly exceeded objective time to REM sleep as indicated in the table below:

<table>
<thead>
<tr>
<th>Grouping by Subjective SOL</th>
<th>Number of Nights</th>
<th>Subjective SOL (min)</th>
<th>Objective SOL (min)</th>
<th>Time To REM Onset (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Slept*</td>
<td>7</td>
<td>Never fell asleep</td>
<td>14***</td>
<td>87***</td>
</tr>
<tr>
<td>4+ hr</td>
<td>10</td>
<td>285</td>
<td>36***</td>
<td>80***</td>
</tr>
<tr>
<td>3-&lt;4 hr</td>
<td>14</td>
<td>193</td>
<td>72***</td>
<td>115*</td>
</tr>
<tr>
<td>2-&lt;3hr</td>
<td>18</td>
<td>130</td>
<td>76*</td>
<td>149</td>
</tr>
</tbody>
</table>

* p<0.05; **p<0.01; ***p<0.001 (paired t-test)

Conclusions: Because maladaptive sleep cognitions are an important mediating factor in insomnia, these data have important implications for the treatment of insomnia. They confirm that insomniacs significantly overestimate sleep latencies and that, the greater the reported SOL, the greater the distortion in their perception of SOL. Indeed, in subjects who reported “never fell asleep,” SOL and time to REM were in the normal range. The results also suggest that the NC may be an ideal method for providing insomniacs with objective data to modify their distorted sleep perceptions. The same psychophysiological arousal that disrupts insomniacs’ homeostatic drive for sleep (and diminishes the effects of their sleep loss) may also cause distorted sleep cognitions or be a consequence of them.

References:

Supported by NIH R29 HL59387, NIDA 1RO1DA1174401A1, NIH MH148832

Socio Economic Status, Insomnia and Daytime Functioning

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Introduction: The available information suggests that lower SES individuals experience a greater risk for insomnia. However, this relationship has seldom been directly examined, and reports have been based on brief sleep assessments. 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 focus on the relationship between insomnia prevalence, daytime functioning, and educational level, a proxy variable for SES.

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 their physical health, mood, and daily functioning. Our measures of daily functioning include: the Insomnia Impact Scale (IIS), the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), the Fatigue Severity Scale (FSS), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI). We measured SES by the highest level of education obtained by the research participant or their spouse.

Results: We have We have education data on 554 participants. Of those 554 participants, 413 (76.1%) were normal sleepers, and they averaged 14.5 (SD=2.9) years of education. There were 116 (21.9%) people with insomnia who averaged 13.5 (SD=2.8) years of school. Among high school drop-outs (HSD), 31.9% had insomnia. Among those who graduated high school (HS), 29.3% had insomnia. Of individuals who had some college (SC), 19.7% had insomnia, and among college graduates (CG), 16.2% had insomnia. Insomnia was significantly greater in lower SES individuals, /chi2 (3,n=116)= 9.018 p<.05. SES was significantly related to daytime functioning. A MANOVA revealed significant differences between groups, Wilks’Lambda = .903, F(18,1527.8)=3.1, p<.001. Follow-up ANOVA’s revealed that HSD had significantly higher ESS, ISS, and ESS scores compared with all other groups. HSD had higher BDI scores than all groups except HS and higher STAI scores than CG.
Conclusions: Lower SES individuals had significantly more subjective sleep complaints than higher SES individuals. The prevalence of insomnia was significantly greater among high school graduates and high school drop outs. Additionally, it appears that high school drop outs have significantly more sleep related daytime functioning complaints. Interestingly, there were negligible differences in insomnia prevalence between HSD and HS, yet HSD had significantly higher FSS and ESS scores. It seems that other factors led to HSD having more impaired daytime functioning.

Research supported by National Institute on Aging grants AG12136 and AG14738.

595.L

Sleep, Daytime Functioning, and Insomnia in Young Adults

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(1) The University of Memphis, Memphis, TN, (2) University of Tennessee, Memphis, TN

Introduction: The relationship between sleep and aging has been well documented in the sleep research literature. Sleep quality and continuity tend to worsen and insomnia becomes more prevalent with age. Changes in the sleep patterns, insomnia prevalence, and daytime functioning in younger adults (aged 20 to 39) have yet to be carefully explored. It is reasonable to suspect changes in sleep patterns, insomnia prevalence, and daytime functioning due to several developmental factors and lifestyle changes as age progresses across young adulthood. The purpose of this investigation is to describe trends in the subjective sleep patterns and daytime functioning of young adults, and to investigate changes in insomnia prevalence across this age group.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Volunteers were paid between $15 and $200 for completing 14 sleep diaries and six questionnaires evaluating associated daytime functioning (IIS, FSS, SSS, ESS, BDI, and STAI). The 228 participants aged 20 to 39 were stratified into four five-year age groups for the present analyses.

Results: A series of one-way ANOVAs revealed that mean TST was significantly higher for the 20 to 24 year-olds compared to the three other groups, F(3, 220) = 4.797, p < .01. Average TIB was also significantly greater for the 20 to 24 year-olds than the 25-29 and the 30-34 year-olds, F(3, 220) = 3.580, p < .05. There were no significant differences in NAP, SQR (sleep quality rating), SOL, NWAK, WASO, or SE across the groups. A chi-square analysis revealed an upward trend in insomnia prevalence at 5.9% for the 20-24 year olds, 11.1% for the 25-29 year-olds, 11.8% for the 30-34 year-olds, and 18.1% for the 35-39 year olds, though this failed to attain significance, χ² (3, N = 228) = 3.87, ns. A MANOVA revealed no significant differences for the six measures of daytime functioning across the four age groups, Wilks’ λ = .95, F(18, 609) = .67, ns.

Conclusions: Mean TST and TIB decline significantly after the 20-24 age range followed by a leveling off of these variables. Our analyses revealed no further significant changes in sleep patterns between ages 20 and 39. Although insomnia prevalence increased with age in our sample of young adults, no significant relationship exists between age group and insomnia prevalence. No significant differences in daytime functioning were revealed in our sample of young adults. Changes in TST and TIB along with a marginal increase in insomnia prevalence in the late 20’s and 30’s could be reflective of developmental factors, reduced time available for sleep, increased workload, and rising stress levels in mid to late young adulthood. These changes are not reflected in subjective
measures of daytime functioning. These data are novel, and these conclusions are preliminary. Further, more thorough investigations concerning the sleep of young adults are clearly warranted. Trend analyses and regression modeling will be available by meeting time.

Research supported by National Institute on Aging grants AG12136 and AG14738.

596.L

Adults’ Beliefs about Sleep: Refinement of the Floyd-Medler Sleep Belief Scale

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Introduction: Chronic insomnia is a debilitating condition that affects 10-20% of otherwise healthy Americans. The incidence is greater in women and older adults. Empirical evidence suggests that dysfunctional beliefs about sleep help maintain chronic insomnia (1), but little is known about normal sleep beliefs or how dysfunctional sleep beliefs evolve. In order to study the development of sleep beliefs, both functional and dysfunctional, the authors have developed an instrument to measure sleep beliefs in the general adult population (2,3). The purposes of this study were to examine a previously identified factor structure for the Floyd-Medler Sleep Belief Scale, identify a Short Form of the instrument for use with clinical populations, and explore background characteristics associated with adults’ beliefs about sleep.

Methods: 302 volunteers residing in a large metropolitan area in the mid-western United States completed the 60-item Floyd-Medler Sleep Belief Scale. Subjects were 35-80 years old. Approximately two-thirds of the subjects were women. LISREL was used for confirmatory factor analysis. Bivariate correlations were used to examine relationships between age and sleep beliefs. Gender differences regarding sleep beliefs were explored using Hotelling’s T followed by post hoc comparisons for each of the five factors.

Results: Results confirmed the original five-factor structure indicating that healthy adults have beliefs about: (a) long-term health consequences of poor sleep, (b) immediate mood and performance consequences of poor sleep, (c) self-care attributions, (d) the importance of circadian regularity, and (e) the importance of sufficient sleep. Sixteen items were identified for a Short Form of the Scale. They accounted for 62% of the total variance. Confirmatory factor analysis showed that all factor loadings were significant. The model demonstrated overall goodness of fit as evidenced by chi square (80 df) = 118.40 (p < .01), RMSEA = .04, GFI = .95, NNFI = .94, and CFI = .96. Age was correlated with stronger beliefs about the importance of sufficient sleep were stronger for men than women (p < .01).

Conclusions: The factor structure of the Floyd-Medler Sleep Belief Scale appears stable and sensitive to age and gender differences. Also, a Short Form of the Scale is ready for testing in clinical settings where subject burden should be minimized. Given the lack of probability sampling and exploratory nature of this instrument development study, it is premature to draw conclusions about the age and gender differences reported for this sample.

References:

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597.L

Progetto Morfeo: Insomnia In Primary Care. A Survey Conducted On The Italian Population

Tergano MG
On behalf of the Progetto Morfeo Committee

Introduction: It is known that insomnia is a highly prevalent sleep complaint and that this disturbance can severely impair a person’s functioning and well-being. In addition, insomnia can increase the risk of comorbid conditions and affect healthcare resource consumption.

Methods: The study was accomplished by 700 GPs operating in the Italian territory. Only patients who referred spontaneously to their GP for some medical problem were surveyed. All data were collected during a 15-day period. Each GP was asked to enroll at least 5 patients across a routine week of clinical activity. The first patient of each weekday was asked to participate in the survey by completing a questionnaire after written consent. The questionnaire was a form of the Health Status Questionnaire with the validated SF-36 Health Survey, a 3-question depression screen, a sleep questionnaire, demographic variables, and questions about medical encounters, prescription and over-the-counter drug use. Training of GPs was conducted by the sleep specialists in charge of 16 Sleep Disorders Centers accredited by the Italian Association of Sleep Medicine (AIMS).

Results: A total of 3284 were enrolled in the survey with a balanced territorial distribution throughout the country (northern area: 46%; central area: 25%; southern area: 29%). The mean age of the survey population was 52 ± yrs. with a prevalence of females (60%). Sixty-four percent of all the interviewed patients reported a complaint of insomnia, which was of level II (difficulty in initiating and maintaining sleep with daytime dysfunction) in 44% of the subjects and of level I (difficulty in initiating and maintaining sleep without daytime dysfunction) in the remaining 20%. Insomnia affected more frequently housewives, and retired or unemployed people. Among the causative factors of insomnia, stressful events were reported in 80% (more frequently in level II patients) followed by physical problems (44%), inadequate sleep hygiene (42%) and environmental disturbances (41%). At the time of the interview, 12% of level I insomnia and 18% of level II insomnia were taking medication for sleep problems. Evaluation of comorbid conditions revealed that the occurrence of cardiovascular diseases was significantly higher among the patients with insomnia. Compared to noninsomniacs, patients with insomnia required more medical encounters (+14%; p < 0.0001), more laboratory tests (+9%; p < 0.0001) and prescriptions filled (+15%; p < 0.0001). Mood disturbances were always found more often among insomniacs, with higher frequencies in level II. Compared to the general Italian population, which was investigated in a previous study, the noninsomniacs of the present survey showed higher SF-36 scores, whereas level II insomniacs presented lower values in all the items of quality of life.

Conclusions: The results that emerge from the present survey are in line with previous studies conducted with the same questionnaire. Among the Italian patients that refer to their GPs, insomnia seems to be a highly diffused though lowly treated complaint, frequently associated with other health problems and with enhanced healthcare resource consumption.
References:

598.L

Nocturnal Plasma Cortisol in Primary Insomnia

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Introduction: Patients with primary insomnia often feel like being wide-awake, overexcited and ‘hyper-aroused’ at night. The aim of this study was to show proof of a neurophysiological correlate which might explain this hyperarousal in insomniacs. Our assumption was that insomnia patients may have an increased activity level in the hypothalamic-pituitary-adrenocortical-system and therefore display higher cortisol secretion during the night. Results of former studies have also shown that insomniacs have higher plasma cortisol levels in the evening and at night and that cortisol in urine taken for 24 hours correlates with the duration of waking periods (see e.g. Vgontzas et al., 1998).

Methods: 10 patients (4 males, 6 females; mean age: 39.2 ± 9.1 years) with primary insomnia (DSM-IV: 307.42) and a group of 10 healthy controls (matched for sex and age), underwent a three night sleep laboratory examination. Eight of the patients were free of hypnotic drugs for at least one week, while two of them had stopped taking sleep agents two and three days ago, respectively. The first night served as an adaptation night while the second was used for diagnostic procedure. During the third night plasma cortisol samples were taken with an intravenous catheter every 30 minutes between 7 p.m. and 9 a.m. For nine of the patients we also determined urinary cortisol-distribution between 11 p.m. and 7 a.m. Additionally, we assessed objective and subjective sleep measures for both groups.

Results: The average plasma cortisol level computed half-hourly, showed no significant differences between insomniac patients and healthy controls. The urinary cortisol excretion increased from the first to the third night. In objective sleep measures we found significant differences for the second (baseline) and third (blood sampling) night, with less REM in % during the sleep period for insomniacs compared to healthy controls. Results of the Pittsburgh Sleep Quality Index subscales showed significant differences with insomniacs reporting impaired sleep quality (p=.001), less feeling of rest (p<.001) and more psychological exhaustion (p=.008) compared to healthy controls.

Conclusions: By subjectively estimating their sleep, our group of patients differed distinctly from the control group. In polysomnographic (PSG) data, however, insomniacs only moderately differed from healthy controls. We also did not observe higher cortisol levels for the insomniac group as described in other studies. One of the reasons could be that our patient group represents a subgroup of patients with primarily sleep state misperception. Thus, the hypothesis of a hyperarousal in patients with primary insomnia remains controversial and might just be apparent in insomnia patients with clear objective (PSG) evidence of disturbed sleep.

References:

599.L

Sex Differences in Objective and Subjective Sleep Measures in Patients with Primary Insomnia

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Introduction: Epidemiological studies show that women more often complain about disturbed sleep than men (see e.g. Hohagen et al., 1993). There is a wide variety of studies concerning gender differences in healthy subjects considering objective and subjective sleep measures. When it comes to primary insomnia however, research usually focuses either on subjective or objective sleep measures. Up to now, to the best of our knowledge, there is a lack of studies addressing the question of possible gender differences of polysomnographically assessed and subjectively estimated sleep measures in patients with insomnia complaints. Armitage et al. (1997) found gender differences in the accuracy of subjectively estimating sleep measures in depressed patients. Women were more accurate in judging sleep characteristics than men. The aim of the present study was to address the same question in a group of female and male insomniacs.

Methods: In this retrospective study we examined sleep measures of all insomniac patients who had been diagnosed in our sleep laboratory within the last four years. The existence of a restless-legs-syndrome, periodic limb movements (Index < 5/h), sleep-related breathing disorders, as well as psychiatric disorders and concomitant organic diseases were excluded for those patient-data for which statistics were finally performed. Thus we obtained 45 female (age-range: 19-63 years, mean: 38.3, ± 12.1 years) and 42 male (age-range: 21-65 years, mean: 42.4, ± 12.0 years) insomniac patients (INS), all of them being free of hypnotic drugs for at least one week before sleep lab examination. 42 males (age-range: 19-63 years, mean: 38.3, ± 12.1 years) and 45 females (age-range: 21-65 years, mean: 42.4, ± 12.0 years), served as an age-matched group of healthy controls (CON).

Results: To evaluate the differences between subjective and objective sleep measures of both groups (INS/CON), statistical analysis was performed for sleep parameters of the second night (baseline-night). CON had a higher percentage of stage 1 in TST for men (men: 9.7 %; women: 7.2 %), but we couldn’t observe any gender differences in subjective sleep measures. Within INS no significant differences were found for sleep period time (SPT), total sleep time (TST), sleep efficiency (SE) or latencies to any of the NonREM-sleep-stages (1-4). We observed a significantly shorter latency to REM-sleep (p=.02) for male in comparison to female insomniacs. Interestingly, women showed more arousals during slow-wave-sleep (SWS; p=.04) than men. For subjective estimation of sleep disturbance no significant differences could be found between men (Pittsburgh Sleep Quality Index [PSQI]:10.4) and women (PSQI: 9.2).

Conclusions: Although it is often postulated that women more frequently complain about symptoms of insomnia, our results show that subjective and objective differences in the sleep of females and males (INS and CON) are rather small. However, women showed more arousals during SWS, what might serve as an explanation for the subjective estimation of disrupted and therefore unrestorative sleep. Further psychometric information is necessary to differentially assess subjective and objective estimation of sleep complaints and gender differences.

References:
Insomnia is Associated with Altered Circadian Interleukin-6 and TNFα Secretion

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Introduction: Chronic insomnia, by far the most commonly encountered sleep disorder in medical practice, is characterized by long sleep latencies or increased wake time during the night and increased fatigue during the day, although in objective daytime sleep testing, insomniacs are unable to fall asleep. We recently reported that chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal (HPA) axis consistent with the view that insomnia is a disorder of behavioral and physiological hyperarousal. Interleukin-6 (IL-6) and tumor necrosis factor (TNFα) are fatigue-inducing cytokines. The circadian secretion of IL-6 is negatively influenced by the quantity and quality of the previous night’s sleep. Both IL-6 and TNFα stimulate the activity of the HPA axis, and their secretion is suppressed by glucocorticoids. Based on the above described associations, we explored whether the circadian secretion of IL-6 and TNFα is altered in insomniacs.

Methods: Eleven young insomniacs (6 men and 5 women) and 11 (8 men and 3 women) age-and-body-mass-index (BMI) matched healthy controls participated in the study. Subjects were recorded in the sleep laboratory for four consecutive nights and serial twenty-four hour plasma measures of IL-6 and TNFα were obtained during the fourth day.

Results: Insomniacs compared to controls slept poorly (sleep latency and wake were increased whereas percentage sleep time was decreased during baseline nights, all P < 0.05). The mean 24-hour IL-6 and TNFα secretions were not different between insomniacs and controls. However, mean IL-6 levels were borderline significantly elevated in insomniacs compared to controls in the mid-afternoon and evening pre-sleep period (1500-2300, P < 0.07). Furthermore, cosinor analysis showed a significant shift of the major peak of IL-6 secretion from early morning (0500) to evening (2000) in insomniacs compared to controls. Also, TNFα secretion in controls showed a statistically significant circadian rhythm with a peak close to the offset of sleep; such a rhythm was not present in insomniacs.

Conclusions: Chronic insomnia is associated with a shift of IL-6 secretion from early morning to evening, which may explain the daytime fatigue and performance decrements associated with this disorder. The daytime shift of IL-6 secretion, combined with a 24h hypersecretion of cortisol, an arousal hormone, may explain the insomniacs’ daytime fatigue and difficulty falling asleep during the daytime and/or the nighttime. The interaction between IL-6 and cortisol levels may determine the timing, quantity and quality of sleep, sleepiness and fatigue in physiologic and pathologic situations.

References:

The Association of Insomnia and Alcohol Use: Is it Purely Pharmacological?

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Introduction: Laboratory studies have demonstrated that use of alcohol adversely affects sleep. However, recent epidemiologic studies have found that insomnia predicted subsequent onset of alcohol abuse, suggesting the relationship between insomnia and alcohol use may be due to more than alcohol’s immediate pharmacological effects. In this study, we assess whether the association between self-reported insomnia and use of alcohol appears to be due to immediate pharmacological effects or appears to be due to a common vulnerability. To test these possibilities we compared the risk of current insomnia among those who currently drink alcohol vs. those who had been drinkers but were not currently drinking. Finding that the association between current insomnia and current drinking is greater than the association between current insomnia and past/not current drinking would suggest that the association between alcohol use and insomnia is due to either the pharmacological effects of alcohol or that insomnia causes alcohol use. However, finding that there is no difference between current vs. past/not current alcohol use in risk of insomnia would suggest a common vulnerability.

Methods: These preliminary data come from the Epidemiology of Daytime Sleepiness Study. To date this study has collected information from a representative sample of 833 people 18-65 years of age in the Detroit primary metropolitan statistical area. The survey used random digit dialing and computer-assisted telephone interviewing techniques. Insomnia was defined by the highest quartile on an insomnia symptom scale.

Results: Use of any alcohol in the past two weeks was not associated with current insomnia (OR = 0.7, 95% CI 0.5-1.1), nor was use of any alcohol in the past year but not in the past two weeks (OR = 1.0, 95% CI 0.6-1.6). Frequency of alcohol use also showed null findings. In contrast, number of drinks per drinking occasion showed a J-shaped association with current insomnia for, drinking in the past two weeks (Chisq = 9.4, p = 0.02) and drinking in the past year but not in the past two weeks (Chisq = 5.6, p = 0.12). Those drinking 1 to 4 drinks per occasion showed a reduced odds of current insomnia relative to abstainers, while those drinking 5 or more drinks per occasion showed linearly increasing odds of current insomnia for current and past year/not current use of alcohol. The magnitude of these associations did not differ.

Conclusions: There is little doubt that use of alcohol adversely affects sleep based on controlled experiments. However, the association between insomnia and use of alcohol based on self-reports maybe largely due to a third factor that makes individuals vulnerable to insomnia also vulnerable to heavy drinking.

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Prevalence of Insomnia Symptoms in a Random Sample of SDB Patients

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Introduction: Few studies have been conducted on insomnia symptoms in sleep-disordered breathing (SDB) patients, perhaps because it is assumed that “recurrent awakenings” associated with SDB are not really an insomnia condition (1). This study focused on the frequency of insomnia complaints in patients diagnosed with OSA and UARS. We hypothesized that a sizeable proportion of SDB patients would report clinically important insomnia symptoms beyond problems with “recurring awakenings.”

Methods: A random sample of 172 SDB patient records (evaluated 7/97 thru 12/99) extracted from the University Hospital Sleep Disorders Center database (n=2000) were assessed for insomnia. All had been diagnosed with SDB by polysomnography and current AASM criteria (1). Demographics: 117 men, 55 women; mean age 51 years; mean body mass index (BMI) 33.4. Insomnia diagnoses were assessed with a three-item dichotomous scale (Yes/No), based on patient self-report of usual sleep pattern: 1) taking longer than 30 minutes to fall asleep; 2) waking up a lot; and, 3) difficulty returning to sleep if awakened; total score range = 0-3. Patients scoring “1”or “0” reported SDB-type recurrent awakenings or no insomnia [“SDB Only” (n=85)]. Patients scoring “3” or “2” reported clinically apparent insomnia [“SDB Plus” (n=87)]. Student’s t-test compared means at p=.05 and effect sizes were calculated as Cohen’s d.

Results: Mean age, BMI and gender were similar in both groups. Objective findings revealed no group differences in snoring pattern, oxygen nadir and OSA or UARS diagnoses; but, AHI was greater [59 vs. 43 events/hour; t(168)=2.63, p<.01, d=.40] in SDB Only. In comparison to SDB Only, SDB Plus reported markedly increased sleep latency [20 vs. 65 minutes; t(159)=6.04, p<.0001, d=1.01], markedly reduced total sleep time [7.1 vs. 5.5 hours; t(163)=6.08, p<.0001, d=95], nearly identical in bed (7.9 vs. 8.2 hours) and markedly reduced sleep efficiency [89% vs. 70%; t(151)=7.37, p<.0001, d=1.19]. An interesting sub-set of 15 SDB Plus patients presented as classic insomnia patients who eventually were diagnosed with SDB.

Conclusions: Clinically meaningful insomnia symptoms were prevalent in 50% of a random sample of objectively diagnosed SDB patients (OSA or UARS). We suspect that “SDB Plus” patients have greater difficulty adapting to CPAP or oral appliances because they probably spend too much time awake and aware of the devices, assuming that their insomnia in fact exacerbates their sleep problems. If so, then vigorous sleep hygiene and cognitive-behavioral treatments for insomnia would be necessary for such patients, which presumably would facilitate adaptation to sleep breathing devices. Yet, in the field of clinical sleep medicine, increasingly dominated by pulmonologists who may perform less than satisfactorily in nonpulmonary cases (2), it will be important to examine whether or not “SDB Plus” patients receive complete diagnoses and proper care. Last, a potential bidirectional relationship between insomnia and SDB must also be considered. For example, how might each condition aggravate the other? And, why do some SDB patients have multiple awakenings at night without suffering from insomnia, while others experience clinically manifest insomnia? We suspect that co-morbid anxiety, depression and posttraumatic stress symptoms will prove most salient in determining which SDB patients report co-morbid insomnia (3).

References:

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Sleep Patterns in Adults of the Rural and Isolated African-Brazilian Community of Furnas do Dionisio, Brazil

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Introduction: The purpose of this research was to verify sleep disorders in the rural population of Furnas do Dionisio, Mato Grosso do Sul state, Brazil.

Methods: The population of the rural and isolated African-Brazilian community of Furnas do Dionisio, in the Municipality of Jaraguari, MS, has been assessed. Interviews made in the period of January 1999 to January 2000 have been used. Census-type sampling has been used, assessing all the community inhabitants, with age 18 or more [Furnas Group], in a total of 120 subjects. The Control Group has been collected in a neighboring rural zone, in the same Municipality, also using Census-type sampling and the same age range, in a total of 101 subjects. A standardized multiple-choice questionnaire was applied in both groups.

Results: The two populations have been compared in relation to age and gender. Furnas Group was composed by 97.5% of African-Brazilian people and Control Group by 39% of African-Brazilian people (p = 0.001). The usual night sleep pattern in Furnas Group showed a trend to have sleeping and waking times earlier than those described in urban populations. Furnas Group sleeping time in the weekends and in the weekdays and waking times, both in the weekdays and in the weekends, later than those of the Control Group. The usual standard of diurnal sleep, in Furnas Group, showed a prevalence of regular siesta, similar to that observed in the Control Group. Both groups are siesta cultures, since 66.3% of the Furnas Group and 59.4% of the Control Group sleep regularly during daytime. The comparison of Furnas Group with Control Group showed higher indices of the following sleep complaints and disorders in the Furnas Group: wish to change the sleeping habits; dissatisfaction with the sleeping place; complaints of sleeping problems. Difficulty in falling asleep; irresistible diurnal sleep; sleepwalking; swallowing difficulty and suffocation during sleep; sleep paralysis; nightmares; current insomnia. None of the sleep disorders has been found more in the Control Group than in the Furnas Group, in a statistically significant manner. Notwithstanding the differences of sleep impairment between the groups, the search for consultation and use of sleeping medication has been similar. Among the assessed clinical diseases, hypertension has been found more in Furnas Group than in the Control Group.

Conclusions: The evaluation rural isolated African-Brazilian communitiy of Furnas do Dionisio,in the Mato Grosso do Sul state, compared with a rural European-Brazilian Control group showed that the Furnas Group
sleeping times in the weekends, and weekends, and wakenig times, both in the weekdays and weekends, later than those of the Control Group. Both groups are siesta cultures, since 66.3% of the Furnas Group and 59.4% of the Control Group regularly sleep during daytime. The following sleep disorders and complaints were more prevalent in the Furnas Group than in the Controls, included: dissatisfaction with the sleeping place; difficulty falling asleep; sleep paralysis; nightmare; current insomnia. None of the sleep disorders has been found more in the Control Group than in the Furnas Group, in a statistically significant manner. Despite the remarkable differences of sleep impairment between both groups, the search for consultation and use of sleeping medication has been similar.

604.L

Ethnicity and the Complaint of Insomnia Across Age: An Analysis from a Randomized Sample

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Introduction: There exists a substantial amount of data on self-reported disturbed patterns of sleep, but very little data on ethnic differences in people complaining of insomnia (PCI). We have no data on the relationship between ethnicity and sleep complaints across age. Given the findings of increased sleep disordered breathing, increased anxiety disorders, and increased life stress in African Americans (AA) compared to Caucasian Americans (CA), it is reasonable to assume that differences may exist between these two ethnic groups in insomnia. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diary data. This paper will focus on the relationship between nighttime and daytime functioning and ethnicity across age in people with chronic complaints of insomnia.

Methods: We used random-digit dialing to collect data from 772 participants from 20 to 98 years old in the metropolitan Memphis (TN) area. Participants completed sleep diaries and questionnaires evaluating health, mood, and daytime functioning, including sleepiness and fatigue. The sleep measures were: sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), and sleep quality rating (SQI, from 1 = very poor to 5 = excellent). Participants were divided into 3 age groups: 1) Young (20-39), 2) Middle (40-69), and Old (70+). Participants were classified as PCI if they currently had a sleep problem of at least 6 months that was related to insomnia difficulty (i.e., their reported sleep problems were with difficulty falling asleep, difficulty maintaining sleep, etc.).

Results: There were 235 PCI, with 172 CAs (73.2%; 28 Young, 66 Middle, 78 Old) and 63 AAs (26.8%; 25 Young, 24 Middle, 14 Old) classified as PCI in this sample. Insomnia complaint prevalence was as follows: Young AA (28.4%), Middle AA (25.8%), Old AA (33.3%), Young CA (21.1%), Middle CA (28.2%), and Old CA (45.3%). The Chi-square goodness-of-fit analysis for these rates was significant, $\chi^2(5) = 18.3$, p < .01. Given these prevalence differences, we examined the interaction of ethnicity and age on the sleep variables mentioned above and on sleepiness (ESS, SSS), fatigue (FSS), and mood (STAI, BDI). We performed two, 2 x 3 MANOVAs comparing the two ethnic groups and three age groups on the set of sleep and daytime functioning variables. Both MANOVAs were nonsignificant for the gender x race interaction. There was a significant main effect for ethnicity on the sleep MANOVA. AA had more WASO, less TST, and lower SQI. There was not a main effect for ethnicity on the daytime functioning MANOVA.

Conclusions: Based upon sleep diaries, these results from a random sample find that (1) sleep disturbance is more severe in AAs with an insomnia complaint compared to CAs, (2) there are no clear ethnic differences in daytime functioning for PCI, and (3) insomnia complaint prevalence is significantly different between AAs and CAs across age; AAs have a consistent prevalence rate across age compared to marked increase in prevalence across age in CAs.

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605.L

Insomnia in Adults of the Rural and Isolated African-Brazilian Community of Furnas do Dionisio, Brazil

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Introduction: The purpose of this research was to verify insomnia prevalence and correlates in the rural and isolated African-Brazilian population of Furnas do Dionisio, in the state of Mato Grosso do Sul, Brazil.

Methods: The population of Furnas do Dionisio, a rural and isolated African-Brazilian community, in the Municipality of Jaraguary, state of Mato Grosso do Sul, has been assessed. Interviews were made in the period of January 1999 to January 2000 have been used. Census-type sampling has been used, assessing all community inhabitants, with age of 18 or more years (Furnas Group), in a total of 120 subjects. The Control Group has been collected in a neighboring rural zone, in the same Municipality, also using Census-type sampling and the same age range, in a total of 101 subjects. The two populations have been compared in relation to age and gender. Furnas Group was composed by 97.5% of African-Brazilian people and Control Group by 3.9% of African-Brazilian people (p = 0.001). A standardized multiple-choice questionnaire related to insomnia was applied and compared.

Results: The prevalence of insomnia was larger in the Furnas Group (40.83%) in comparison with the Control Group (16.83%); such prevalence has been calculated based on the last week (one-week prevalence). The event of insomnia in the Furnas Group showed to be directly related to the following: subjects with insomnia are older than those without insomnia; wish to change sleeping habits; complaints of sleep disorders; difficulty in falling asleep; wake up many times during the night; earlier awakening at the end of the night; headache during sleep; nightmare. In Furnas Group, the search for health care of sleep disorder and use of sleeping medication was similar among subjects with current insomnia and those without current insomnia. In the Control Group, the occurrence of current insomnia has been shown to be directly related to the following: wish to change sleeping habits; complaints of sleep disorders; difficulty in falling asleep; earlier awakening at the end of the night; excessive daytime sleepiness; asthma during sleep; tachycardia during sleep; headache during sleep; cramp during sleep; falling asleep earlier both in the week days and in the weekends. In the Control Group, the search for care of sleep disorder, use of sleep medication and hypertension has been directly related to current insomnia. The occurrence of previous insomnia in the Furnas Group showed to be directly related to the following sleep complaints: subjects with severe insomnia were older than those without insomnia; wish to change sleeping habits; with to increase sleep duration; dissatisfaction with the sleeping place; episodes of irresistible sleep during daytime; excessive daytime sleepiness; sleepwalking; nightmare; current insomnia. In the Furnas Group, the search for care of sleep disorders and the use of sleeping medication was similar among those with previous insomnia and those without previous insomnia. In the Control Group, the occurrence of previous insomnia showed to be directly related to the following sleep
disorders and complaints: subjects with severe insomnia were older than those without insomnia; wish to change sleeping habits; complaints of sleep disorders; episodes of irresistible sleep during daytime; excessive daytime sleepiness; swallowing difficulty during sleep; feeling of suffocation during sleep; tachycardia during sleep; presence of current insomnia. In the Control Group, the search for care of sleep disorders, the use of sleeping medication and the presence of hypertension were higher in the subjects with previous insomnia than in those without previous insomnia.

Conclusions: The prevalence of insomnia was larger in the rural and isolated African-Brazilian Furnas do Dionisio adult population (40.83%) in comparison with the rural European-Brazilian paired control population (16.83%). Such prevalence was calculated based on the last week (one-week prevalence).

606.L

Comparison of Insomnia Prevalence in the General Population of Portugal and Spain

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Introduction: Insomnia can be a disabling sleep disorder that affects up to one third of the general population in the industrialized countries (1). However, discrepancies in the reported prevalence of insomnia can be found between epidemiological studies. These differences can be the result of different methodologies and questionnaires but cultural aspects may also play an important role in the disparity of these results. This study aims to compare the prevalence of insomnia in two countries using the same methodology and questionnaire.

Methods: 5,923 subjects from Portugal (n=1,858) and Spain (n=4,065) representative of the general population of their country were interviewed by telephone using the Sleep-EVAL system (2). The minimum age for the participation in the study was set to 15 years old in Spain and 18 years old in Portugal according to the ethic committee recommendations for each country. Each sample was drawn according to a two-stage sampling design. The participation rate was 83% in Portugal and 87.5% in Spain. To achieve this participation rate, the initial refusers were called a second time at least three weeks later unless the individuals stressed on the first phone contact that they do not wish to be called again. The questionnaire included the assessment of sleep habits, insomnia symptomatology according to DSM-IV classification, associated and sleep/mental disorders and daytime consequences.

Results: Overall, 12.2% of the subjects reported insomnia complaints at least three nights per week. This prevalence was higher in Portugal than in Spain (15.8% vs. 10.6%; p<.001). In both countries, this prevalence increased with age and remained significantly higher in Portugal. Difficulty in maintaining sleep was the most frequent complaint: 10.4% in Portugal and 6.8% in Spain (p<.001). Prevalence of any DSM-IV insomnia diagnosis was higher in Portugal (8.7%) than in Spain (6.0%; p<.001). Primary insomnia diagnosis was the most frequent (4.4%) without significant difference between the two countries. The difference between the countries was due to a slightly higher prevalence in Portugal of Insomnia related to another mental disorder and Insomnia due to a general medical condition. Dyssomnia not otherwise specified was also higher in Portugal (6.4% vs. 4.4%; p<.005). Several sleep habits may explain the differences between these two countries: Portuguese subjects twice more frequently claimed they have a bad sleep compared to Spanish subjects. They were more numerous to extend their sleep on week-ends and days-off and when they do it, they sleep on average 20 minutes more than Spanish subjects. The sleep duration is also shorter of at least 10 minutes on average for Portuguese subjects between 40 to 64 years compared to Spanish subjects in the same age range. Excessive daytime sleepiness is twice more frequent in Portugal than in Spain.

Conclusions: Although Portugal and Spain are neighboring countries, sleeping habits are dissimilar between them and lead to higher prevalence of DSM-IV insomnia disorders in Portugal. Otherwise, evolution of symptoms according to age and gender and importance of symptoms followed the same pattern between these two countries.

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607.L

Excessive Daytime Sleepiness and Insomnia in an Elderly Population

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Introduction: Sleeping problems, especially insomnia, frequently are reported to increase with age. Excessive daytime sleepiness (EDS) is one of the most harmful daytime consequences of insomnia. The combination insomnia-EDS significantly contribute to deteriorate the quality of life (1). Surprisingly, few studies explored these two symptoms in elderly population. This study aims to assess the prevalence of insomnia and EDS and its associated factors in an elderly general population.

Methods: The targeted population was individuals 60 years of age or older living in the community in the metropolitan area of Paris (France). This strata represent 19.9% of the population in this area (approximately 2 millions of inhabitants). To find these subjects, 7,010 randomly selected households were called: 1,269 of them had at least one household member in this age range and 1,026 accepted to be interviewed (participation rate: 80.9%). These subjects were representative of the general population aged 60 years or older living in this area. The subjects were interviewed by telephone using the Sleep-EVAL expert system (2,3). In addition to the DSM-IV and ICSD diagnoses, the system administered to participants the Psychological General Well-Being Schedule; the Cognitive Difficulties Scale (French version) (Mac Nair-R), an independent living scale, and a scale assessing the social network. The sample includes 28.7% of subjects aged between 60 and 64 years; 25.4% between 65 and 69 years old; 21.2% between 70 and 74 years; and 24.7% were aged 75 years or over.

Results: EDS was reported by 13.6% of the sample with no significant difference between age groups. Insomnia symptoms (difficulty initiating or maintaining sleep, nonrestorative sleep) occurring at least three nights per week significantly increased with age due mainly to a growing number of subjects who reported disrupted sleep with age. DSM-IV insomnia diagnoses were found in 9.6% of the sample with no significant difference between age groups. EDS was found in 20.2% of subjects with
a DSM-IV insomnia diagnosis. However, the co-occurrence of EDS and insomnia symptoms was found in 9.6% of the sample. Logistic regressions were calculated to determine in what extend insomnia symptoms and EDS are predictive of cognitive difficulties assessed six dimensions (attention-concentration deficits, praxis, delay recall, difficulties in orientation for persons, difficulties in temporal orientation and prospective memory). The models were controlled for age, gender, physical activity, occupation, organic diseases, use of sleep or anxiety medication, sleep duration and psychological well-being. EDS alone (i.e. without insomnia symptoms) was one of the stronger predictive factors of cognitive difficulties followed with the co-occurrence of insomnia symptoms and EDS. Insomnia symptoms alone were significantly associated with cognitive difficulties only on two dimensions (attention-concentration deficits and praxis). Older age made a significant independent contribution only on praxis.

Conclusions: Co-occurrence of EDS and insomnia symptoms are frequent in the elderly general population. However, EDS (with or without insomnia symptoms) has a greater impact on cognitive difficulties than insomnia symptoms alone.

References:
(3) Ohayon MM. Improving decision making processes with the fuzzy logic approach in the epidemiology of sleep disorders. J Psychosom Res 1999;47:297-311.

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608.L

Major Exclusion Factors for Elderly Subjects in Primary Insomnia Research Studies

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Introduction: Insomnia, a highly prevalent sleep disorder, particularly among older adults, frequently coexists with other physical and psychological factors that independently contribute to initiating and maintaining sleep. In recruiting for an ongoing study of behavioral treatments for elderly insomniacs, we identified factors that precluded a diagnosis of Primary Insomnia. We excluded subjects with these factors, because, similar to most studies of behavioral insomnia treatments (Lichstein et al., 2000), our study was designed to treat only Primary Insomnia subjects. We describe the factors that we believe are representative of elderly individuals with complaints of insomnia.

Methods: Individuals 55 years and older with a six-month minimum complaint of insomnia were recruited by local newspaper advertisements. Potential subjects were provided a study description, including the requirement of hypnotic medication abstinence for a three-week minimum prior to study initiation and for the length of the study. A research psychologist then administered a telephone interview that screened for physiological and psychiatric conditions associated with insomnia; specific sleep disorders, e.g., obstructive sleep apnea; and use of stimulating or sedating medications. Eligible subjects proceeded to in-office evaluations by a research psychologist who screened for DSM IV Axis I diagnoses and by a board-certified sleep medicine physician who conducted a medical history and physical exam. Subjects completed 14 days of sleep logs to determine the severity of sleep disturbance and an in-home sleep study screening for sleep apnea. If subjects met criteria for Primary Insomnia, they were asked to participate in the study, involving behavioral treatments of insomnia.

Results: From a pool of 222 respondents, we had 160 willing to participate. A total of 101 subjects (50 female; median age 66 yrs; range 55-84) were excluded from study participation for failing to meet Primary Insomnia criteria (two subjects did not meet inclusion criteria of sleep efficiency < 80% or a total sleep time < 6 hrs on sleep logs). Major factors precluding diagnosis of Primary Insomnia in our elderly population are listed in Table 1. The top three conditions in our elderly respondents were: suspected sleep-related breathing disorders, chronic illnesses (e.g. diabetes and painful conditions), and sleep-interfering medications (primarily prescription psychotropics). These three factors excluded three-fourths of those wanting to participate in our study. Notable gender differences existed for some factors: there was a higher ratio of women:men for hypnotic-dependence (7:1) and psychiatric symptoms/depression (5:1); and a higher ratio of men:women for suspected sleep-related breathing disorders (1.8:1). A higher ratio of older subjects (>66 yrs) had a dependency on hypnotics (7:1) and, as might be expected, had chronic illness(es) (3:1).

Table 1

<table>
<thead>
<tr>
<th>Disqualifying Factors</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-disordered breathing symptoms</td>
<td>45 (45.6)</td>
</tr>
<tr>
<td>Chronic illnesses</td>
<td>20 (19.8)</td>
</tr>
<tr>
<td>Sleep-interfering medications</td>
<td>12 (11.9)</td>
</tr>
<tr>
<td>RLS/PLMD symptoms</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Hypnotic-dependence</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Psychiatric symptoms/depression (GDS ≥ 7)</td>
<td>6 (5.9)</td>
</tr>
<tr>
<td>Failed insomnia criteria</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>101 (100)</td>
</tr>
</tbody>
</table>

Conclusions: Of those willing to participate in a comprehensive, rigorous treatment study, 101 were excluded for failing inclusion criteria. For older subjects who self-report insomnia, the complaint could reflect a number of factors that can directly and independently result in poor sleep. The diagnosis of Primary Insomnia is difficult to establish without considering these factors. Any screening process must be particularly thorough to rule out these factors in this age group.

References:

Research supported by Medical Research Service of the Palo Alto Veterans Affairs Health Care System, by the Department of the Veterans Affairs Sierra-Pacific MIRECC, and by AG 12914-09.

609.L

Efficacy of Sophrology in the Treatment of Chronic Insomnia

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Introduction: Sophrology is a non medical original synthesis treatment between occidental relaxation techniques (Jacobson, Schultz) and oriental methods like buddhism and zen. It was created by A.Caycedo in the sixties. At present, sophrology has not been evaluated in the treatment of...
chronic insomnia, unlike other methods such as behavioral therapy or classical relaxation (1,2,3).

**Methods:** Between January 1999 and June 2000, 50 patients (18-60 years old) with a DSM-IV diagnosis of primary insomnia and insomnia with anxiety, were included in this study, following an out-patient visit to our sleep center. Five one-hour sessions of sophrology, once a week, were proposed to the patients. The evaluation was based on subjective and objective tests one month before and one month after treatment. Subjective tools were visual analogical scales VAS (sleep quality, morning clarity, dynamism and diurnal alertness) and sleep questionnaires (Spiegel and the Pittsburgh Sleep Quality Index PSQI). Anxiety and depression were assessed according to the Hamilton Anxiety Scale (HAS) and the MADRS. The objective assessment was a seven day actimetry concomitantly with a sleep log. Patients under hypnotic drugs had their treatments monitored both before and after all the sophrology sessions. We used a paired t-test to compare the results.

**Results:** Only information on 33 subjects was gathered because 17 patients did not respond to the post-treatment evaluation. The analysis of the results showed a significant improvement in all the subjective parameters (see table). We also observed a significant decrease in the level of anxiety and depression after treatment. However, no significant difference was noted regarding actimetry (total sleep time and number of arousals). Finally, one third (11 of 33) of the patients were able to reduce or completely stop their use of hypnotic medications.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>BEFORE SOPHROLOGY</th>
<th>AFTER SOPHROLOGY</th>
<th>PAIRED T-TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD)</td>
<td>MEAN (SD)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>HAMILTON</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>-</td>
<td>11 (7)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (4)</td>
<td>4.8 (3)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Diurnal alertness</td>
<td>9 (7)</td>
<td>5.7 (4)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td><strong>MADRS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time (mn)</td>
<td>21 (10)</td>
<td>14 (4)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Ketoalube</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Total time of sleep</td>
<td>428 (76)</td>
<td>459 (118)</td>
<td>NS</td>
</tr>
<tr>
<td>Arousal Number</td>
<td>14 (5)</td>
<td>12 (9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusions:** The absence of improvement on actigraphy data may be related to the small number of subjects and to the limited number of the sessions. However, sophrology appears to be useful in the treatment of chronic insomnia and in the withdrawal of hypnotics-drugs-intake. It allows not only an improvement in the patients’ perception of the quality of their sleep but also a better diurnal functioning. Sophrology may also help patients to perceive more positively their insomnia. But, it seems necessary to follow the patients over a longer period to assess the continuous success of this treatment.

**References:**


610.L

**Assessing the Quality of Sleep of Intensive Care Patients**

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**Introduction:** Numerous studies have been devoted to the poor sleep of patients addressed to intensive care units in hospitals. Many environmental factors are playing a role against sleep: noise, light, temperature,... Pain and infection are also contributors. Sleep is finally disturbed by the equipment and the activity of the staff of these intensive care units. Patients in intensive care are therefore frequently sleep deprived and it may interfere with the rehabilitation of the patients. The staff of these units are aware of these conditions, however they have difficulties to assess the sleep of their patients.

**Methods:** We used a mobile visual analogic scale VAS, which is similar to that used to assess pain, to estimate the quality of sleep of 22 patients hospitalised in an intensive care unit after heart surgery. The patients were evaluated the day before and the day after surgery. Patients were also asked to complete the PSQI (Pittsburgh, Sleep Quality Index) before the surgery and when returning home (based on their intensive care period).

**Results:** All patients agree to participate to the study. There were all males with an average age of 66 years old, hospitalised for heart surgery, usually coronary bypass. The results of the VAS evaluation of the sleep quality is shown on the following table. Sleep quality is generally very impaired in these patients, with an average decrease of 40% points in the whole group. Only one patient sleep better and another one sleep similarly. PSQI index have also be compared before and after surgery and we found a significant difference.

**Figure 1**

**Conclusions:** We recommend the use of a mobile VAS to assess the quality of sleep of patients hospitalised in intensive care units. It seems to be a very easy and valid method to compare sleep with a reference basis. It can also be useful to implicate the staff of these units in a better management of their patients’ sleep.

611.L

**Epidemiology of Anxiety, Depression, and Sleep.**

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**Introduction:** Several epidemiological studies of sleep have simultaneously assessed depression and anxiety. However, sleep assessment usu-
ally consists of asking respondents to confirm or deny the presence of insomnia, with little additional data collected on sleep patterns or other medical problems. Rarely are attempts made to exclude those with insomnia secondary to other disorder.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Participants completed 2-weeks of sleep diaries, the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory-Form Y Trait Scale (STAI), and a health questionnaire. People were then assigned to the people with insomnia (PWI) group if they had 1) a report of insomnia for at least the past six months; 2) sleep onset latency or wake time after sleep onset of ≥30 min at least three nights a week. Individuals who did not complain of insomnia and did not have the insomnia sleep pattern were assigned to the people without insomnia (PWOI) group. All others were excluded from these analyses. We have collected and analyzed data from 772 participants. This sample is composed of 381 men and 391 women, ranging from 20 to 98 years of age. We had 151 (19.6%) PWI and 393 (50.9%) PWOI. Below is a sampling of the typical results we will report.

Results: As can be seen in Figure 1, after controlling for age, BDI and STAI scores were higher for PWI than for PWOI, Wilk's $\lambda = .774$, F(2, 536) = 78.233, p < .001. Univariate analyses found significant differences between groups on both the BDI, F(1, 538) = 132.738, p < .001, and STAI, F(1, 538) = 129.036, p = .001. We next performed a MANOVA after removing any individuals whom might have secondary insomnia (i.e., cancer, pain, urinary problems, or other possible sleep disorders), to see if the primary disorder may be causing the elevated scores on the BDI and STAI. We were left with 27 (3.5%) PWI and 240 (31%) PWOI. After controlling for age, BDI and STAI scores were still higher for PWI than for PWOI, Wilk's $\lambda = .842$, F(2, 263) = 24.713, p < .001. Univariate analyses again found significant differences between groups on both the BDI, F(1, 264) = 44.370, p < .001, and STAI, F(1, 264) = 37.578, p < .001.

Figure 1

![Figure 1](image)

Conclusions: Based on self-reported sleep derived from 14 days of sleep diaries and on the BDI and STAI, we conclude that depression and anxiety levels are higher in PWI than PWOI even after controlling for age, and the influence of secondary insomnia.

Research supported by National Institute on Aging grants AG12136 and AG14738

612.L.

Insomnia and its Relationship to Sleepiness in a Community-based Sample

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Introduction: Insomnia appears to be a heterogeneous disorder. DSM-IV diagnosis of insomnia explicitly combines individuals who may have substantially different symptom profiles (e.g., difficulty falling asleep vs. nonrestorative sleep) under one diagnosis. In this study we examine: 1) whether a comprehensive group of insomnia items compose a single factor or multiple correlated factors, and 2) if there are multiple factors, whether the factors show meaningful differences in their relation to measures of daytime sleepiness, depression and anxiety.

Methods: These preliminary data come from the Epidemiology of Daytime Sleepiness Study. To date this study has collected information from a representative sample of 832 people 18-65 years of age in the Detroit primary metropolitan statistical area. The survey used random digit dialing and computer-assisted telephone interviewing techniques. The phone interview included items related to sleep habits, mood, substance use, medical disorders, sleep disturbance, and demographic information. Eleven questions regarding difficulty falling asleep, difficulty maintaining sleep and nonrestorative sleep were examined for inclusion in measure(s) of insomnia. The analyses of factor structure and tests of internal consistency were conducted with split-half samples to assess replicability of the results. The association of the resulting factors with total sleep time and daytime sleepiness (ESS, DSS) were examined in the full sample. The association of the resulting factors with the Multiple Sleep Latency Test, the Beck Depression Inventory, and the Spielberger Anxiety Trait Scale were assessed in a random subset of subjects for whom these measures were available.

Results: For each split-half sample very similar results were found. A two-factor model appeared to best account for the variance among the insomnia items, accounting for 53% of the variance. Factor one was a measure of difficulty achieving and/or maintaining sleep while factor two was a measure of nonresortative sleep. These factors were correlated at $r = 0.5$. Factor based scales showed good internal consistency for scales with only 5 items each: DIMS scale $a = 0.79$ mean single correlation $= 0.43$, Nonrestorative scale $a = 0.74$ mean single correlation $= 0.36$.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Total Sleep Time and Subjective Sleepiness (N=832)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DIMS scale</td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>-0.28**</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale</td>
<td>0.19**</td>
</tr>
<tr>
<td>Daytime Sleepiness Scale</td>
<td>0.26**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>MSLT, BDI, Anxiety (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DIMS scale</td>
</tr>
<tr>
<td>MSLT</td>
<td>0.05</td>
</tr>
<tr>
<td>BDI-II</td>
<td>0.59**</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.40**</td>
</tr>
</tbody>
</table>

*p < 0.05; ** p< 0.01.
Conclusions: Factor analysis of insomnia symptoms identified two correlated dimensions, DIMS and nonrestorative sleep. Scales based on these factor analytic results were similarly associated with total sleep time, subjective daytime sleepiness, depression and anxiety symptoms. However, only the nonrestorative sleep scale was significantly associated with the MSLT.

Research supported by MH59338

Table 1

<table>
<thead>
<tr>
<th></th>
<th>ESS/SSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>.26 ns</td>
</tr>
<tr>
<td>END</td>
<td>.68 p &lt; .01</td>
</tr>
<tr>
<td>FUP</td>
<td>.70 p &lt; .01</td>
</tr>
</tbody>
</table>

Conclusions: ESS measurement of daytime somnolence suggests that the benefits of a behavioral insomnia treatment may survive and even improve after treatment ends. The ESS measures somnolence in different situations distinguishing it from the SSS that taps internal sleepiness at specific times of the day regardless of situation. Our results suggest that the ESS is sensitive to treatment outcome in older insomniacs. Given that it is more economical than the MSLT, as well as more user-friendly than the SSS (which requires repetitive reporting), it should be considered for use as a treatment outcome measure in this age group.

References:

Research supported by the Medical Research Service of the Palo Alto Veterans Affairs Health Care System, by the Department of Veterans Affairs Sierra-Pacific MIRECC, and by AG 12914.
Conclusions: Frequent CAP activity was: 1) distributed across various sleep disorders; 2) commonly associated with insomnia; 3) not associated with specific sleep-related symptoms on the SAQ\(^1\).

References:
(3) Cesta A., Moldofsky H., Sammut C., The University of Toronto Sleep Assessment Questionnaire,\ldots, Sleep Res, 26:646:, 1997
(4) Dept of Psychology

Characterizing Sleepwalking Events in a Natural Environment

Housman DM,\(^{1,2}\) Gorny S,\(^{1,4}\) Allen RP\(^{1,2}\)
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Introduction: Somnambulism is viewed as an arousal disorder. Data gathered from sleep labs suggest that somnambulists are typically deep sleepers. They appear to have a high arousal threshold, which raises further with sleep deprivation, increasing the individual’s susceptibility to sleepwalking episodes. In this model, stimuli that might normally lead to arousal instead, owing to the high arousal threshold, engender an incomplete arousal with sleepwalking. The suddenness of the observed arousal observed in sleep labs suggests an abrupt, jarring incomplete awakening, resulting in sleepwalking.

Methods: However, this may not be the case. Gathering data in a sleep lab involves invasive monitors and unfamiliar environments, which likely alter arousal threshold. These disruptions may mask the frequency, complexity, and periodicity of the events in a natural environment. A self-contained, ambulatory monitor designed to identify body position, Ambulatory Position Monitor (APM, IM Systems, Baltimore, MD), was utilized. The APM consists of two, lightweight, unobtrusive sensors placed on the chest and thigh, identifying and recording the dominant body position for each 30-second epoch. The APM allows activity and body position recordings to occur at home where individuals are most comfortable. Two known somnambulists and three control volunteers wore APMS for one week, while completing a brief daily survey and sleep log. Disturbed sleep was defined by exclusion of all recumbent body position changes during sleep. The somnambulists were found to have, on average, >27 minutes of sleep movement events per night, including position changes during sleep. The somnambulists were found to have, on average, >27 minutes of sleep movement events per night, including sleepwalking episodes.

Results: Among the sleepwalking episodes involving standing and/or walking (the sleepwalkers being the only subjects who demonstrated standing and/or walking behavior), 64% of the episodes involved abrupt arousals, the type that are commonly found during somnambulists lab studies. The remaining 36% of the episodes were characterized by slow and gradual awakenings. There were mini-events and brief arousals throughout the sleep period of somnambulists (comprising over 50% of all events). These mini-events occurred either: alone, before a large event or after a large event. The mini-events comprise about 19 minutes each night for each somnambulist. The controls were found to have, on average, <10 minutes of sleep movement events per night, including position changes during sleep. The somnambulists were found to have, on average, >27 minutes of sleep movement events per night, including sleepwalking episodes.

Conclusions: The data suggest both, the existence of at least two distinct types of sleepwalking episodes, abrupt and the gradual onset types and also the occurrence of a significant amount of mini-events not previously described for somnambulists. Further studies within the natural environment are needed to classify the various sleepwalking episodes. Contrary to results achieved in sleep laboratories, these data suggest that sleepwalkers have very active, frequent movements disrupting sleep, only some of which lead to sleepwalking events.

References:

Vocalization During Episodes of Prolonged Expiration: A Parasomnia Related to REM Sleep

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Ghent University Hospital

Introduction: We report on a sleep-related respiratory dysrhythmia that is characterized by episodes of bradypnea associated with vocalization. To date, many parasomnias with affinity for NREM sleep, REM sleep or both sleep states have been identified. While the reported clinical syndrome may resemble these known parasomnias, different clinical features are pointed out.

Methods: Ten patients (seven males and three females) aged between 20 and 49 years, were included. All patients underwent standard clinical examinations and full polysomnography.

Results: The principal complaint was unusual sound-making during sleep. Polysomnography demonstrated the presence of clustered bradypneic events associated with prolonged expiration and expiratory sound production (Fig. 1). Replay of the sound signal revealed monotonous vocalization, consistent with groaning. These episodes occurred predominantly during REM sleep. Repeated sleep studies showed a remarkably constant night-to-night consistency of these vocalization episodes. Medical and neurological examinations disclosed no particular abnormalities, except in one patient, in whom a frontal meningioma was detected. Different empirical treatments, including pharmacotherapy and nasal continuous positive airway pressure therapy, provided insufficient symptomatic control.
Conclusions: The syndrome described above clearly has distinct features with respect to well-defined sleep disorders, such as central sleep apnea syndrome and somniloquy. Therefore, it is proposed as a separate nosological entity.

References:
(1) parasomnia
(2) central sleep apnea
(3) vocalization

Research supported by Flemish Fund for Scientific Research (FWO grant n° 3.0092.93)

617.M

Slow Wave Activity in Adult Sleepwalkers and Control Subjects: Effects of 38 Hours of Sleep Deprivation

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Introduction: Sleepwalking is a parasomnia characterized by behavioral manifestations occurring primarily during slow wave sleep. Recent studies demonstrated that sleepwalkers have a slower decrease of slow wave activity (SWA) during the night than control subjects, possibly as a result of their frequent transitions from SWS to waking (1). Sleep deprivation may be used as a diagnostic tool for sleepwalking. A dramatic increase in the frequency and complexity of the sleepwalking episodes was found following 38 hours of sleep deprivation (2). It was hypothesized that this increase in clinical events during recovery sleep would affect the expression of the homeostatic process even more than previously demonstrated. This study was designed to assess the effects of sleep deprivation on the SWA of sleepwalkers and controls.

Methods: Ten sleepwalkers (3 males, 7 females, mean age: 25.1, SD:4.09) and 10 sex and age-matched controls (mean ages: 25.2, SD: 3.55) were investigated. All participants underwent one screening night prior to the study. They were then monitored during one baseline night and one recovery night following 38 hours of sleep deprivation. During the procedure, EEG, EMG, and EOG were continuously recorded with a portable device and subjects remained under observation. Half the subjects had the baseline and sleep deprivation sequence reversed to control for any habituation effect. Spectral analysis of the SWA (750 - 400 Hz) was performed on the C3/A2 derivation. A 3 factors ANOVA was used for statistical analyses. Values were expressed as the percentage baseline level of SWA (combining the first four sleep cycles).

Results: There was no between group differences in the sleep variables (sleep latency, stage percentage, total sleep time) for the baseline and recovery night, except for a shorter REM latency in sleepwalkers during the baseline night (F1, 18 =10.84, p = .004). Figure 1 illustrates the dynamic of SWA in both groups for the two nights. There was a significant Night X Cycle interaction, demonstrating the expected increase in SWA in the first (F1, 18 =26.01, p < .001) and second (F1, 18 =29.21, p < .001) sleep cycles following sleep deprivation. There was no between group differences in SWA for the baseline or the recovery night, although an increase of SWA was seen during the second sleep cycle in controls but not in sleepwalkers.

Figure 1

Conclusions: In contrast to previous work (1, 2), this study did not find significant differences in sleepwalkers’ versus controls’ baseline levels of SWA, nor were any such differences obtained for the recovery night. There is no simple explanation for this discrepancy. The results might be partially attributed to the inter-individual differences in the SWA power especially in the third decade. The decrease in the rebound of SWA during the second sleep cycle in sleepwalkers need further validation.

References:
(1) Gaudreau H, Joncas S, Zadra A, & Montplaisir J. Sleep Deprivation increases the second sleep cycle in sleepwalkers need further validation.
(2) Joncas, S., Zadra, A., & Montplaisir, J. Sleep Deprivation increases the second sleep cycle in sleepwalkers need further validation.

Research supported by the Medical Research Council of Canada and the « Fonds de la Recherche en Santé du Québec ».

618.M

Nocturnal Groaning: A New Type of Parasomnia

Istituto di Clinica Neurologica, Università degli Studi di Bologna

Introduction: Sleep-related vocal noises characterise a variety of disorders, from breathing disorders, i.e. snoring and stridor, to sleep talking (somniloquy). Vocalisation and word utterance may also occur during sleep-related epileptic seizures. In all of these clinical conditions the noises produced during sleep are typical and easily recognised by the
Methods: We report four patients, three males and one female, aged between 15-25 years, in whom a unique groaning noise occurred during sleep, from ages 7-20 years, almost every night, without the patients being aware of it, but causing concern and alarming relatives and bed partners. General physical and neurological examination, laboratory investigation, rhinolaryngologic evaluation including fibroscopy of the upper airways with static and dynamic evaluation of vocal cords and videopolysomnographic (VPSG) studies were performed.

Results: Physical and neurological examination, laboratory investigation and otolaryngology evaluation were all normal. VPSG studies revealed that the groaning arose from REM sleep and NREM sleep stage 2, was repeated in clusters and occurred during expiration only. Expiratory groaning was associated with a slight slowing of heart rate and fall of blood pressure with minimal positive intrathoracic pressure and was followed by an end-sprint with a sudden slight increase in heart rate and blood pressure, SaO2 remaining at 95-98 %.

Conclusions: Our patients presented nocturnal sleep-related expiratory groaning in the absence of other physical and neurological affections. The origin of groaning is unknown. Sleep-related functional impairment of neurological structures that control ventilation and/or vocalisation may be possible. The long-term prognosis and treatment of nocturnal groaning remain undetermined.

Chocolate Ingestion and REM Sleep Behavior Disorder: A Case Report

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Introduction: Introduction: REM Sleep Behavior Disorder (RBD) is usually idiopathic although it may be secondary to other disorders. We report on a precipitating agent not previously identified. A 64 year old white male presented with a chief complaint of “Snoring, sleep apnea and nightmares”. He related classic symptoms of sleep apnea including loud snoring, nocturnal pauses in respiration and excessive daytime sleepiness. Additionally, subsequent to a motor vehicle accident ten years prior to his visit that caused significant facial trauma), he developed violent sleep related turning as well as kicking and thrashing. These events occurred approximately five out of seven nights and were associated with “hollering.” The patient admitted to violent nightmares with content that included striking at others and protecting himself from intruders. In lashing out he had injured his right hand. Both the patient and his wife agreed that ingestion of chocolate had repeatedly caused exacerbation of these events. He denied medications that lead to RBD. He admitted to one cup of coffee, noncaffeinated tea only and rare soft drinks. He denied alcohol. He denied other neurologic symptoms and averaged 6 to 8 hours of sleep per night. Physical exam revealed a healthy gentleman with BMI of 33 kg per m2. Neurologic exam was nonfocal.

Methods: Methods: The patient underwent a nocturnal polysomnogram including EEG(C3-A2, O1-A2), EOG, EMG(chin, arm and leg), respiratory channels, oxygen saturation, ECG and video monitoring.

Results: Results: His study revealed an overall respiratory disturbance index (RDI) of 14. REM RDI was 21. Low oxygen saturation was 90 percent. He had increased muscle activity in REM sleep but no overt behaviors. Diagnosis was of OSAS and RBD. He has been treated with CPAP for his OSAS. Clonazepam dramatically reduced RBD symptomatology.

Conclusions: Conclusions: Stolz and Aldrich (1) reported a patient with RBD and prolific caffeine intake. Their patient ceased caffeine intake with improvement in RBD. On recurrence of small amounts of caffeine ingestion symptoms began to recur. Our patient differs in that his intake was of chocolate and his intake was modest. Caffeine can affect REM sleep. Usual reports are of suppression although it has also been reported to cause REM rebound (2). Caffeine also antagonizes the putative sleep substance adenosine a substance which has been noted to decrease locomotor activity. (3) Therefore it appears that this methylxanthine may have worsened RBD by affecting the REM sleep motor control system.

References:

620.N

Characteristics And Scoring Criteria For Leg Movements Recorded During The Suggested Immobilisation Test In Restless Legs Syndrome

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Introduction: The restless legs syndrome (RLS) is characterized by sensory and motor symptoms occurring primarily at rest during the evening and/or during the night. In order to evaluate the presence of these symptoms, a test called the “Suggested Immobilization Test” (SIT) has been designed. This test allows us to quantify, among other measures, leg movements from right and left anterior tibialis muscles EMG during a one-hour period of immobility prior to bedtime (1). The aim of the present study was to further characterize leg movements recorded during the SIT and to investigate whether the criteria defined by Coleman (2) to score periodic leg movements during sleep (PLMS) can also be applied to leg movements recorded during the SIT.

Methods: Forty patients (22 men, 18 women; age: 50.6 ± 12.9 years) diagnosed with primary RLS and who showed a PLMS index > 5 were selected for these analyses. The SIT preceded the nocturnal PSG; it started between 21h00 and 21h30. During the test, patients remained in bed reclined at a 45-degree angle with their legs outstretched. They were asked to limit their voluntary movements for the entire duration of the test. All movements lasting more than 0.5 second were scored. The 0.5-second criterion for minimal duration was used in order to avoid scoring myoclonic discharges. A 4-second criterion for minimal inter-movement interval (IMI) duration was used to avoid counting several EMG bursts.

Results: In general, Coleman’s criteria for scoring PLMS were appropriate for scoring leg movements during the SIT. However, a substantial number of leg movements lasted between 5 and 10 seconds, exceeding Coleman’s maximum duration criterion (see figure 1). Indeed, in 10 patients leg movements of 5 to 10 seconds represented less than 10% of all the movements whereas in 14 patients, they represented more than 20% of the movements and for one individual they constituted more than 60% of all leg movements. The other criteria used to score PLMS (i.e. movements separated by 4 to 90 seconds and occurring in series of 4 consecutive movements) allowed detection of 92.6% of all leg movements. The distribution of inter-movement intervals (IMI), showed in...
figure 2, suggests that a great majority of leg movements recorded during the SIT are periodic, with a IMI modal value between 11 and 12 seconds.

Figure 1

![Graph](image)

**Conclusions:** Considering that leg movements recorded during the SIT last longer than those occurring during sleep, we recommend using a duration criterion of 0.5 to 10 seconds for scoring the former. We also recommend using the same periodicity criteria for the SIT as those used for scoring PLMS.

**References:**

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621.N

**Refractory Periodic Limb Movement Disorder in Patients with Mild Hypertension Treated with Amlodipine Besylate**

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**Introduction:** Periodic limb movements in sleep (PLMD) is a disorder of unknown etiology characterized by recurrent episodes of repetitive, stereotyped limb movements and sleep fragmentation. Although impaired central dopaminergic mechanisms have been suggested in the pathophysiology of PLMD, ionic imbalance may be another important contributing factor. In fact PLMD is strongly associated with uremia and other metabolic disorders including conditions requiring hemodialysis. Theoretically pharmacological agents affecting ionic metabolism may induce or exacerbate existing muscular disturbances. Amlodipine Besylate is a calcium ion influx inhibitor and is a treatment of choice for mild to moderate hypertension. It has been reported that Amlodipine may produce muscle cramps. Although the interaction between leg cramps and muscle jerks in sleep is yet to be established, there may be an impact of the medication on the severity of PLMD and treatment outcome. We report three cases of treatment resistant PLMD in hypertensive patients treated with a calcium channel blocker Norvasc (5-10 mg daily).

**Methods:** Three patients (1 male and two females, Patient 1, 2 and 3; 55, 52 and 58 years old) attended the sleep clinic with a complaint of insomnia and excessive daytime sleepiness. Two consecutive overnight polysomnographic studies were performed and the diagnosis of PLMD (moderate to severe) was established. Patients were commenced on selected dosages of Clonazepam (0.5 - 3 mg). Subsequently they had another pair of overnight sleep studies. A pair of follow-up overnight sleep studies were performed. Polysomnograms were analyzed according to international criteria. Bilateral anterior tibialis EMG was recorded on all occasions and periodic limb movements in sleep were scored based on Coleman’s criteria.

**Results:** Polysomnographic studies showed that PLM index in all three patients remained essentially unchanged in pre- and post-treatment conditions. Patients had high arousal index before and after treatment. There were minimal changes in total sleep time. There was a dramatic increase in the amount of stage 2 (patients 2 and 3) and dramatic decrease of slow wave sleep in all three patients. These changes are most likely related to Clonazepam use. Other parameters of sleep architecture and sleep continuity were similar on both occasions. The essence of the studies is presented in Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient 1 pre-treatment</th>
<th>Patient 1 post-treatment</th>
<th>Patient 2 pre-treatment</th>
<th>Patient 2 post-treatment</th>
<th>Patient 3 pre-treatment</th>
<th>Patient 3 post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam dose (mg)</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Norvasc dose (mg)</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PLM index (hour)</td>
<td>55</td>
<td>46</td>
<td>25.1</td>
<td>26.2</td>
<td>29.9</td>
<td>14.2</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>381.5</td>
<td>362.0</td>
<td>341.0</td>
<td>396.0</td>
<td>404.0</td>
<td>392.0</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>89.1</td>
<td>87.4</td>
<td>95.7</td>
<td>97.9</td>
<td>88.6</td>
<td>94.1</td>
</tr>
<tr>
<td>Arousal index (%)</td>
<td>26.9</td>
<td>18.2</td>
<td>26.4</td>
<td>11.4</td>
<td>18.1</td>
<td>16.9</td>
</tr>
</tbody>
</table>

**Conclusions:** Administration of Clonazepam in patients with concurrent use of Norvasc may not be an effective treatment for PLMD. Alternative treatment for hypertension (angiotensin converting enzyme inhibitors) may be warranted in patients with comorbid PLMD.

**References:**

622.N

**Greater Prevalence of Attention Deficit Hyperactivity Disorder Symptoms in Adults with Restless Legs Syndrome than in Controls.**

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**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) occurs in 3-5% of children and persists into adulthood. Children diagnosed with
ADHD had a greater prevalence of periodic limb movements of sleep (PLMS) and restless legs syndrome (RLS). Treatment with dopaminergic agents improved PLMS, RLS, and ADHD symptoms (1-3). This is the first study of its kind to look at the reverse correlation in adults: the prevalence of ADHD in patients with RLS.

Methods: We determined the prevalence and severity of ADHD symptoms in 58 adult patients with RLS (age 40-94) on stable doses of medication and in 59 adult controls without RLS (age 29-78) using the Brown ADD scale (0-120), and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD (attention 0-9 and hyperactivity 0-9). The prevalence and severity of RLS was assessed in all subjects using criteria and rating scale for RLS developed by the International RLS Study group. Statistical analyses were performed with ANOVA and Chi-square tests.

Results: The mean ADD score was greater (p<0.02) in the RLS group (35 ± 28) than in the Control group (24 ± 19). Highly probable ADD (score ≥55) occurred in 20% of RLS patients versus 7% of controls (p<0.04) and 16% of the RLS patients met full DSM-IV criteria for ADHD versus 3% of controls (p<0.07). According to DSM-IV criteria, the mean attention score was 1.8 ± 2.6 vs 0.4 ± 1.3 (p<0.01) and the mean hyperactivity score was 2.7 ± 2.4 vs 0.5 ± 1.0 (p<0.0001) in patients and controls, respectively. The severity of RLS symptoms was greater (p<0.001) in RLS patients with concomitant ADD (27 ± 9) than in RLS patients without ADD (20 ± 10). The ADD scores were lower in patients with RLS who received dopaminergic drugs (33 ± 27) versus those who did not (42 ± 32) although this did not reach statistically significance.

Conclusions: Patients with RLS have a greater prevalence of ADHD and severity of RLS symptoms. The leg discomfort from RLS or its associated sleep disruption may increase ADHD symptoms. Alternatively, RLS and ADHD may be genetically linked. Concurrent dopaminergic medications, used to treat RLS may improve ADHD symptoms and lead to an underestimation of ADD scores and the prevalence and severity of ADHD in patients with RLS. Statistical significance may have been achieved if the doses of dopaminergic drugs had been titrated to ADHD symptom relief rather than RLS symptoms.

References:

Methods: One large French-Canadian family was analyzed from which 25 individuals were sampled for linkage studies. Of these, 14 were considered affected. Exclusion criteria included presence of conditions known to be associated with RLS. None of the subjects reported the use of medication known to affect sleep, sensory or motor functions. The presence of any other neurologic or sleep disorder was ruled out by interviews and appropriate polysomnographic recordings. Subjects younger than 20 years old were excluded. The genotyping was performed using a modified TECAN Genesis 150 Robotic Sample Processor and two ABI sequencers. The screening set of markers comprised 378 polymorphic and robust fluorescently labeled markers, mostly spaced at an average distance of 10 cm. Parametric linkage analysis was computed by use of the MLINK program from FASTLINK package. Haplotypes were analyzed using the SIMWALK2 program. Since the mode of inheritance of RLS is unknown, lod score analysis was maximized over four major genetic models.

Results: Marker GGAT1A4 on locus 10q22 gave a maximum lod score of 2.17 (at a recombination fraction of 0; p=0.002), suggesting evidence of linkage. Another interesting result was observed for an 18cM region spanned by three microsatellites loci on locus 5q31 (lod score = 1.03 at D5S1505; p=0.017; lod score = 1.51 at D5S816; p=0.05; lod score = 1.34 at D5S1480; p=0.05). Interesting candidate genes in these regions included gamma-aminobutyric acid (GABA) A receptor (5q31.1) and Neuropeptide Y receptor Y6 (5q31).

Conclusions: Although still preliminary, our findings suggest that loci on 5q31 and 10q22 may play a role in the etiology of RLS. However these results deserve further investigation with additional families and complementary analysis in order to confirm these findings.

This work was financially supported in part by MRC and NIH grants to GAR and JM. AD is supported by MRC studentship.

624.N

Sleep-related Markers of Idiopathic and PTSD Nightmare Sufferers: Nighttime Awakenings vs. Leg Movements in Sleep

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Introduction: Several sleep disturbances have been observed in PTSD patients in the sleep laboratory (Nielsen & Zadra, 2000). However, no unique profile of sleep anomalies has yet been established. Sleep disturbances in PTSD are perceived as a result of hyperarousal associated with PTSD (Ross et al., 1989; Boudewyns & Brown, 1996; Mellman et al., 1995). However, sleep disturbances may be due to the recurrent experi-
ence of nightmares (NM), rather than to the expression PTSD hyper-arousal processes. The goal of the present study was to investigate sleep differences among PTSD patients with nightmares (PTSD-NM), non-PTSD idiopathic nightmare sufferers (Idio-NM) and healthy subjects.

Methods: Nine PTSD-NM sufferers and 11 Idio-NM patients reporting > 1 NM/week, using no medications, drugs, or alcohol, and who had no other major psychiatric, sleep or neurological disorders were studied. Nine healthy participants constituted the control group (CTL). All slept in the laboratory for 2 consecutive nights. They were fitted with electrodes for recording sleep stages (EEG, EOG, EMG), as well as a 19-channel EEG montage, digitized at 128Hz. Data collected on the 2nd night were scored by an experienced polysomnographer. When assumptions of homogeneity of variance and distribution normality were respected, one way ANOVAs were computed to assess potential sleep differences across the 3 groups, and Neuman-Keuls post-hoc comparisons used when required. Otherwise, Kruskal-Wallis ANOVAs were conducted, with Mann-Whitney U tests for post-hoc comparisons.

Results: Differences were found among groups on number of nocturnal awakenings (F2, 26=5.79, p = 0.008) and leg movements during sleep (F2, 25= 6.22, p = 0.006). PTSD-NM exhibited more nocturnal awakenings than both IDIO-NM (p = 0.007) and CTL (p = 0.01), whereas no difference was observed between the latter two groups. More leg movements during sleep were observed in both PTSD-NM and Idio-NM compared to CTL (p < 0.001 and p = 0.02 respectively), but the two NM groups did not differ.

Conclusions: Only a greater number of awakenings appears to be unique to PTSD-NM, which supports the hypothesis that a lowered arousal threshold characterizes sleep in PTSD (Ross et al. , 1989; Boudewyns & Brown, 1996; Mellman et al., 1995). However, leg movements during sleep, which maybe present in as many as 76% of PTSD patients (Boudewyns & Brown, 1996), may be a correlate of intense negative dreaming rather than a marker of hyperarousal during sleep in PTSD.

References:

Research supported by Medical Research Council of Canada

625.N

Critical Age for Development of Daily RLS Symptoms

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Introduction: Prior studies have found indications that there are at least two phenotypes for RLS. One phenotype is characterized by RLS symptom onset at an earlier age (<45 years old) and is associated with a high degree of occurrence in families. The other phenotype is characterized by symptom onset later in life (>45 years old) and is much less commonly seen within the same family. These differences suggest an etiological diathesis. Our work has previously shown that patients with early-onset of RLS symptoms show a correlation between age and severity of symptoms, a relationship not shown for patients whose symptoms start later in life. It was hypothesized that the early-onset form of RLS would show a slow progression of symptoms, while the late-onset form would have a more rapid onset of symptoms. This study directly tests this hypothesis by examining self-reported progression of symptoms from a cohort of RLS patients volunteering for a research project on RLS.

Methods: Most of these patients had heard about the research through publications of the Restless Legs Syndrome Foundation. As part of volunteering for the studies, they completed a validated diagnostic questionnaire that included questions characterizing their RLS. One question was asked about the number of years from the start of RLS symptoms to the point that they became daily. This information along with current age, gender and the self-reported age of onset of symptoms were obtained from the questionnaires of 20 consecutive consenting RLS patients (5 early-onset females, 5 late-onset females, 5 early-onset males, and 5 late-onset males), and were analyzed.

Results: There were no significant gender differences for number of years from symptom onset until consistent daily symptoms, or age at which symptoms become daily, (p>0.4 and p>0.37 respectively). However, the data did indicate a profound relationship between age of onset and both the number of years until symptoms became daily and the actual age at which symptoms become daily (p<0.0001 and p<0.0001 respectively). (See figures 1 and 2) Of the late-onset females, two females had yet to perceive daily symptoms. (The number of years between age-of-onset till age at completion of the questionnaire, for these two females, were 2 and 7.) These data are excluded from the figures.

Figure 1

Conclusions: The early-onset-group-symptoms seem to progress to daily occurrence at a rate inversely related to age of onset (Slope range = -0.569 to -0.858). The age-of-onset range separating the two pheno-
typical groups appears to be 40-50 years old. For all but one patient with RLS age of onset greater than 50 years syndrome onset rapidly progresses to a severe daily disturbance of sleep and sleep quality. This range is critically important, as it appears to be the age at which all of the early-onset group’s symptoms become daily. That patients develop daily symptoms within this age range, and RLS onset beyond this age range progresses quite rapidly, suggests a developmental or aging aspect of RLS not previously appreciated. This developmental affect may be due to a fundamental neurological aspect of the disorder that reaches significant expression, in this age range associated with development of daily symptoms in many patients. The rapid progression of symptoms for the late-onset group further suggests a developmental/aging aspect of RLS. It is interesting to note that the iron levels in some brain areas increase for the first part of life and begin to stabilize at about this age. If these data are confirmed in future studies they provide an indication of a strong developmental/aging component of RLS not previously appreciated and may provide further indication of the role of brain iron in the neurological mechanism of RLS.

References:

626.N

A Test of the Reliability and Validity of a Brief, Patient-completed Severity Questionnaire for the Restless Legs Syndrome: The International RLS Study Group Rating Scale

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Introduction: A reliable and valid subjective scale for assessing the severity of the Restless Legs Syndrome (RLS) has not been available. This has hindered the assessment of patients and the evaluation of the results of therapeutic trials (1). Therefore, the International RLS Study group (IRLSSG) now comprising 90 investigators from 15 countries undertook to develop and validate such an instrument.

Methods: To prepare a questionnaire that would be optimally useful for patient evaluation, candidate questions were iteratively submitted to the members of the IRLSSG until there was a general consensus on questionnaire length and content. The final form of the questionnaire included 10 questions that probed both symptom severity and the effect of RLS on sleep, mood, and function in social and occupational settings. Each question allowed answers that could vary numerically from 0 to 4 giving a total 40 point scale. 0 indicated the absence of a problem and 4, a very severe problem. These questions were then administered both to RLS patients and controls in 15 centers in 6 countries. Controls were interviewed once, while patients were interviewed at 2 sessions spaced by about 2 weeks to assess the rest-retest reliability of the questionnaire. Between administrations, patients were kept on the same therapeutic regimen. Patients were also interviewed twice at each administration by different examiners to determine inter-rater reliability and indicated an overall subjective severity rating; they were also seen by a blinded clinician who made an independent global rating without knowledge of the answers to the questionnaire.

Results: 168 patients and 177 controls were rated at the first administration. The mean summed scores (with standard deviations) were: patients: 21.82 (8.55); controls, 0.86 (3.49), p<.0001, indicating strong discriminant validity in separating patients from controls. A factor analysis revealed one major factor accounting for 63 and 71% of the variance, respectively, in the two patient administrations. The one question that contributed least to this factor addressed the issue of relief with walking. Without this question, the severity factor accounted for 68% and 75% of the variance, respectively. A secondary factor clearly loaded on questions concerning the impact of illness. Internal consistency for the instrument was assured by a Cronbach alpha greater than 0.90. Correlations of the summed scores obtained by the two patient raters were 0.927 and 0.974, respectively, at the two administrations. These indicated excellent interrater agreement for questionnaire administration. Correlations between summed scores and the clinician’s global rating were .787 and .844, respectively, indicating good external validity. Test-retest reliability revealed a correlation between summed scores of 0.706. While this is still a very strong result, it may be slightly lower than other correlations because of changes in RLS severity between administrations, which can occur even in the absence of changes in therapy.

Conclusions: This study has found that IRLSSG rating scale to be a reliable and valid instrument. It loads predominantly on one factor indicating disease severity. It should be an easily administered and useful instrument for assessing RLS severity and changes in severity. Ongoing studies will evaluate its sensitivity to changes induced by therapeutic interventions and allow a final determination on whether the question about relief with walking should be included within the questionnaire.

References:

627.N

The Use of Actigraphically Determined Activity Ratios to Measure the Presence of Excessive Motor Activity in the Restless Legs Syndrome

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Introduction: No current objective measure is relevant to all patients with the Restless Legs Syndrome (1). Polysomnography, including measurement of periodic leg movements (PLM), can measure periodic leg movements (PLM) and sleep parameters. This methodology, however, has several disadvantages, including cost and the lack of a universal application to all patients. In recent studies, actigraphy has been used to measure activity and PLM. Miniaturized actigraphs provide increased convenience for the patient, little adaptational effect, decreased cost and feasible long duration recordings. However, PLM do not occur in all patients and levels of activity have not standardized. Therefore, we sought to develop an objective measure of RLS based on the excess activity, both PLM and motor restlessness, which occur in the evening and during the night. In the current study, our aim was to demonstrate that the ratio of night-time to daytime activity would be abnormally elevated in patients with RLS permitting discrimination between symptomatic RLS patients and controls without RLS.

Methods: To date, seven RLS patients and five controls have been studied in a parallel group comparison. Control subjects were screened using a Sleep Screening Questionnaire to exclude those with sleep disturbances. RLS patients qualified for the study with International RLS rat-
Arousal Response During Periodic Leg Movements: an EEG and ECG Study

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Introduction: In patients with periodic leg movements during sleep (PLMS) the analysis of microarousals (MA) remains the reference method to assess the degree of sleep fragmentation and its effect on diurnal performances. However, phasic events in slow wave activity, such as K-complex and delta bursts (1), may occur in association with a motor phenomena and may represent a type of spontaneous arousal (1). Moreover, recent studies have demonstrated that autonomic and quantitative EEG changes may occur during the PLMS even when no obvious alterations in the EEG signal are associated, consisting in a cardiac activation and an increase in delta and alpha power (2). This study has attempted to examine whether a similar over-time changes in the EEG and MA signal occur during PLMS whatever an MA or not was associated.

Methods: The polygraphic recordings of 8 patients, 3 women and 5 men aged 47.8±9.4 yrs., having a PLMS index of 47±17.5, were examined. PLMS were classified into three levels, including PLMS associated with microarousal (PLMS with MA), PLMS not associated with visible microarousal (PLMS without MA) and PLMS associated with an arousal response in K- or delta bursts (PLMS with slow activity). The dynamics of EEG changes was examined for all type of PLMS during 10-sec before the onset and 10-sec after the onset of the PLMS during stage 2 and 3 of the NREMS sleep. Fast Fourier transform (FFT) analysis was done on the PZ-02 lead for 1-sec mini-epochs and five frequency bands were defined: delta (1-4), theta (4.5-7.75 Hz), alpha (8-12 Hz), sigma (12.25-15.0 Hz) and beta (15.25-31Hz). Heart rate (HR) was analyzed for 10 beats before and 10 beats after the onset of the PLMS. PLMS with artifacts on the EEG or MA signal were discarded from the analysis.

Results: Both ratios were notably higher in the patient group: 6 hour, 14.92% (SD) and night-to-day, 9.17% than in the controls, 6 hour 3.80% and night-to-day, 2.36%. Both these differences were significant (p<.05) with minimal overlap between the groups and a four-fold higher mean in the patient groups. In plotting normalized data, it was clear that the relative levels of diurnal activity were similar in the 2 groups, but that during the night, activity was selectively elevated in the patient group.

Conclusions: Our initial data indicate that activity meters may provide a pertinent and efficient means of measuring the elevated levels of evening and nocturnal activity which is characteristic of RLS. These ratios differentiate individuals with active RLS from normal controls without sleep problems. Because restlessness is a universal feature of active RLS, this measure should be applicable to all patients with RLS and not just those with PLM or altered sleep architecture. While it is not likely that increased ratios are specific for RLS, they may prove very useful in tracking changes in clinical status and response to therapeutic interventions.

References:

628.N Restless Legs Syndrome: Clinical Experience with Long-term Treatment

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Introduction: There are almost no data on both long-term treatment efficacy and predictors of good treatment response in patients with restless legs syndrome (RLS) outside study protocol conditions. The value of a newly described RLS-score (RLSS) for assessing evolution of RLS-symptoms is unknown.

Methods: Over the last three years 51 patients (pts, 24 men, 27 women; mean age of 60 years, range 29-79) with RLS were prospectively assessed and seen at least twice in our sleep clinic. Diagnosis of RLS was made according to international criteria [1]. Clinical and polysomnographic data as well as severity of RLS symptoms, as esti-
minated by RLSS, were assessed at study begin. Periodic limb movements in sleep (PLMS) were scored according to conventional criteria. Treatment was chosen individually according to clinical judgement. After a follow-up time of 1-106 months (mean=19) evolution of symptoms was assessed by both overall clinical impression (much better, better, unchanged, or worse as compared to study begin) and RLSS. Clinical characteristics and treatment effect were compared between naive pts (N, never treated for RLS before study begin) and pts with previous treatment for RLS (T). Predictors of treatment response were searched for comparing pts with good treatment response (G, much better or better on follow-up) and those with bad treatment response (B).

Results: There were 29 N-pts and 22 T-pts. The mean RLSS at baseline was 26 (range 12-38). No significant differences were found between the two groups in age, gender, etiology and duration of RLS, familiarity, presenting sleep complaint, RLSS, and percentage of pts with PLMS. At final follow-up 24 (83%) of 29 N-pts and 17 (77%) of 22 T-pts had a good treatment response. The mean RLSS at follow-up was 19 (range 1-36). There was a significant correlation between improvement of overall clinical impression (better or much better on final follow-up) and reduction of RLSS (p<0.01). There was a trend (p=0.07) towards a higher percentage of pts with PLMS in B-pts (100%) as compared to G-pts (62%). In all other variables considered G-pts and B-pts did not differ significantly.

Conclusions: 1) A good long-term treatment response can be obtained and maintained in a clinical setting in about 80% of RLS. 2) The RLSS represents a useful tool for assessment of evolution of RLS-symptoms in individual patients over time. 3) Prediction of a good treatment response is difficult, however, patients with no PLMS may have better chances for a good long-term treatment response.

References:

630.N

Gender and Age Differences in Autonomic Responses to Periodic Leg Movements During Sleep

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Introduction: A high proportion of patients with restless legs syndrome (RLS) show periodic leg movements during sleep (PLMS). These motor phenomena are often associated to EEG changes such as microarousals (MA) and to heart rate (HR) variation essentially characterized by a tachycardia. 1-2 However, little is known about the effect of age on autonomic responses associated to PLMS. The aim of the present study was to evaluate, in patients with RLS, the effect of age and gender on HR response to PLMS.

Methods: 30 RLS patients with a PLMS index greater than 10 were included in this study. They were divided into 3 groups of 10 subjects (5 women and 5 men) according to the age i.e. young (25 to 40 years), middle-aged (41 to 55 years) and elderly patients (56 to 71 years). PLMS were scored according to Coleman’s criteria. Fifty PLMS were selected randomly for each patient across stage 2 sleep. The R-R interval was calculated for 6 heartbeats before and 15 heartbeats after the onset of PLMS. The mean of the five R-R intervals prior to PLMS was considered as baseline and was subtracted from R-R intervals following PLMS. Values were then converted in beats per minute.

Results: No between-group difference was observed for PLMS mean index. The change in HR associated to PLMS is characterized by a tachycardia followed by a bradycardia and was observed in both men and women. A significant age-related difference in the amplitudes in both tachycardia and bradycardia was found for men (F(28,168)=5.58; p<0.001) but not for women (see figures 1 and 2). In male subjects, amplitudes of both bradycardia and tachycardia was significantly higher in young than in middle-aged and elderly patients (p<0.05), but no difference was found between middle-aged and elderly patients. Time course analysis of the autonomic response showed a shift from tachycardia to bradycardia with a progressive return to baseline.

Figure 1

| Mean R-R intervals associated with PLMS for men |

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>young men</th>
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Figure 2

| Mean R-R intervals associated with PLMS for women |

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>young women</th>
<th>middle-aged women</th>
<th>elderly women</th>
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<tr>
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Conclusions: The present study shows for the first time that the autonomic response to PLMS is characterized not only by tachycardia, but this initial response is also followed by a significant bradycardia lasting approximately 10 s. This bimodal response was seen both in men and in women. The effect of age on this response was restricted to men and was characterized by a progressive decrease of this response. These results are in agreement with other studies showing an age-related decrease of cardiovascular response measures in various physiological conditions as well as after the administration of pharmacological agents. The gender difference in the influence of age on autonomic responses parallels what was found for sleep architecture and especially for slow-wave sleep. The time course of tachycardia is more likely to represent an inhibition of a parasympathetic innervation rather than direct sympathetic activation, while the bradycardia can then be seen as a rebound of parasympathetic activation.

SLEEP, Vol. 24, Abstract Supplement 2001
Results
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before and at 2 and 4 weeks and then monthly after injections included:
medications for at least 5 days prior to the study. Evaluations obtained
to 8 consenting RLS patients who had discontinued their RLS and sleep
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Results: Six of 8 patients reported no RLS symptoms at all starting 1–2
weeks after treatment and persisting for 2 to 8 months (fig 1). Sleep effi-
ciency and total sleep time improved. PLM/hr dropped below 20/hr for
all responders and below 10/hr for two. Serum ferritin increased and
then rapidly decreased at rates at least 8 times normal suggesting rapid
loss of body iron by mechanisms. Minor adverse effects, mostly tran-
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measures and subject characteristics failed to predict response, although
changes in MRI measures of iron after treatment correlated with dura-
tion of response

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those that are reversible (i.e. end stage renal disease, iron deficiency ane-
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which was attenuated in RLS patients compared to normal controls. This
may indicate that increasing peripheral iron to higher levels may lead to
increased CSF ferritin with less brain iron insufficiency and, possibly,
reduced RLS symptoms. But dietary iron is unlikely to lead to signifi-
cant serum iron increases since body regulation relies largely on severe-
ly limiting absorption. IV iron, however, bypasses this regulation and
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Conclusion: The results are consistent with our model that brain iron
insufficiency causes RLS. The particular basis for the iron deficit in some
but not all patients permits some utilization of higher levels of serum
iron. Thus the dramatic response to IV iron strongly supports the causal
iron-RLS relation and also reveals at least two different types of RLS
pathology. While a placebo response seems unlikely, a double-blind
study is needed.

Research supported by Generous private donation by Richard
Levin, MD

632.N

Periodic Limb Movements in the United Kingdom General Popula-
tion: Relationship to Age and Sex

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Introduction: Previous studies in elderly populations have shown that
periodic limb movements (PLM) can occur without a sleep-wake relat-
ed complaint. The prevalence of PLM in these studies has been similar,
but the relationships with age and sex have been variable. Two studies
which have been carried out using younger subjects have shown a posi-
tive relationship between age and PLM (1,2) but no difference between
the sexes (1). The aim of this study was to determine the prevalence of
PLM in a UK population with no reported sleep-wake complaints and to
examine, (a) correlation with age, and (b) differences between males and
females, in PLM.

References:
(1) Sforza E, Nicolas A, Lavigne G, Gosselin A, Petit D, Montplaisir J.
Neurology 1999; 52:786-791.

Research supported by the Canadian Institutes of Health Research
(grant to J. Montplaisir, G. Lavigne and studentship to M. Michaud)
and by the National Sciences and Engineering Research Council
(studentship to N. Gosselin).
Methods: The population consisted of unrelated volunteers aged between 20 and 70 years, screened to exclude, (i) reported sleep related problems, including daytime sleepiness / fatigue, (ii) medication to aid sleep, and (iii) an overnight oxygen desaturation index greater or equal to 5 per hour. The volunteers underwent a home study of foot movements for 3 consecutive nights using actigraphy previously validated for this type of movement detection and analysis. The movement data from the two legs was combined electronically and scored for PLM using the following criteria: (i) movement length of 2-8 seconds, (ii) inter-movement interval of 8-90 seconds, (iii) at least 4 consecutive movements. The number of PLM per hour of self-reported time in bed (TIB) was calculated for each night and averaged for the 3 nights. Non-parametric statistical analyses were used to examine for correlations with age and differences between men and women.

Results: The PLM per hour of TIB meaned for the 3 nights ranged between 0 and 55.97 (mean = 8.9, median = 3.7). The proportion of the population who had 5 or more PLM per hour was 40.4%. The relationship between PLM per hour and age is shown by figure 1. There was a weak positive correlation between age and PLM per hour (p = 0.042, Kendall's correlation coefficient = 0.135). Males had significantly more PLM per hour than females (medians = 7.2 and 2.4 respectively; p = 0.001).

Figure 1

Conclusions: We have shown that 40% of our population of 20-70 year olds had 5 or more PLM per hour even though none had sought medical advice. Men had significantly more PLM per hour than females and there was only a small, though significant, correlation with age. The proportion that had 5 or more PLM per hour was slightly lower than that previously reported in elderly populations.

References:
(2) George B, Ancoli-Israel S, Kripke DF. Comparison of sleep apnea and periodic movements in sleep in two age groups of females. Sleep Research 1985;14:156.

PLMS and Autonomic Activation in Patients with Restless Legs Syndrome and REM Sleep Behavior Disorder

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Introduction: We recently found that periodic leg movements in sleep were elevated in a series of conditions associated with dopaminergic dysfunction especially restless legs syndrome (RLS), REM sleep behavior disorder (RBD), and narcolepsy (1). The aim of the present study was to look at similarities and differences between PLMS recorded in patients with RLS and RBD. Most specifically, we were interested in investigating whether or not leg movements in RBD patients were associated with a similar degree of autonomic activation (expressed by changes in heart rate) as those previously reported in RLS patients (2).

Methods: Ten men diagnosed with chronic idiopathic RBD (age 64.5 ± 3.4 yrs) and ten age-matched men suffering from primary RLS (age 64.9 ± 4 yrs), showing a PLMS index greater than 10, were included in the study. All patients were free of medication for at least two weeks prior to the recording. Approximately fifty PLMS, scored according to Coleman’s criteria, with or without microarousals (MA), were selected randomly across Stage-2 sleep, for each patient. For selected PLMS, the R-R interval was calculated for 6 heartbeats before and 10 heartbeats after the onset of the movement and converted in beats per minute. The mean value of the five R-R intervals prior to PLMS onset was regarded as baseline and subtracted from each R-R interval after PLMS onset.

Results: No between-group difference was found for PLMS mean index. Changes in heart rate associated to PLMS in RBD subjects were similar to those observed in RLS subjects and were characterized by a tachycardia lasting approximately 10 seconds. Indeed, the ANOVA showed a main effect for time course (F(9,162)=16.29; p<0.00015). The group x time interaction was near significance (p=0.07, before applying sphericity correction) suggesting a trend for reduced cardiac response in RBD patients compared to patients with RLS, as shown in the figure.

Figure 1

Conclusions: The present study showed that cardiac activation occurs in association with PLMS in both patients with RLS and patients with RBD. This is characterized by a period of tachycardia lasting approximately 10 sec. However a tendency for a decrease of the autonomic response in patients with RBD was observed, compared to age-matched RLS patients. This is in concordance with previous investigations of changes in the cardiovascular functions during sleep and wakefulness in patients with RBD for whom a decrease in both sympathetic and
parasympathetic functions was found (3). These changes are thought to be related to degenerative alterations occurring in the brain stem, especially in areas associated with autonomic control, such as the locus coeruleus. A greater number of subjects should be included in the study in order to better evaluate the amplitude of the cardiac response to PLMS in these two populations.

References:

Research supported by the Canadian Institutes of Health Research (grant to J. Montplaisir and studentship to Martin Michaud), by the Government of Canada (fellowship to L. Fantini) and by the National Sciences and Engineering Research Council (studentship to N. Gosselin)

634.N

Periodic Chin EMG Activity of Long Duration and Interval

Girish MR, Harris C, Shepard JW
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Introduction: Periodic limb movements of sleep (PLMS) have been defined as movements occurring at intervals between 5 and 90 seconds, with a duration of 0.5 to 5 seconds. We describe a patient who demonstrated periodic bursts of EMG activity recorded by the chin electrodes with duration and interval well in excess of these defined parameters.

Methods: The subject was a 60-year-old male who presented with the complaint of excessively loud snoring and witnessed apneic episodes. Sleep history was otherwise insignificant and his medical history and physical examination were negative, except for hypertension and obesity. During PSG, the subject had 465 minutes of total sleep time of which 12% was stage 1, 30% stage 2, 12% stage 3/4, and 18% REM. The apnea/hypopnea index of 66 per hr was decreased to 12 per hr with nasal CPAP with duration and interval well in excess of these defined parameters.

Results: There were bursts of chin EMG activity with a duration of 17-24 sec (mean 21 sec) that occurred at an interval of 200-350 seconds (mean 270 sec). These were continuous through all stages of sleep, including REM and the CPAP titration. They were not associated with arousals. The periodicity was not disrupted by intervening brief periods of wakefulness.

Figure 1

Conclusions: A patient is described with highly stereotypical periodic submental muscle activity of approximately 21 second duration recurring at intervals closely approximating 5 minutes. These events were not associated with arousals and no apparent clinical sequelae. This observation indicates that: 1. Periodic muscle activity can occur in axial as well as limb muscles and elicited off-duty napping [ t (51) = -2.73, p < .01]. (This is periodic for muscle activation may be of longer duration and interval length than the published criteria for the scoring of PLMS.

635.N

Familial Nocturnal Faciomandibular Myoclonus: Neurophysiological and Videopolysomnographic Findings

Istituto di Clinica Neurologica, Università degli Studi di Bologna

Introduction: Sleep bruxism is a stereotyped movement disorder characterised by grinding and clenching of the teeth during sleep. Phasic-rhythmic or tonic-sustained motor activity of jaw muscles has been described. Nocturnal myoclonic jerks in the oromandibular region, a poorly known condition, have to be separated from nocturnal bruxism. We investigated the clinical and neurophysiological findings of two cases of nocturnal faciomandibular myoclonus.

Methods: Two patients, mother and son, aged 74 and 46 years, were investigated for 40 and 25 years of nocturnal tongue biting and bleeding, which were attributed to sleep bruxism. Neurological investigation showed slight brisk tendon reflexes in the mother whose brain MRI revealed multiple scattered periventricular lucencies. Complete laboratory investigation, including iron metabolism, was normal. Both patients underwent somatosensory evoked potentials (SEPs), transcranial magnetic stimulation (TMS), blink reflex, wake EEG and videopolysomnographic (VPSG) recording.

Results: SEPs, TMS and blink reflexes were normal in both patients. EEG did not show any paroxysmal cortical activity. Nocturnal VPSG recording disclosed in both patients myoclonic jerks involving masseter and orbicularis oris and oris muscles bilaterally, often accompanied by tooth biting sounds. The myoclonic activity occurred in a quasi periodic rhythm, also in repetitive bursts, prevailing during NREM sleep. Jerks could determine arousals that were accompanied by stereotyped chewing movements. Independent arousals often presented with chewing movements too, without myoclonus. EEG-EMG back-averaging did not show any jerk-related cortical potentials. The masseter jerks preceded by about 15 ms (range 7-20 ms) the jerks of orbicularis oris and oris muscles. Considering facial and masseter nerve distal motor latencies and F waves and the delay between the activation of the masseter and the orbicularis oris we concluded that the efferent volley engaged a polysynaptic pathway to travel from the fifth to seventh nucleus, in agreement with similar finding in reticular myoclonus (Rothwell JC et al. 1986). Clonazepam 0.5-1.5 mg at night led to some improvement.

Conclusions: Faciomandibular myoclonus can simulate sleep bruxism and, as in our patients, should be recognised as a distinct pathological condition. Neurophysiological analysis suggested a brainstem origin with state dependent sleep modulation. Clonazepam can improve faciomandibular myoclonus.
Long-term Treatment for Restless Legs Syndrome with Pramipexole: Augmentation Effect Findings

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Introduction: Dopaminergic agents are the most studied and seems to be the most successful drugs for the treatment of Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) (1). An important effect reported by patients after the dopaminergic treatment is the worsening of symptoms with long-term use of these medications, referred to as RLS augmentation: this complication is seen most commonly with levodopa, but also in more than 25% of patients treated with pergolide (2). The symptoms of augmentation may present as a progressively earlier onset of RLS symptoms on a daily basis and can be characterized by the expansion of symptom beyond the legs (e.g., involving the trunk or upper limbs).

Methods: In our open-label clinical series we examined the occurrence of RLS augmentation in consecutive RLS patients treated with pramipexole for at least 6 months. RLS diagnosis was made according to ICSD (3) criteria and nocturnal PSG showed PLMS in all the patients.

Results: Sixty patients were included in the study (mean age 58 yrs, range 37-90 yrs; mean RLS duration= 28 yrs, range 0.5-50 yrs; primary form= 39; secondary form= 21). Fifty-one patients have been previously treated with other medications (clonazepam in 29, gabapentin in 17, l-dopa in 15, pergolide in 15, others compounds in 19). Pramipexole dose was variable: 0.25 mg in 40 patients, 0.5 mg in 7 patients, 1 mg in 13 patients. The administration was by means of a single dose 1h before bedtime for all patients. RLS augmentation has been observed in 5 patients (mean age= 58, range 49-75 yrs; mean RLS duration= 24 yrs, range 11-30; primary form= 1; secondary form= 4; pramipexole dose= 0.25 mg in 4 patients and 1.0 mg in 1 patient). Augmentation has been observed after 4 weeks in 1 case, after 8 weeks in 2 cases, after 12 weeks in 1 case and after 15 weeks in 1 case.

Conclusions: Our study showed that RLS augmentation may occur in a very low percentage of patients treated with pramipexole (8.3%). This complication seems to be unrelated to the dose of medication and occurs within the first 4 months after initiation of treatment. Augmentation seems to be more frequent in secondary forms respect to idiopathic ones of RLS.

References:

Decision Making Process for Periodic Limb Movement Disorder

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Introduction: Periodic Limb Movement Disorder (PLMD) is a disorder characterized by repetitive stereotyped limb movements during sleep. Unlike restless leg syndrome, clinical criteria to diagnose PLMD without polysomnography were rarely assessed. The aim of this study was to identify a set of clinical criteria that would allow one to reliably diagnose PLMD without using polysomnography. This set of criteria could be then used in epidemiological studies to determine the prevalence of the disorder.

Methods: Seventy two patients attended for the first time to the Sleep and Alertness Clinic at the Toronto Western Hospital were included. Each patient was interviewed twice, once by a physician using Sleep-EVAL system and again by a sleep specialist. The sleep specialist provided up to three initial diagnoses. These diagnoses were revised once polysomnographic recordings were completed. The physician interviewing the patient with Sleep-EVAL remained blind to all diagnoses by Sleep-EVAL. Diagnoses were given by four different sleep specialists. The Sleep-EVAL questionnaire assessed several aspects of sleep disorders: insomnia symptoms, daytime sleepiness, leg symptoms (pain, creeping, discomfort, cramps, jerks). Medical history, medications, and psychiatric history were also assessed. The mean age of these subjects was 47.34 (±12.55) years and 48.8% were women. Most were married (66.7%). Most of them were caucasian (85.7%).

Results: Twenty-four subjects had a PLM index of 5 or more including 12 men and 12 women (48.7±9.4 years); 48 subjects with various sleep disorders were used as control group (23 men and 25 women; 46.7±13.1 years). Nightly complaint of non-restorative sleep was more frequent in the PLMD group (66.7%) as compared to the control group (39.6%; p=0.03). Difficulty in initiating or maintaining sleep did not differentiate the two groups. Report of excessive daytime sleepiness was also comparable in the two groups (PLMD group: 70.8% vs.54.2%). A factor analysis was used to identify what are the self-reported symptoms associated with a PLM index of five or more. Excessive limb movements during sleep occurring more than 3 times per week (loading value .67), agitated sleep more than 3 nights per week (.64), nightly complaint of non-restorative sleep or disrupted sleep (.61) and excessive daytime sleepiness (.40) and PLM index were grouped together by the factor analysis. These self-reported symptoms allowed to identify 83.3% of subjects with a PLMD of 5 or more.

Conclusions: Clinical criteria can be useful to identify subjects with PLMD. However, minimal criteria proposed by the International Classification of Sleep Disorders 2 need to be amended to allow a better recognition of this disorder.

References:
ing 5 to 5 seconds and recurring at intervals of 5 to 90 seconds. PLM's are often associated with a variety of complaints including early sleep onset difficulty, excessive daytime sleepiness (EDS) and nocturnal awakenings (NA). A multicenter collaborative study involving 18 sleep disorder clinics reported PLMS to be the primary pathological finding in 17% of the patients complaining of insomnia and 11% of the patients complaining of EDS. In assessing the degree of severity, the number of PLM per hour of sleep or PLM index (PLM-I) is calculated along with the PLM arousal index (PLM-AI) which is the number of arousals per hour associated with PLM. An arousal index greater than 5 is considered significant and may justify treatment. Ambiguity however remains regarding whether PLM inherently, without the association of arousals, produce clinically significant sleep disturbance symptoms that warrant further treatment.

Methods: A retrospective review of 300 polysomnograms was performed for PLM-I defined as greater than 20 not associated with concomitant obstructive sleep apnea (OSA) or depression. These studies were reviewed with special attention to PLM-I, PLM-AI, Epworth Sleepiness Scale (ESS) scores, sleep efficiency (SE) and number of NA.

Results: 45 of 300 (15%) had PLM-I>20 without associated OSA or depression with an average of 47.4 (range 20-104). Of these 45 patients, 24 (53%) had an increased PLM-AI>5 with an average of 12.7 (5.1-30). Averages and ranges of ESS, SE and number of NA in increased PLM-AI group were as follows respectively: 11 (4-22), 76.5% (0-100%) and 3.1 (1-7). These values were strikingly similar to those of normal PLM-AI group which were respectively: 12.2 (0-25), 76.2% (38-100%), and 3.1 (0-7).

Conclusions: These results were obtained via the evaluation of subjective sleep disturbance parameters (ESS, SE and NA) assessing daytime somnolence, sleep fragmentation and insomnia. Our findings suggest that sleep disturbance occurs just as often in patients with PLM associated with increased arousals as those which had no significantly associated arousals. This indicates that pathophysiological factors other than scored arousals may need to be investigated to determine the degree of PLM severity. It also may be reasonable to consider reevaluation of established diagnostic criteria to include those patients with a solely elevated PLM-I without PLM-AI increase as abnormal and on this basis institute appropriate treatment measures.

References:
(3) Stip E, Godbout R: akathisia scale. Sch-NA were 6 patients (age: 32-53 yrs) without akathisia (Barnes <1). None of the patients took antiparkinsonian drugs. Controls were 6 healthy subjects (35-58 yrs). The SIT involves surface EMG recording of anterior tibialis muscles for 60 min. while the participant is sitting with legs outstretched. Each 5 min. participants reported level of discomfort in the lower limb on a visual analog scale.

Results: Sch-A patients showed a higher rate of EMG-detected leg movements compared to controls (see Figure 1). Regarding the subjective sensation of discomfort, ANOVA revealed a significant principal effect for the different periods (F (1,176)=9.14, p=0.0001 ) during the SIT. Both group of patients showed a higher discomfort during the SIT, compared to controls (see Figure 2).

Figure 1

Figure 2

Conclusion: SIT results showed an association between RLS and neuroleptic-induced akathisia and we suggest that common neural structures (e.g., striatum) may be involved. Subjective results suggest the existence of a paresthesia-type of hypersensitivity in schizophrenia that would be independent from objective measures.

References:

Supported by “Fonds de la Recherche en Santé du Québec”
Heart Rate Response To Periodic Leg Movements During Sleep In Restless Legs Syndrome, Narcolepsy And Idiopathic Hypersomnia

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(1) Centre d’étude du sommeil et des rythmes biologiques, Hôpital du Sacré-Coeur de Montréal, Canada, (2) Département de Psychiatrie, Université de Montréal, Canada, (3) Département de Psychologie, Université de Montréal, Canada

Introduction: Periodic leg movements during sleep (PLMS) are a frequent manifestation of sleep disorders involving a dopaminergic impairment, namely narcolepsy, REM sleep behavior disorder and restless legs syndrome (RLS)(1). PLMS have also been reported in patients with idiopathic hypersomnia (IH) as well as in insomniacs. The association between PLMS and changes in autonomic functions such as microarousals (MA) and cardiac activation has been documented for patients with RLS only (2). The aim of the present study was to evaluate whether this heart rate change was also present in patients with narcolepsy and in patients with IH, two conditions in which excessive daytime sleepiness is a primary feature.

Methods: Ten patients suffering from narcolepsy (8 men, 2 women; age: 45.7 ± 9.6 yrs.) and ten age-and sex-matched patients diagnosed with IH (46.4 ± 7.8 yrs.), who showed a PLMS index greater than 10, were selected for this study. The results obtained with these two group of patients were compared to those of patients with primary RLS (45.3 ± 7.7 yrs.) matched for age and gender. Analyses were performed for the first night of polysomnography. PLMS were scored according to Cole’s criteria. Fifty PLMS with or without MA were selected randomly across the night in stage-2 sleep for each patient. For each of these PLMS, the R-R interval was calculated for 6 heartbeats before and 10 heartbeats after the onset of movement and converted in beats per minute.

Results: No between-group difference was seen for PLMS index. The figure shows the distribution of the change in mean R-R intervals before (Bn) and after PLMS. Intervals were normalized by subtracting the mean value of the five intervals preceding the onset of the movement, considered as the point of reference, from each interval value. ANOVAs revealed no interaction and no between-group difference in the pattern of R-R interval changes but showed a main effect for time course (F(9,234)=30.2; p<0.00001) characterized by a tachycardia. Analysis of this time effect revealed a significant quadratic trend (F(1,26)=110.3; p<0.0001). The figure shows the distribution of the change in mean R-R intervals before and after PLMS.

Conclusions: These preliminary results suggest that the heart rate response to PLMS, as previously documented in RLS, are also present in narcolepsy and IH. However, further studies should be performed with a greater number of heartbeats after the onset of PLMS in order to specify the time course of the changes in R-R intervals. This would also allow to better verify whether or not there are differences among these three conditions.

References:

Research supported by the Canadian Institutes of Health Research (grant to J. Montplaisir and studentship to M. Michaud) and by the National Sciences and Engineering Research Council (studentship to N. Gosselin)

Frequency and Neurophysiological Parameters of PLM: A Comparison between RLS Patients and Healthy Controls

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Introduction: This study compares frequency and pattern of periodic leg movements (PLM) as well as polysomnographic sleep parameters of a large group of patients with restless legs syndrome (RLS) with an age-matched healthy control group.

Methods: A sample of 95 unrelated patients (mean age 54.7±11.1 years, 49 men, 46 women) with idiopathic RLS according to the international standard clinical criteria and 31 healthy controls (mean age 59.3±9.4 years, 15 men, 16 women) underwent two nights of polysomnography. All patients were untreated or withdrawn from RLS medication at least 10 days prior to the investigation. Seventeen of the RLS patients had additionally participated in a controlled, double-blind trial with the dopamine receptor agonist pergolide (1). Sleep stages and PLM of the second night, including the time of onset of PLM, their duration and associated arousals in the EEG, were scored visually by standard methods.

Results: Gender or duration of the illness did not correlate with any of the PLM parameters, but there was a significant increase in PLM frequency as well as a decrease in SWS with advancing age of the patients. Polysomnographic measures showing a significant difference between untreated patients and controls are summarized in table 1. Discriminant analysis between the untreated patients and the controls using several PLM and sleep parameters showed an overall correct classification rate to the examined groups of 84% (85% sensitivity, 81% specificity). Among all parameters describing the pattern of the PLM, the mean duration of PLM during NREM sleep and wakefulness, as well as the percentage of PLM associated with arousal contributed reasonably to the discrimination power (see table 2). The PLM index was significantly different between the 3 groups of non-treated, treated RLS patients and controls, with treated RLS patients having the lowest PLM index (4.2±3.8/h, p<0.05). The mean duration of PLM during wakefulness remained relatively unchanged in RLS patients under treatment (2.5±0.3 sec), and in both, untreated and treated patients it was significantly longer than in the control group (p<0.05). During NREM sleep, the mean duration of PLM was 2.0±0.4 sec in treated RLS patients. The difference was significant, if RLS patients were compared to controls as well as to treated patients (p<0.05). The relative number of PLM associated with arousal was similar in the RLS group without and under treatment (60.6±20.9% and 66.1±24.0%, respectively) and significantly different from controls (p<0.05).
Results: As a result of the first step of the protocol, the suspicion of RLS and PLM had been proved in 49 patients. Recently, 31 RLS patients underwent eletrophysiological evaluation (EMG) and nerve conduction velocities, 15 of which were abnormal (14 had neuropathy of mixed types and one had L5 radiculopathy). RLS has also been reported in association with lumbo-sacral radiculopathy. RLS has also been associated with uremia and 3 patients under hemodialysis do actually complain of RLS symptomatology. RLS has also been reported in association with iron deficiency anemia in 18 elderly patients. Low serum ferritin levels were found in the RLS patients. In a recent study, 9 RLS patients had fibromyalgia. In this survey we found 13 idiopathic RLS and 7 idiopathic PLMS patients. In the idiopathic group we distinguished patients who complain of pain associated RLS (group A) and patients with mild symptoms or periodic limb movement alone (group B). The treatment was gabapentin at doses ranging from 1200 to 1800 mg per day. On the base of SIT index and actigraph control after treatment the sleep efficiency was better in group A.

Conclusions: This management system offers many advantages both from professional and cost-beneficial aspects. We are able to provide individually selected and combined treatment for each patient. Patients has painful limb disorder may do very well on gabapentin.

References:

643.N

Lack of Statistical Association between Antidepressant Use and Clinical Restless Legs Syndrome in Patients Referred for Insomnia

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Introduction: Restless legs syndrome (RLS) is both highly prevalent and also an important cause of insomnia. There is good evidence that iron deficiency anemia and renal insufficiency are causes of RLS, but many of the other associations that have been part of RLS clinical lore remain largely anecdotal. In particular, antidepressant medications such as tricyclic antidepressants (TCA’s) and selective serotonin reuptake inhibitors (SSRI’s) have been widely believed to cause the emergence or worsening of RLS, but only case reports involving 1-3 patients have been published with these data. We performed a retrospective chart review in order to investigate a possible association between RLS and the use of antidepressant medications.

Methods: The charts of 100 consecutive patients evaluated for a chief complaint of sleep initiation insomnia at the New Mexico Center for Sleep Medicine between September 1998 and February 1999 were retrospectively reviewed. The following information was abstracted: age, gender, current diagnosis of depression, current use of antidepressant medication (categorized as TCA, SSRI, or other), and physician diagnosis of RLS (using standardized clinical criteria). Statistical analyses were carried out using the SAS System and JMP Statistical Discovery Software (both from SAS Institute Inc., Cary NC). The chi square or Fisher’s exact test was utilized for proportions, and Student’s t-test was used for continuous variables. The null hypothesis was rejected for P<0.05.

Results: Sixty-two patients were female and 38 were male. Age (mean±SD) was 53.9±14.8 years, and was similar in men and women. Forty-five percent of the patients and 37% of the men used antidepressants (p=NS). Physician diagnosis of RLS was present in 49 and absent in 51; RLS was present in 60% of the women but only 32% of the men.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>RLS patients mean ± SD</th>
<th>controls mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency (min)</td>
<td>22.1 ± 32.8</td>
<td>15.3 ± 11.7</td>
</tr>
<tr>
<td>PLM index (n/h)</td>
<td>28.3 ± 23.6</td>
<td>14.6 ± 15.4</td>
</tr>
<tr>
<td>PLMS index (n/h)</td>
<td>27.8 ± 26.2</td>
<td>12.1 ± 14.6</td>
</tr>
<tr>
<td>PLMW index (n/h)</td>
<td>32.3 ± 28.2</td>
<td>24.6 ± 32.6</td>
</tr>
<tr>
<td>PLM duration im NREM (sec)</td>
<td>2.5 ± 0.6</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>PLM duration during wakefulness (sec)</td>
<td>2.6 ± 0.4</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>PLMS index (n/h)</td>
<td>60.6 ± 20.9</td>
<td>46.2 ± 21.8</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>within-group correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of single PLM during NREM sleep</td>
<td>0.62</td>
</tr>
<tr>
<td>Total number of LM</td>
<td>0.41</td>
</tr>
<tr>
<td>Mean duration of single PLM during wakefulness</td>
<td>0.38</td>
</tr>
<tr>
<td>Fraction of PLMS associated with arousal</td>
<td>0.36</td>
</tr>
<tr>
<td>PLM index</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Conclusions: RLS patients differ from healthy controls not only in the frequency of PLM, but also in neurophysiological features of a single leg movement within a sequence of PLM: The duration of a limb movement during wakefulness discriminates between RLS patients and healthy controls and is not influenced by treatment with pergolide in contrast to the PLM frequency (1). In accordance with earlier reports, the severity of the PLM syndrome does not correlate with parameters of sleep quality.

References:
The presence of RLS did not vary with age in this relatively narrow sample. SSRI's were used by 17 patients, TCA's by 13, and 18 used antidepressants of other types (some used 2 types of antidepressants). Of the patients with RLS, 26 were on antidepressants and 23 were not. No statistically significant relationship was found between antidepressant use in general and the presence of clinical RLS. In addition, no individual relationship was present between the use of any category of antidepressant (TCA, SSRI, or other) and RLS symptoms.

Conclusions: The association between RLS and antidepressant use may not be clinically significant.

References:

644.N

Periodic Limb Movements: Effect of CPAP

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Introduction: Obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD) are relatively common disorders that frequently occur as co-morbid conditions. While the pathophysiologic events present in OSA could lead to the development of PLMD, there is little evidence to suggest that the acute correction of OSA with CPAP alters the frequency of periodic limb movements (PLM). We hypothesized that the application of CPAP in patients with OSA would result in a net decrease in PLMs.

Methods: We retrospectively reviewed all polysomnograms done at the Indiana University sleep laboratory during the period from January 1, 1997 through August 30, 2000. Sleep was scored using Rechtschaffen and Kales criteria and limb movements were scored according to criteria for periodic limb movements.1 Criteria for inclusion were: studies with an AHI > 15 during the first two hours of baseline sleep, studies performed using a split-night format, and a PLM index > 5 per hour of sleep during the baseline portion of the study or during the CPAP titration. The effect of CPAP was calculated by subtracting the number of PLMs per hour of sleep during the baseline from the number during the CPAP titration phase.

Results: A total of 109 studies met the selection criteria. The subjects were 53.6 ± 10 years old, 69.1 ± 3.6 inches tall and weighed 255.4 ± 66.5 pounds. The group included 15 females. The changes in PLMs followed a Gaussian distribution (mean 2.8 ± 57.1). Thus, the difference in PLMs per hour of sleep from the baseline to the titration phase was not significant (p<0.05). PLM frequency increased in 65 patients (60%) and decreased in 44 patient (40%) (36.6 ± 38.4, and 47.0 ± 41.7 per hour, respectively). Subgroup analysis in patients with greater than 45 PLMs decreased in 44 patient (40%) (36.6 ± 38.4, and 47.0 ± 41.7 per hour, respectively). PLM frequency increased in 65 patients (60%) and not be clinically significant.

Conclusions: The association between RLS and antidepressant use may not be clinically significant.

References:

645.N

Validation of a Structured Diagnostic Interview for the Restless Legs Syndrome: Reliability, Sensitivity, and Specificity

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Introduction: The diagnosis of the Restless Legs syndrome (RLS) is currently a purely clinical diagnosis, based primarily on the patient’s history of the disorder. Indeed, current AASM standards indicate that the use of sleep laboratory evaluation through polysomnography is not indicated for routine diagnosis or evaluation of RLS. As a result, there is a clear need to establish efficient, standardized means for the diagnosis of RLS. In the past several years, the group at Johns Hopkins has been working to develop and validate both patient completed and expert administered structured questionnaires that will be reliable, specific, and sensitive in diagnosing RLS in both patients and those unaffected by the disorder. The goal of the project reported here was to develop an instrument that could make accurate diagnoses with a brief telephone interview.

Methods: A structured diagnostic interview was developed based on criteria for diagnosis of RLS established by the International RLS Study group. The interview also contains items relating to likely confounding conditions, including leg cramps and peripheral neuropathy. In order to validate the questionnaire, 3 independent clinician-investigators interviewed 59 individuals by phone. RLS patients were selected from the clinics of the Johns Hopkins Bayview medical center and controls were either related individuals or persons previously screened and found not to have RLS. 28 patients and 31 controls were interviewed. All interviews were done anonymously with code names and with a varied order so that each interviewer occupied one of 3 possible positions about one third of the time. After following the script of the interview, the interviewers made a determination of the presence or absence of RLS in each interviewee.

Results: The interviewers were unanimously correct on 56 interviews; one interviewer was in error on one each diagnosis of RLS or its absence. All 3 interviewers were in error regarding a final interviewee, finding RLS where the diagnosis had been excluded. These results gave a pair-wise interviewer concordance of 98%, a sensitivity of 99%, and a specificity of 95%.

Conclusions: The structured diagnostic interview developed at Johns Hopkins Bayview can be used by experienced RLS diagnosticians with a high degree of confidence as to outcome. Sensitivity of the instrument is excellent and specificity is also quite high. This instrument can, therefore, be used for studies of RLS based on a brief, less than 10 minute telephone interview. This interview, therefore, is a reliable, sensitive, specific, and efficient instrument for use in epidemiological studies.

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Nocturnal Oximetry and Daytime Gas Exchange in Patients (PTS) with Amyotrophic Lateral Sclerosis (ALS).

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Introduction: ALS is a relentlessly progressive motor neuron disease that commonly involves respiratory muscles. In later stages, the resulting hypoventilation may require nocturnal non-invasive positive pressure ventilation (NPPV). Our objective was to assess the ability of overnight oxygen saturation patterns by pulse oximetry (SpO2) to predict daytime hypercapnia. We predicted that hypercapnia would not occur with mild abnormalities of nocturnal SpO2.

Methods: Records of pts with a diagnosis of ALS seen at from 1990 to 2000 were reviewed and those pts with both overnight oximetry and arterial blood gases (ABGs) were selected for inclusion in the study. Data regarding gender, latency of symptoms, pulmonary function tests (PFTs), ABGs, and polysomnography (PSG) as available were recorded. The pts were classified (grade 1-4) according to the clinical staging system of Gurney. The overnight oximetry was graded without knowledge of ABGs as 1) mild, 2) moderate, or 3) severe abnormality by consideration of 1) normal mean (> 92%) but mild clustered (presumed REM-related) falls in SpO2 (< 90%), 2) minimally reduced mean (92-90%) or more frequent clustered falls in SpO2 (< 90%) or 3) reduced mean SpO2 (< 90%) and frequent clustered falls in SpO2 (< 85%). Any differences were settled by consensus. Non-parametric measures of association were established using the Spearman and Kendall formulas.

Results: Our results showed that 40 pts (30 males and 10 females) met the inclusion criteria with a mean latency of symptoms of 12.7 months. According to the Gurney staging system, there were 5 pts in stage 1, 21 in stage 2, 10 in stage 3 and 3 in stage 4. The overnight oximetry could be grouped as normal or mild (11), moderate (14), severe (13), and 2 were considered excessively artifactual. The ABG analyses revealed a mild abnormality of nocturnal SpO2.

Conclusions: We conclude that in ALS pts, mild isolated REM-like reductions in overnight SpO2 alone are not associated with hypercapnia while reductions in mean SpO2 < 90% easily identifies pts with PaCO2 > 45mmHg. When to start NPPV in ALS pts remains controversial but if daytime hypercapnia is considered a strong indication, overnight oximetry could be used to aid decisions in these pts.

References:
Melatonin Secretion in Parkinson’s Disease: A 2.5 Year Follow-Up.

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Goldman Institute on Aging Research Center, University of California, San Francisco Center on Aging

Introduction: Aging is associated with numerous changes in sleep and circadian rhythms. Endogenous melatonin production has been reported to decrease with aging and may further be decreased in people with Parkinson’s disease (PD). While sleep disturbance tends to increase with age, the severity of disturbance is greater in people with PD than in similarly aged healthy individuals. Despite the fact that 74-98% of patients complain of sleep-related symptoms, the etiology of these symptoms remains poorly understood. Melatonin, with both circadian rhythm and hypnotic effects, plays an important role. While melatonin secretion pattern in levodopa treated PD patients is similar to age matched controls, these patients’ rhythms may be phase advanced. There have, however, been no longitudinal studies of melatonin secretion patterns in this population.

Methods: As part of a pilot study designed to assess circadian functioning in people with PD by determining the time of dim light melatonin onset (DLMO) and endogenous melatonin secretion level, subjects were admitted (4-6/1997) to the General Clinical Research Center. Admission occurred approximately 5 hours before usual bedtime with blood sampling beginning four hours before usual bed time and continuing at 30 minute intervals under low light conditions (<50 lux) until awakening the next morning. Approximately 2.5 years later (11/1999 – 1/2000) three subjects, ages 58, 64 and 75, were readmitted and underwent a follow-up evaluation as part of a subsequent study protocol.

Results: Analysis of the 2.5 year follow-up data (see table) revealed minimal changes in medication regimen (all subjects were on levodopa at both evaluations), disease severity, habitual bed times or rise times. Radioimmunoassay of blood samples, revealed small phase advances (30 minutes) in DLMO in two subjects. Peak melatonin levels decreased in subjects #1 and 2 by 24.2 and 46.0 pg/ml respectively, while subject #3 demonstrated an increase of 16.1 pg/ml.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rise time</td>
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<td>06:00</td>
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</tr>
<tr>
<td>Bed time</td>
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<td>23:00</td>
<td>22:49</td>
</tr>
<tr>
<td>DLMO</td>
<td>21:00</td>
<td>21:00</td>
<td>19:00</td>
</tr>
<tr>
<td>Peak melatonin level (pg/ml)</td>
<td>68.2</td>
<td>119.6</td>
<td>31.1</td>
</tr>
<tr>
<td>2.5 year follow-up</td>
<td></td>
<td></td>
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<tr>
<td>Hoehn &amp; Yahr</td>
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<td>2.5</td>
<td>3</td>
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<tr>
<td>Rise time</td>
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<tr>
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<td>22:07</td>
</tr>
<tr>
<td>DLMO</td>
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<td>20:30</td>
<td>19:00</td>
</tr>
<tr>
<td>Peak melatonin level (pg/ml)</td>
<td>44.0</td>
<td>73.6</td>
<td>47.2</td>
</tr>
<tr>
<td>DLMO phase advance (min)</td>
<td>30</td>
<td>30</td>
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</tr>
</tbody>
</table>

Conclusions: The small phase advance in two subjects at follow-up could be attributed to normal aging or an acceleration of phase shifting secondary to the effects of PD. Disease progression is most likely not a major contributor since the subject (3) who deteriorated the most (2 to 3 on Hoehn & Yahr) exhibited no change in DLMO and a slight increase in peak level. Future analyses will examine subjective and objective sleep parameters in these subjects.

References:

Research supported by NIH R01 NR04774, P30 NR03927, M01 RR00079

Effect of Modafinil on Excessive Daytime Sleepiness Associated with Parkinson Disease

Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J
Mayo Clinic Scottsdale

Introduction: Many patients with Parkinson’s disease (PD) experience excessive daytime sleepiness (EDS). Modafinil (PROVIGIL), a novel wake-promoting agent, significantly improves the EDS associated with narcolepsy and other sleep disorders.1-3 This study was designed to evaluate the efficacy and safety of modafinil as adjunctive therapy in patients with EDS associated with PD.

Methods: 21 patients with idiopathic PD (aged ≥ 30 years) and an Epworth Sleepiness Scale (ESS) score ≥ 10 were enrolled in this randomized, double-blind, placebo-controlled, crossover study. Patients augmented their current therapy for PD (eg, levodopa, dopamine agonists, amantadine, selegeline, COMT-inhibitors) with modafinil 200 mg/d or placebo for a week (period 1), followed by a 1-week washout period, then the alternate treatment for 3 weeks (period 2). The primary efficacy measure was the change from baseline in mean ESS score. Secondary outcomes reported here include the patient-evaluated Clinical Global Impression of Change (CGI-C), Unified Parkinson’s Disease Rating Scale (UPDRS), Timed Tap test, and diary data. A carryover effect from period 1 to 2 was observed in the ESS data. Therefore, per protocol, only changes from baseline in mean ESS scores for period 1 were compared between modafinil and placebo. There was no significant carry over effect for any other efficacy measure. Adverse events (AEs) were recorded throughout the study.

Results: Twenty of 21 patients (mean ESS: 16.9 ± 4.2; mean age: 65 ± 12 years; duration of PD: 7.4 ± 4.9 years; 95% with motor fluctuations; 70% males) completed the study. The likelihood of falling asleep during the day, as measured by the ESS, was significantly reduced by modafinil, but not by placebo (Figure 1). Seven patients (35%) reported improvement on modafinil compared with only one patient (5%) on placebo (Figure 2). The mean CGI-C score improved by 0.75 points for patients receiving modafinil and 0.15 points with placebo (p=0.07). Treatment with modafinil did not improve or worsen UPDRS I, II, or III scores, or have an adverse effect on patient movement (Timed Tap test), percent of time in “ON” and “OFF” PD states, or time asleep (diary).
Modafinil was well tolerated in this elderly population: only two patients experienced AEs considered possibly related to treatment with modafinil (hot flashes, gas, increased “OFF” time [ n=1] and puritic rash, sore tongue [ n=1]).

**Figure 1**

![Graph showing Mean RSTT ESS Score between Placebo and Modafinil at Baseline and Week 3.](image)

*P<0.05 for change from baseline vs placebo*

**Figure 2**

![Graph showing Percent of Patients With SWS Improved based on CGI-C Scores.](image)

Conclusions: The severity of EDS in the patients with PD enrolled in this study was similar to the severity seen in patients with narcolepsy. Treatment with modafinil significantly improved wakefulness (based on ESS improvement) compared with placebo, and the change in ESS scores was of the same magnitude found in narcolepsy patients receiving modafinil. Treatment with modafinil was well tolerated in this elderly patient group, all of whom were taking concomitant anti-parkinsonian medications. Our results suggest that modafinil 200 mg/d is an effective and well-tolerated treatment for EDS in patients with PD.

**References:**


This study was supported by Cephalon, Inc.

**Anticholinesterase Drug Donepezil Increases REM Sleep Duration in Alzheimer’s Disease Patients: Preliminary Data**

Moraes WA,1 Poxares DL,1 Ramos LR,2 Bertolucci PH,4 Tufik S1

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**Introduction:** Cholinergic deficit has a fundamental role in Alzheimer’s disease (AD). The same cholinergic structures involved in learning and memory, which are damaged in AD, are responsible for REM-sleep desynchronization (1). It was previously described that patients with Alzheimer’s disease present sleep disturbances like shorter delta and REM sleep stages, increased non-REM stages 1 and 2, sleep fragmentation, diffuse delta and sundowning hallucinations (2). Anticholinesterase drugs, that increase acetyl-choline levels, are a treatment proposed for this disease. Donepezil is a safe central anticholinesterase drug, that improves cognitive performance of AD patients (3). We analyze the effects of this drug on the sleep of AD patients. The present results are part of a larger study that includes 60 patients.

**Methods:** This preliminary study is double-blind and includes 26 patients, 12 males and 14 females. They were divided in three groups, group 1: 6 aged people (73-86 years) with no neurologic diseases, group 2: 10 AD patients treated with placebo and group 3: 10 AD patients treated with donepezil 10mg/daily. AD patients had CDR scores 1 and 2 and mini-mental scores from 10 to 26. They were submitted to polysomnography monthly for 6 months and to neuropsychological evaluation every 3 months. The protocol was approved by the Ethics Commission of the Federal University of São Paulo (Brazil). In this preliminary study, macrostructure of sleep was analyzed including sleep latency, REM sleep latency, sleep efficiency, wake time after sleep onset (WASO), number of microarousals, percentage (duration/total sleep time) of stages 1, 2, delta (stages 3 and 4) and REM. Respiratory parameters were also assessed. T-test was used for group comparisons.

**Results:** Donepezil-treated AD patients compared to the placebo-treated group showed: increased percentage of REM and delta sleep, decreased percentage of stages 1 and 2, decreased latency for sleep and REM sleep, improved sleep efficiency and reduced WASO. Increased REM sleep percentage was the only change that reached statistical significance (p<0.01). Placebo-treated AD patients presented a significant reduction of REM sleep percentage compared to normal aged people (p<0.01). Sleep of donepezil-treated AD patients was not significantly different from that of normal aged people.

**Conclusions:** Donepezil probably corrects REM sleep deficit in AD patients. A possible mechanism could be the improvement of the cholinergic transmission, necessary to REM sleep initiation. This result remains to be confirmed by the conclusion of ongoing study.

**References:**


Supported by FAPESP and AFIP

**Epileptic Anterior Operculum Syndrome Presenting as Obstructive Sleep Apnea**

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**Introduction:** Nocturnal choking spells associated with arousals are often due to obstructive sleep apnea. However, similar symptoms may also be present in patients with structural or functional lesions involving the anterior operculum or perisylvian area of the brain. We report two cases of patients with such lesions who presented with symptoms sug-
gestive of obstructive sleep apnea.

**Methods:** Patient 1: Patient 1 is a white male who presented at 8 years of age with complaints of nocturnal episodes of arousal and respiratory difficulties, including drooling and throat tightness. His physical exam was unremarkable and showed no focal neurologic deficits. Patient 2: Patient 2 is a Hispanic male who presented at 9 years of age to the pediatric neurology clinic with a history of sleep apnea with symptoms of nocturnal grunting and choking spells. Previously he had been diagnosed with sleep apnea and underwent tonsillectomy and adenoidectomy without improvement of his symptoms. On evaluation in the neurology clinic, a history of facial twitching and increased oral secretions was also reported. His physical exam was also unremarkable and without focal neurologic findings. Valproic acid and carbamazepine had been tried with significant behavioral side effects and he was on no medication at the time of presentation.

**Results:** Patient 1: Patient 1 was started on carbamazepine with limited improvement of symptoms. He also underwent polysomnography which revealed frontal lobe partial complex seizures. Following this he underwent a brain MRI which showed a 2X2cm intra-axial mass lesion in the right insular cortex, predominantly affiliated with gray matter, consistent with dysplastic neuro-ectodermal tumor (DNET). Patient 2: Patient 2 was diagnosed with rolandic epilepsy and was improving spontaneously with decreasing frequency of nocturnal spells over the previous six months and continued to improve spontaneously over the next six months.

**Conclusions:** Epileptic activity involving the anterior operculum and perisylvian area may present with symptoms of oral motor incoordination and apraxia, which may be mistaken for obstructive sleep apnea. Therefore, if patients have oral motor apraxia on clinical exam, one should consider extended EEG montage during polysomnography to assess for epileptiform abnormalities. Likewise, in patients with persistent symptoms of OSA despite initial clinical intervention, utilization of EEG monitoring and/or neuroimaging may be helpful.

652.O

Evolution of Sleep and Sleep EEG after Hemispheric Stroke

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**Introduction:** The effects of focal hemispheric damage on sleep and sleep EEG and their evolution over time are poorly known. The aim of our study is to assess the evolution of sleep and sleep EEG after hemispheric stroke and their relationship to stroke outcome.

**Methods:** We prospectively studied 27 patients (pts) with first hemispheric ischemic stroke and no sleep apnea. Clinical assessment included estimated sleep time/24h (EST) and Epworth Sleepiness Score (ESS) before stroke, as well as EST, ESS and stroke outcome 12 (2-19) months after stroke. Sleep EEG data in the chronic phase (5-24 months after stroke) were compared with those in the acute phase (1-8 days), and with those of 11 hospitalized controls.

**Results:** Changes in EST (≥2h, 38% of pts) and ESS (>3 points, 26%) were frequent but correlated poorly with sleep EEG changes. In the chronic phase no significant differences in sleep EEG between hospitalized controls and patients were found. In patients, high sleep efficiency (SE) and low wakefulness after sleep onset (WASO) in the acute phase were associated with a good long-term outcome. Both SE and WASO improved significantly from the acute to the chronic phase. The figure shows the improvement of sleep continuity, slow wave sleep and REM sleep between recordings in the acute (3 days) and chronic phase (12 months) of stroke in a 39 year-old woman with a large superficial left hemispheric infarction (volume on diffusion-weighted MRI=168 ml).

**Figure 1**

**Figure 2**

**Conclusions:** After hemispheric stroke insomnia and hypersomnia are relatively frequent, whereas sleep EEG changes are modest and non-specific. A good sleep continuity in the acute phase heralds a good stroke recovery.

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653.O

Pergolide Induced Insomnia and Daytime Sleepiness in a Patient with Parkinson’s Disease Resolved by Switch to Rotirol

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**Introduction:** Recently “sleep attacks” and daytime somnolence have been reported in Parkinson’s disease patients on therapy with dopamine agonists, mainly non ergoline D2/D3 receptor agonists (1). We report on a 59-year old woman with a 5-year history of idiopathic Parkinson’s disease (Hoehn and Yahr stage 2), who was co-treated with levodopa (300mg/d) and entacapone (600mg/d) One month after pergolide (0,9mg/d) was added, the patient complained about severe insomnia, constant daytime sleepiness and increased daytime napping without a feeling of refreshment afterwards. She denied an increased sleep propensity in sleep inducing situations, like reading or watching T.V.

**Methods:** Full night polysomnography, using a Schwarzer Brain Lab 2000, was performed in two consecutive nights under pergolide and after three months of receiving an equivalent dose of ropinirole (2,55mg/d). The first night was considered as an adaptation night and not taken into consideration. On the following morning a Multiple sleep latency test was performed. In addition a neuropsychological testing included the
Results: The main results in polysomnography are shown in Table 1. Under treatment with pergolide the patient showed severe reduction in sleep efficacy, slow wave sleep and REM sleep suppression. Respiratory and PLMS-indices were within the normal range. After three months receiving ropinirole, sleep efficacy, REM latency and REM sleep time were normalised. Sleep latency in the MSLT increased after switch to ropinirole, but was not pathologically decreased under pergolide either. REM sleep did not occur in any of the sleep opportunities. As shown in Table 2 the patient showed improvements under ropinirole in reaction time, concerning alertness and vigilance, as well as an increased psychomotor speed and mental flexibility.

Table 1

| Polysomnographic data of 2 therapy nights and 2 Multiple sleep latency tests |
|---------------------------------|----------|----------|
| **variables**                   | **pergolide** | **ropinirole** |
| time in bed                     | 481.9     | 508.3     |
| total sleep time                | 301.0     | 455.0     |
| total wake time                 | 180.9     | 53.3      |
| sleep efficiency                | 62.0      | 90.0      |
| wake until sleep onset %        | 34.1      | 6.9       |
| non-REM sleep%                  | 56.6      | 66.6      |
| REM stage %                     | 8.0       | 23.6      |
| sleep latency (min)             | 22.5      | 12.3      |
| REM latency (min)               | 74.5      | 112.0     |
| MSLT: sleep latency to S1       | 14.4 (6-30)| 23.7 (12-30)|

Table 2

<table>
<thead>
<tr>
<th>Neuropsychological testing</th>
<th><strong>pergolide</strong></th>
<th><strong>ropinirole</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAP/alertness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple reaction time</td>
<td>395.5 msec</td>
<td>252 msec</td>
</tr>
<tr>
<td>Reaction time with indication</td>
<td>473 msec</td>
<td>264 msec</td>
</tr>
<tr>
<td><strong>TAP/vigilance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time</td>
<td>638 msec</td>
<td>565 msec</td>
</tr>
<tr>
<td><strong>TRAIL A/psychomotor speed</strong></td>
<td>21 sec</td>
<td>16 sec</td>
</tr>
<tr>
<td><strong>TRAIL B/mental flexibility</strong></td>
<td>51 sec</td>
<td>42 sec</td>
</tr>
</tbody>
</table>

Conclusions: At present the specific risk of the dopamine agonists currently available to induce somnolence or insomnia is insufficiently known. In previous studies, both insomnia and somnolence were reported as side effects of ropinirole (2) and pergolide (3). Possible individual dispositions influence the type of response. This case demonstrates that drug induced modification of sleep and alertness in Parkinson disease patients can not be classified as specific and that switching between different agonists can be a possible treatment strategy. Prospective controlled trials are needed to identify specific risks for each substance.

References:
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654.O

Insomnia and Oneiric Behavior in Parkinson’s Disease: A Case Report

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Introduction: Sleep disorders including sleep fragmentation, REM sleep behavior disorder and insomnia commonly occur in Parkinson’s disease, affecting up to 90% of patients. Whether sleep disorders in PD are caused by medication or by the disease process or both remains controversial. We here report a patient with Parkinson’s disease and unusual sleep disturbances characterized by marked insomnia associated with oniric behavior.

Methods: A 48-year old patient with a two year history of idiopathic Parkinson’s disease was transferred to the sleep laboratory because of suspected REM sleep behavior disorder. Sleep disturbance included violent dreams associated with movements and vocalization, sleep initiation and maintenance difficulties. Drug therapy at time of admission consisted of bromocriptine 7.5mg and amantadine 300mg. Visual hallucinations repeatedly occurred during daytime. Standard polysomnography was performed during five nights from May to October 2000.

Results: In May 2000 two polysomnographic recordings were performed. During both nights the patient was mainly awake in bed. Videography revealed oniric behavior with talks, movements into the air and more complex actions such as standing up and leaving the bed. During these actions the patient appeared mostly not violent. Medication had been withdrawn three days prior to a third night sleep registration one month later. This time, the patient fell asleep in the last third of the night. A distinctive REM behavior disorder (RBD) was observed with violent jerks and flailing arm movements. To explore whether insomnia was related to medication two further night sleep registrations without amantadine and following i.v. application of 200mg amantadine were obtained. Sleep efficiency was not significantly changed by amantadine (73% versus 76%).

Conclusions: Nearly continuous insomnia associated with oniric behavior was observed in two nights of consecutive polysomnographic recordings in a PD patient who had a history of sleep disturbance and RBD only. We suggest that nighttime oniric behavior while awake represents another form of sleep disorder in PD.

655.O

The Influence of Dopamine agonists on Daytime Sleepiness, Sleep Disturbances, and Quality of Life in Patients with Parkinson’s Disease

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Introduction: Recent reports that dopamine agonists (DA), in particular the D2 and D3 receptor agonists pramipexole and ropinirole, precipitate daytime sleepiness with sudden sleep episodes in Parkinson’s disease (PD) patients have received widespread attention.1-3 It was speculated that the sedating effect of the non-ergoline DAs may be due to their stronger D3 receptor activity as compared to ergoline DAs.1 However, other reports suggest that sedation may be rather a class effect of DAs.2,3

Methods: We present cross-sectional and longitudinal results of a one
year follow-up study on daytime sleepiness, sleep disturbances, and the quality of life (QOL) in PD patients with different dopaminergic treatments. This analysis is part of the FAQT-study, a prospective German cohort study evaluating determinants of QOL in PD patients (n=209). A subgroup of 111 PD patients (50 female, mean age 64.1 ± 10.3 years) was evaluated twice, at baseline and after one year of follow-up. All patients were neurologically examined, the following instruments were used: Unified Parkinson’s Disease Rating Scale, Hoehn and Yahr classification, German versions of Short Form-36 (SF-36), Parkinson’s Disease Questionnaire (PDQ-39), and the Center for Epidemiologic Studies Depression Scale (CESD, 10-item short form). The impact of different antiparkinsonian treatment strategies on daytime sleepiness, bad dreams and hallucinations (items of the PDQ-39), bad sleep (item of the CESD), and QOL (SF-36) in PD patients was analysed separately for ergoline DAs (pergolide, 0.075-5 mg/day; cabergolide 1-8 mg/day; bromocriptine 5-30 mg/day and lisuride 0.2-10 mg/day), non-ergoline DAs (ropinirole, 1.5-35 mg/day and pramipexole 0.36-8 mg/day), and no DA with regard of the Levodopa dose (25-1,550 mg/day).

Results: There were no significant differences on the severities of sleeping badly at baseline and after one year, on having bad dreams or hallucinations at the follow-up, on disease severity, on depressive symptoms, and on QOL in the different therapeutic groups, both cross-sectionally and longitudinally. At follow-up, 14% of the patients taking an ergoline DA, 25% of the patients taking a non-ergoline DA, and none of the patients taking no DA reported excessive daytime sleepiness (EDS). Patients with DAs showed a significantly higher occurrence of EDS than patients without DAs (Fisher’s exact test, p=0.036). In post-hoc analysis, there was only a significant difference of EDS between the patients taking non-ergoline DAs and no DA (Fisher’s exact test, p=0.025) but no significant difference between either DA groups.

Conclusions: Our results suggest that sedation may be rather a class effect of DAs than a specific effect of non-ergoline or ergoline DAs. However, there is a trend towards a higher occurrence of EDS in patients taking non-ergoline DAs than in patients taking ergoline DAs.

References:

The FAQT-Study is supported by the William-Woort-Stiftung für Altersforschung Essen, Germany and Hoffman LaRoche AG, Germany.

Benzodiazepine Chronic Use: Possible Protective Role in Dementia

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Introduction: In the animal models of cerebral ischemia, the inhibitory transmitter gamma-aminobutyric acid (GABA), and GABA-mimetic drugs have been reported to be effective against neuronal damage. GABA-mimetic drugs have been tested also in Alzheimer Disease (AD) and vascular dementia. Benzodiazepines (BDZ) possess a GABAergic effect and are also commonly used in the elderly. In a recent population-based study, elderly patients using BDZ showed a significantly lower incidence of AD than the non-users, suggesting a BDZ protective effect for neuronal damage (1). Aim of our study was to evaluate the chronic use of BDZ as possible protective agents in a sample of dementing patients.

Methods: Patients affected by dementia and admitted to our neurological department from January 1 to December 31, 1999 were evaluated in the present study. For each demented patients we choose as control group 2 subjects of the same age and gender admitted the same day to a non-neurological department. Dementia was diagnosed following DSM-IV criteria. NINCDS-ADRDA criteria have been followed for AD diagnosis and the Hachinski Scale for vascular dementia. Chronic BDZ use was defined as daily BDZ intake for at least 6 months during the 3 years preceding the onset of neurological symptoms.

Results: Seventy-four (55 females and 19 males) aged between 53 and 90 years were included in the study. Forty-seven patients had a diagnosis of AD, 4 were affected by frontotemporal dementia and the remaining were diagnosed as having a vascular or mixed type of dementia. Level of education, smoking and alcohol intake were not significantly different between the demented patients and the controls. Only 2 out of 74 patients (2.7%) (1 female in lorazepam affected by initial AD and 1 female in bromazepam affected by vascular dementia) already assuming BDZ were detected in the demented patients group. In the control group chronic BDZ use was observed in 39 patients (26.2%, 18 using lorazepam, 10 triazolam, 5 clordemethyl Diazepam, and 3 lormetazepam). Chronic BDZ use was significantly different between the two groups (Fisher’s exact test, p<.0001). In 32 out of 39 subjects of control group BDZ compounds were taken as hypnotic agent.

Conclusions: Interestingly, Asada et al (2) recently reported that limited napping up to 60 min had an apparently protective effect against the development of AD. It is possible that limited napping itself and improved nocturnal sleep may contribute to adult neurogenesis, for example, in terms of alleviating stress and strengthening neurogenesis-enhancing factors. Further prospective studies may shed light on the chronic use of BDZ (and non-BDZ) hypnotic medications as possible protective agents against dementia.

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(2) Asada T et al. Sleep 5: 629-634, 2000

Narcolepsy-like Phenotype in Parkinson’s Disease: How Frequent in Sleepy Patients?

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Introduction: In patients with Parkinson’s disease (PD), we previously reported (1) that 60 % of patients with dopaminergic-induced hallucinations presented with polygraphic criteria of narcolepsy: 2 or more sleep onset in rapid eye movement period (narcolepsy-like phenotype) over 5 multiple sleep latency tests (MSLT). Sleepiness may affect 10-20% of patients with PD. We underwent a prospective study of sleepy PD patients to determine how frequent was the narcolepsy-like phenotype.

Methods: Forty-seven patients suffering from idiopathic Parkinson’s disease for 10 ± 7 yrs, aged 53-85 yrs were referred for sleepiness by local university hospital neurologists. All patients were treated with levodopa, of whom 23 used dopaminergic agonists as adjunct therapy (bromocriptin 15; peribedil 6; ropinirole 2; pergolide 2; apomorphine 1). Patients were assessed using night-time polysomnography, followed
by MSLT, Epworth sleepiness score, Minimental state examination (MMS) and Hoehn and Yahr score.

**Results:** Mean MSLT was 6.1±0.7 min (range 0-19.2) and mean Epworth score was 14.4±4.3 (8-22). 53% patients had MSLT ≤5 min. A subgroup of 17 patients had narcolepsy-like phenotype, of whom 9 reported hallucinations. This subgroup was sleepier than the other patients (MSLT: 3.5±0.8 min vs. 7.6±0.8 min; p=0.002). However, there were no differences between groups for Epworth score, age, MMS, disease course, Hoehn and Yahr score, use of dopaminergic agonist (n=8/17), daily doses of levodopa, bromocriptine equivalent and total equivalent dose of levodopa. Nocturnal sleep (total sleep time, sleep efficiency, arousal index, REM sleep duration) was similar in both groups. However, there was a trend for night sleep latencies to be shorter in the “narcolepsy-like” subgroup (10±7 min vs. 24±40 min, p=0.17).

**Conclusions:** Among sleepy PD patients, 36% had a narcolepsy-like phenotype, although they were similar for motor and cognitive impairment, treatment and nocturnal sleep. This suggests that this phenotype might result from lesion in sleep-wakefulness control different from lesion of the extrapyramidal pathways.

**References:**

**658 O**

**Sleep EEG Changes Following Hemispheric Stroke**

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**Introduction:** Although the thalamus is known to be critical in generating sleep EEG patterns, the importance of the cerebral hemispheres is less well established. Prior animal research indicates that corticothalamic projections are necessary for the generation of synchronized spindle frequency activity. Previous human research suggests that brain damage reduces spindle frequency activity in the affected hemisphere. We investigated possible alterations in the sleep EEG power spectra in human subjects following a single cerebrovascular accident.

**Methods:** All-night polygraphic recordings were conducted in patients with hemispheric stroke (BDs, n=34, mean age=49.8 years) and hospital controls (HCs, n=12, mean age=47.0 years). Individuals with sleep apnea were excluded. For 33 of the BDs, 1-3 recordings were obtained within 10 days of the stroke, yielding a total of 43 recordings. To track the evolution of the sleep EEG over time, 38 later recordings were obtained in 24 of the patients. Sleep stages were scored visually for 20-s epochs. All-night mean power spectra were computed for non-REM sleep (stages 2, 3, and 4) using bipolar EEG derivations. For each derivation in which spindle peaks are usually visible (F3C3, P3O1, F4C4, P4O2), we measured the height of the spindle peak, defined as the difference between the peak of the power spectrum in the spindle frequency range and a power law function fitted to the mean power spectrum in the range 2-30 Hz, excluding the spindle frequency range. Differences between groups were analyzed using repeated measures ANOVAs.

**Results:** In acute phase recordings, the mean spindle peak height was significantly reduced in BDs compared to HCs (means±s.e.’s: BDs=0.16±0.04 µV/0.25 Hz, HCs=0.33±0.07 µV/0.25 Hz; F(1,43)=6.212, p=0.017). In the BD and HC groups respectively 46.7% and 16.7% of the subjects had no detectable spindle peak in one or more derivations. In the BD group, mean spindle peak heights did not differ significantly between derivations ipsilateral and contralateral to the lesion (ipsilateral=0.15±0.03 µV/0.25 Hz, contralateral=0.17±0.03 µV/0.25 Hz). Peak heights in the acute phase (≤10 days post stroke) did not differ significantly from peak heights in chronic phase (≥60 days post stroke) recordings (acute=0.16±0.03 µV/0.25 Hz, chronic=0.13±0.03 µV/0.25 Hz; F(1,123)=1.276, p=0.261). However, visual inspection of the power spectra suggested that some individual subjects showed progressive recovery of spindles over time.

**Conclusions:** Previous studies of neurologic patients suggested that sleep spindle activity is depressed primarily in the pathologically affected hemisphere. In contrast, we did not observe significant differences between spindle peak heights measured from derivations ipsilateral and contralateral to the lesion. Compared to HCs, patients with unilateral hemispheric lesions exhibited a significant decrease in mean spindle peak height across all derivations. The results imply that each cerebral hemisphere is critically involved in generating spindle activity in both hemispheres.

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**659 O**

**Sleep EEG in De Novo Patients with Parkinson’s Disease: Effects of Dopamine on the Spectral Profiles**

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**Introduction:** The typical sleep abnormalities of patients with Parkinson’s disease include a sleep fragmentation, loss of deep sleep, and in particular rapid eye movement (REM) sleep disorders. However, most of the previous studies have been conducted in patients receiving a dopaminergic treatment.

**Methods:** Therefore we investigated the sleep EEG in a carefully selected group of de novo patients with Parkinson’s disease (n=14, 63.7±11.8 yr) and compared it to a control group matched for age (n=10, 65.4±6.9 yr). Some of the patients were reinvestigated under a dopaminergic medication (n=7, 67.0±12.8 yr). Polysomnographic sleep recordings were visually analyzed according to standard criteria. In addition, we submitted the digitized EEG data to a serial spectral analysis (EEG power spectrum from 0.39-19.1Hz; frequency resolution 0.39 Hz). The EEG power spectra were cumulated across the delta (0.8-4.3Hz), theta (4.3-7.8Hz), alpha (7.8-11.7Hz), sigma (11.7-15.2Hz) and beta (15.2-19.1Hz) range. Statistical evaluations were made by MANOVAs for between subjects and repeated measures design.

**Results:** The quantitative analysis of the sleep EEG in de novo patients with Parkinson’s disease showed an enhanced sigma EEG activity during non-REM sleep. The REM sleep EEG was characterized by a significant increase in the higher theta/lowest alpha frequency range including a lack of the physiologic decline of these power densities throughout the night. The treatment effects of a dopaminergic medication appeared to be restricted to the non-REM sleep specific changes. The conventional parameters describing the sleep architecture and sleep continuity revealed no significant differences between the groups.

**Conclusions:** In summary, the results of our study point to moderate, but distinct changes in the spectral profiles of the sleep EEG in patients with an early stage of Parkinson’s disease that responded only in part to a dopaminergic treatment.
Is Fluctuating Cognition in Dementia with Lewy Bodies Attributable to an Underlying Sleep Disorder?

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Introduction: Fluctuating cognition in Dementia with Lewy bodies (DLB) refers to recurrent alternating episodes of daytime confusion with periods of lucidity. It reflects times when the patient is unable to carry out certain tasks that he or she could normally perform later, periods of unresponsiveness while awake or variable daytime arousal despite adequate nighttime sleep. The etiology of fluctuations are unclear but one hypothesis involves disrupted mechanisms subserving brainstem sleep and arousal systems. An alternate hypothesis is that fluctuations may reflect disturbed sleep associated with an underlying sleep disorder. The purpose of this study is to test the latter hypothesis.

Methods: Retrospective study of overnight polysomnogram (PSG) data of 46 patients (44M, 2F), with DLB and a documented history of fluctuating cognition. The Global Deterioration Scale Score was used as a measure of dementia severity. Interview data regarding collateral report of excessive daytime sleepiness and possible REM sleep behavior disorder (RBD) was recorded. PSG documentation of apnea/hypopnea index (AHI), arousal index/hour, periodic limb movements (PLM)/hour, percent of PLMs with arousals, percent sleep efficiency (Total sleep time/Time in bed) and presence or absence of normal REM sleep atonia was determined.

Results: The mean age of the group was 71.5 years (sd=6.74), with levels of dementia including mild, mild to moderate and moderate severity. Daytime hypersomnolence was reported in 29 patients with no significant difference between the presence of hypersomnolence and dementia severity (χ²=1.70, p=0.50). A clinical history of RBD was present in 45 patients. PSG data revealed the absence of REM sleep atonia in 38 patients, no recorded REM sleep in four patients and a NREM parasomnia in one patient. The mean arousal index/hour was 27.6 (sd=20.4) and mean AHI was 16.7 (sd=19.1). The mean PLM/hour index was 48.7 (sd=50.5), the mean percentage of PLMs causing arousals was 17.4% (sd=21.18). There were 15/46 patients with AHI values /geq 16 and 17/46 patients with PLM % with arousal /geq 16, with 6 patients belonging to both groups. Mean sleep efficiency was 69.3% (sd=17.3) and 32/46 patients had percent sleep efficiency values /geq 80%. Statistical comparisons between patients with and without reported daytime hypersomnolence revealed no significant group differences in AHI (t = 0.93, p > 0.05), arousal index/hour (t = .82, p > 0.05), PLM/hour (t = 1.22, p > 0.05), PLM % with arousal (t=-0.67, p > 0.05) or percent sleep efficiency (t=1.81, p > 0.05).

Conclusions: In patients with DLB and fluctuating cognition, REM sleep without atonia and diminished sleep efficiency were commonly observed, but sleep disorders consisting of disordered breathing and periodic limb movements occurred in about a third of the group. There were no differences in PSG indices between patients with and without reported daytime somnolence. These data suggest that sleep disorders may contribute, but do not entirely account for fluctuating cognition in DLB. Further work is needed to better understand other potential sleep mechanisms and associated neurologic etiology of fluctuating cognition in DLB.

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Pre-injury Sleep Complaints in Patients with Mild Traumatic Brain Injury

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Introduction: Traumatic brain injury (TBI) is the leading cause of death and disability among young people in the United States. Even relatively
mild brain injury may result in disturbed sleep, daytime sleepiness, and chronic fatigue (1). The time course and clinical impact of abnormal sleep in this patient population is unclear, although it may contribute to development of the post-concussive syndrome. We are prospectively collecting data on the sleep complaints of a large population of military members with mild TBI.

**Methods:** The Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were part of a battery of neuropsychiatric tests administered to 182 patients and 145 controls. The ESS provides a subjective estimate of sleepiness based on the likelihood of dozing in eight soporific situations (2). A score >10 suggests excessive sleepiness. The PSQI was designed to rate sleep complaints over the previous month and has been applied to several clinical populations (3). A global score >5 discriminates bad sleepers from good sleepers. Patients were specifically instructed to answer questions regarding sleep for the month preceding injury. All subjects were young (mean age 21.93 ± 3.86) active duty U.S. Marines with recent head trauma. Controls were matched by age (mean 23.52 ± 4.38), sex, and military rank. Exclusionary criteria included prior TBI, depression, alcohol/drug abuse, and neurologic disorders. Mild TBI was defined as a Glasgow Coma Scale of 13-15, loss of consciousness <30 minutes, and post-traumatic amnesia lasting less than 24 hours. Patients were interviewed a mean 7 days (SD 10) post injury.

**Results:** There was a significant difference between the patient and control groups on both the ESS (F=4.93, p=.02) and PSQI (F=6.97, p=.009). The average total score on the ESS was 9.74 (SD 4.9) for the patient group and 8.60 (SD 4.11) for the controls. Overall, 41% of patients versus 31% of controls reported significant daytime sleepiness (ESS >10). The average Global Score on the PSQI for the patient group was 8.0 (SD 3.9) versus 6.8 (SD 3.4) for the control group. 72% of patients scored >5 on the PSQI versus 62% of controls.

**Conclusions:** Pre-existing sleep complaints and subjective daytime sleepiness were more common in our acutely brain injured population than controls. It may be that disturbed sleep/excessive sleepiness are risk factors for accidents or they may be related to other factors or behaviors that might predispose to head injury. This study presents only the initial sleep data on our brain-injured patients and controls who will be longitudinally followed for 12 months. We hope to better define the nature and time course of sleep disturbance in this population.

**References:**

**Research supported by Defense and Veterans Head Injury Program**

**663.P**

**Sleep Quality of Patients Enrolled in an Adult Cystic Fibrosis Clinic**

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**Introduction:** Few studies have inquired into the quality of sleep in persons with cystic fibrosis (CF). They may be more predisposed to sleep-disordered breathing as well as to other potentially sleep-disrupting pathologies. Medications such as glucocorticoids and fluoroquinolones are known to affect sleep; vitamin E deficiency among others may potentiate periodic limb movement disorder. Disease-associated chronic anxiety and depression, and its pharmacotherapy, may also affect sleep quality. In addition, if their sleep quality is affected, their quality of life may also be affected.

**Methods:** All patients enrolled in an adult CF clinic (total of 35 patients; 19 females and 16 males) were mailed three questionnaires: SF-36, Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI). They were asked to answer the questionnaires as if it were a typical week for them and not in an acute exacerbation of their CF. The questionnaires were scored according to published guidelines and patients were considered to have poor sleep quality if the PSQI score was greater than 5. The PSQI was chosen because it has been well validated.

**Results:** 35 questionnaires were mailed out and 23 (66%; 14 females, 9 males) were completed and returned. 14 patients (10 females, 4 males) scored higher than 5 on the PSQI. Thus 61% of the patients who completed the questionnaires have poor sleep quality based on a standardized and validated questionnaire. 71% (10/14) females and 44% (4/9) males have poor sleep quality. Of the patients with a PSQI higher than 5, their SF-36 average physical health score (PCS) was 38.1 and their average mental health score (MCS) was 41.4. While the patients with a PSQI less than or equal to 5, their average PCS was 45.7 and their average MSC was 57.7.

**Conclusions:** Persons with CF frequently perceive poor sleep quality, and these persons score lower on a quality of life questionnaire than those persons with CF who have normal sleep quality. Further studies are needed to explore the relative contributions and frequencies of the many potential causes in an attempt to treat these disorders and improve their quality of life.

**References:**

**Research supported by Jacob I. Sznajder, MD, Chief of Pulmonary, Northwestern University Medical School**
Fatigue and Sleep in Women with Breast Cancer: Preliminary Results

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Introduction: Fatigue is described as a major complaint in patients undergoing chemotherapy. Cancer-related fatigue is a complex and unique clinical phenomenon that has been conceptualized as encompassing multiple domains or dimensions: i.e., physical, emotional, mental and general/motivational(1). It is unknown, however, whether cancer-related fatigue or its dimensions bears any relationship to the quality or quantity of sleep or to the sleep/wake circadian rhythm cycle. This report presents preliminary data in what will be a large study of fatigue, sleep and circadian rhythms in women with breast cancer.

Methods: Six women recently diagnosed with stage I-IIIA breast cancer and referred for adjuvant or neoadjuvant anthracycline-based chemotherapy were studied. The mean age was 51 years (SD 9.3; range 40-65 years). Each woman wore an ActiWear (Ambulatory Monitoring Inc, Ardsley, NY) for three consecutive 24-hour periods and completed the Multidimensional Fatigue Symptom Inventory (MFSI)(1) the Pittsburgh Sleep Quality Index (PSQI)(2) and the Functional Outcomes of Sleep Questionnaire (FOSQ)(3), as well as the Center for Epidemiological Studies-Depression scale (CES-D), and the Functional Assessment of Cancer Therapy (FACT) quality of life scale. Data from the quality of life and depression questionnaires in these patients are reported separately (see Cohen-Zion et al.)

Results: The mean scores were: PSQI 8.3 (SD 3.1), MFSI 31.4 (SD 16.6), FOSQ 18.9 (SD 3.2). TST averaged 7.6 hours (SD 0.5), mean WASO = 63.8 min (SD 38.3), with a mean of 11.0 (SD 7.3) awakenings. The average duration of awakenings was 7.6 min (SD 4.6). Because of the small sample obtained so far, the following selection of correlations is presented only to illustrate some of the possible outcomes of the study. Reports of fatigue (MFSI total combined subscale scores) correlated with increased WASO (r=.83), increased number of awakenings (r=.67), poor sleep efficiency (r=.82), and longer sleep period (r=.63). Higher scores on the MFSI Emotional Fatigue subscale were related to increased WASO (r=.89) and decreased sleep efficiency (r=-.92). MFSI Mental Fatigue subscores were related to decreased sleep efficiency (r=-.77). MFSI subscale of Vigor was associated with increased total sleep time (r=.87). Correlations between questionnaires suggest relationships between increased reports of fatigue and subjective reporting of poor sleep (total PSQI scores) (r=.77), fatigue and depressive symptoms (r=.81), and fatigue and total FOSQ scores (r=-.97).

Conclusions: These preliminary results suggest that women with breast cancer report and experience poor, disrupted sleep. Their overall level of fatigue is related to the amount of time spent awake at night. Disturbed sleep at night in these patients may also be associated with individual dimensions or different aspects of fatigue (i.e., emotional and mental fatigue). Additional data will help to illuminate these relationships. It is unknown whether or not attempts to improve sleep quality and/or circadian rhythmicity in these patients can ameliorate the fatigue they experience.

References:
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(3) Weaver T et al. Sleep, 1999;20:835-43

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Relationship Between Poor Sleep and Disease

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Introduction: Studies have shown that sleep deprivation can cause dysfunctions in metabolism, hematological changes, nervous system activity, physical work capacity, and mental health. Daytime consequences of poor sleep include fatigue, lack of energy, difficulty concentrating, and irritability. This study tested whether sleep is related to health in patients being seen in a doctor’s office. The hypotheses were that the less sleep people obtain, the less healthy they will be, and that people with more sleep complaints would have more illness than those with fewer sleep complaints.

Methods: Questionnaires on sleep (satisfaction with sleep, quality of sleep, quantity of sleep, Epworth Sleepiness Scale [ESS]) and health (current medical problems, past medical history, current medication use; purpose of their visit [check-up, new complaint, and on-going complaint]) were placed in an office of general internists. In a two-week period, 300 questionnaires (55% of patients seen; 36% men) were returned. Data were analyzed with SPSS. Variables analyzed included total sleep time, sleep satisfaction, and total number of diseases. A disease was included in the analyses if 10% of patients reported having it.

Figure 1

Results: The mean age of the patients was 54.8 years (SD 17.4; range 17-95 years). Overall, 65% of the patients were satisfied with their sleep; 57% reported a TST between 6-8 hours; 13% scored as excessively sleepy (≥10) on the ESS (mean ESS 6.5; SD=3.2; range 0-21); 30% reported having 3 or more diseases. Kruskal-Wallis analyses were computed comparing patients satisfied with sleep vs. those dissatisfied. Satisfied patients had significantly fewer diseases (p ≤ 0.0001)(see Fig 1); significantly greater TST (p ≤ 0.0001), being less tired when first waking up (p ≤ 0.0001). Patients who reported having an on-going complaint were assumed to be more chronically ill and reported still being tired after waking up (p ≤ 0.018), still being tired during the day (p ≤ 0.019), to be less satisfied with their sleep (p ≤ 0.015)(Fig 2). Patients with less sleep had more diseases (p ≤ 0.02). Correlations were computed between sleep and health variables. Patients with higher total number of diseases had less TST (r = -0.15; p ≤ 0.011), were less satis-
Chemical Odor Intolerance and Sleep Symptoms in a Community Based Sample

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Introduction: Chemical odor intolerance (OI) is the subjective report of feeling ill on exposure to low levels of common in/outdoor odors. OI has been reported in several “unexplained” illnesses, including fibromyalgia, Gulf War syndrome, and chronic fatigue syndrome[1], all of which are associated with polysymptomatic, multisystem complaints, including sleep disturbances. Although OI and respiratory problems have been well studied[2], OI and sleep symptoms have yet to be investigated.

Methods: Subjects (n=177) were derived from a stratified cluster population study of Pima County government employees (Tucson, AZ). Subjects completed the Tucson Epidemiological Study of Obstructive Airways Disease 12th survey, which included several questions on sleep symptoms (difficulty falling asleep, staying asleep, early morning awakening, insufficient sleep, daytime sleepiness, nightmares, snoring), and several respiratory-related questions relevant to sleep disturbances (e.g., wheeze, mucous production)[3]. Subjects also completed a validated measure of OI[1,2]. Nominal categories of frequency of feeling ill from each of five odors (fresh paint, pesticide, perfume, new carpet odor, auto exhaust) were used as dichotomous variables with ‘often’ and ‘almost always’ representing the OI group, and ‘never’, ‘rarely,’ and ‘sometimes’ representing the non-OI group. Chi-square was used to compare the OI and non-OI on their sleep and respiratory complaints. Relative risk ratios (RR) were computed and reported with 95% Confidence Intervals (CI).

Results: Sleep data were provided by 126 respondents (71% compliance). The prevalence of OI among this sample was 20% (12 men/13 women). The OI were significantly more likely to report difficulty falling asleep (RR=2.04; CI 1.3-3.2), not enough sleep (RR=2.02; CI 1.4-2.9), and nightmares (RR=2.60; CI 1.4-5.0). These sleep symptoms were amplified in OI individuals with a current history of hay fever, but not asthma. Respiratory complaints also exacerbated sleep symptoms in the OI. Specifically, when sleep symptoms were stratified by respiratory histories, the OI who reported nightmares, or had seen a physician for asthma or hay fever in the past year indicated significant difficulty staying asleep. The OI who cited chest wheeze, dyspnea, or physician visits in the past year for asthma or hay fever reported insomnia. The OI who reported nightmares were significantly more likely to have seen a physician for hay fever. Notably, the OI who endorsed a history of mucous production in the early morning indicated that they were troubled significantly by early morning awakening with difficulty returning to sleep (RR=2.41; CI 1.1-5.5). There were no significant differences between groups for daytime sleepiness, snoring, use of sleep aids, or questions regarding anxiety or depression.

Conclusions: Although the prevalence of OI in this study is similar to the general population (15-30%)[1], no gender differences in OI were noted. Other studies have reported significantly greater proportions of OI in women than men (75-90% women)[1,2]. This analysis suggests that OI and sleep symptoms are not associated with gender, that the OI are more likely to report specific sleep symptoms, and that sleep symptoms are associated with respiratory complaints. Prior research has reported associations between respiratory problems and OI host susceptibility[2], as well as relationships between sleep and respiratory symptoms[3]. Further research may elucidate relationships between OI and sleep.

References:

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Subjective Sleep Complaints in Patients on Renal Replacement Therapy

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Introduction: Previous studies reported high prevalence of sleep disorders in patients on hemodialysis and peritoneal dialysis. The aim of our study was to develop a set of screening questionnaires for this population. We conducted pilot study to assess the prevalence of sleep complaints and their consequences in patients on hemodialysis.

Methods: 75 patients on hemodialysis (HD) (44% male, median age 56 years, 17-84 ys) completed the questionnaire. The questionnaire consisted of standard scales regarding sleep complaints, quality of life and
Results: Median time on dialysis is 25 months (range 1-180 months). 71 % of patients reported any sleep complaints and 19 % of patients takes hypnotics regularly. Insomnia was reported by 52 %, symptoms of PLMS by 13 % and symptoms by RLS in 27 %. Snoring was reported by 29 % of the patients. Mean score (±SD) of the Epworth Sleepiness Scale (ESS) was 11.1±5.97. Mean score of the Illness Intrusiveness Rating Scale (IIRS), a measure for quality of life, was 43.50±18.07, which is worse than published data from similar populations. Both ESS and IIRS scores were higher in patients complaining for at least one sleep problem (ESS: 12.0±6.2 vs 8.8±4.59, p=0.026 in patients with sleep problems, and in those without any, and IIRS: 47.68±16.59 vs 33.36±17.80, p<0.01). Time on dialysis tended to be longer in poor sleepers but this correlation did not reach statistical significance. IIRS reflecting impaired quality of life showed a weak but significant correlation (Parrson) with time on dialysis (r= 0.27, p =0.016).

Conclusions: Our study confirmed the high prevalence of sleep complaints in patients on hemodialysis. Sleep disorders may contribute to the impaired quality of life of this population.

The study was supported by a grant of the Ministry of Health (ETT 244/2000).

668.P

Sleep Patterns of Patients with Different Types of Gerd

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Introduction: Demeester et al.(1) studied patients with symptoms and pHmetry of gastroesophageic reflux disease (GERD), and classified them in 3 different groups: patients who presented reflux only on the prone position (orthostatic), on decubitus or on both positions. During sleep, there are prolonged periods with absence of continuous peristaltic movements. These prolonged periods may contribute to the development of esophagitis, followed, many times, by a structural narrowing of the esophagus, in case this situation perpetuates. There are few reports in the literature comparing polysomnographic findings among patients exhibiting GERD only on decubitus and orthostatic position. The present study sought to evaluate the sleep in these patients.

Methods: Sixteen patients were included, with mean (± S.D.) values of age = 48 ± 10 years and body mass index = 33 ± 15 Kg m2, with clinical features of gastroesophageic reflux and no previous sleep complaints, of which eight presented reflux only on the orthostatic position, eight presented reflux on decubitus or combined positions, in the following protocol:1- Clinical interview and examination;2- Whole night polysomnography with the Oxford SAC System with EEG, EOG, chin EMG, tibial EMG, ECG, airflow, thoracic-abdominal movements, SaO2 e body position were recorded during 2 nights (adaptation and recording);3- 24 h pHmetry with Synetics Digitrapper III monitor, where pH measurements were recorded and analyzed by the apparatus computerized system and with polysomnography recording on the second night. Statistical analysis: Polysomnographic variables in GERD patients on decubitus and/or combined positions (Group A) were compared with those of GERD patients on orthostatic position by the unpaired Student’s t test.

Results: Mean ± S.D. values for groups A and B were, respectively: arousals = 13.3 ± 6.4 vs. 9.25 ± 10.3 (p = 0.34), wakefulness = 17.1 ± 9.2 vs. 15.2 ± 6.7 (p = 0.62), stages 1 and 2 = 55 ± 7 vs. 55 ± 4.9 (p = 0.88), stages 3 and 4 = 24.3 ± 9.6 vs. 29.5 ± 16 (p = 0.45) and REM = 19.8 ± 6.2 vs. 17.3 ± 5.9 (p = 0.42).

Conclusions: According to the data obtained in the present study, polysomnography is not influenced by reflux episodes on decubitus or orthostatic position.

References:

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669.P

The Impact of a Physical Therapy Program on Sleep and Pain in Fibromyalgia (Preliminary Data)

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Introduction: Fibromyalgia corresponds to a chronic musculoskeletal painful condition with a frequent complaint of disturbances. Non-medication interventions (1) proved to be an effective approach to this condition, improving pain symptoms. Hypothesizing that the sleep disturbances can also be improved by such therapy modalities, we studied the effects of a specific combined physical therapy on pain and sleep manifestations in four fibromyalgia patients.

Methods: Four patients, 65 ± 3 years old, fulfilling criteria for fibromyalgia (2) with active complaints for more than 6 months were included in this study. The patients were submitted to clinical and sleep questionnaires, tender point (TP) evaluation and to all-night polysomnography (PSG) after an adaptation night. Pain manifestations were evaluated subjectively using a body map of the painful areas (PA), and a visual analog scale (VAS) for the intensity of pain in these areas. A Fisher’s dolorimeter was used to determine the number and the tenderness threshold (TT) of the (TP). For the all-night PSG Sonolab, Medtronic Sonosleep, Medtronic 4200, Sleepsoft, Medtronic 8560, Sleepsoft, Medtronic 8560 was used and the sleep scoring was performed blindly by two examiners. After the mentioned evaluation, the patients were submitted to a physical therapy, three times a week during three weeks, consisting of an interfidential analgesic medium frequency electric current associated with a pulsed ultrasound of 1Mhz (Sonopuls 992, Enraf-Nonius Partner for Life, Delft, Netherlands). After the therapy, the patients were evaluated again by same initial protocol.

Results: The treatment effects over clinical and sleep parameters are shown in the table.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL PARAMETERS</th>
<th>SLEEP PARAMETERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>number of patients before sleep</td>
<td>22.5 ± 9.9</td>
<td>0.5 ± 1.0 *</td>
</tr>
<tr>
<td>PA intensity before sleep (VAS)</td>
<td>17.0 ± 5.0</td>
<td>0.5 ± 1.0 *</td>
</tr>
<tr>
<td>stage 1 (%)</td>
<td>6.8 ± 2.5</td>
<td>12.2 ± 2.5</td>
</tr>
<tr>
<td>stage 2 (%)</td>
<td>7.0 ± 3.6</td>
<td>6.2 ± 2.5</td>
</tr>
<tr>
<td>stage 3 (%)</td>
<td>7.0 ± 3.6</td>
<td>10.9 ± 4.2</td>
</tr>
<tr>
<td>REM (%)</td>
<td>14.4 ± 6.6</td>
<td>17.7 ± 2.6</td>
</tr>
<tr>
<td>number of cycles</td>
<td>3.2 ± 0.5</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>Sleep latency (VAS)</td>
<td>14.0 ± 2.1</td>
<td>0.25 ± 1.0 *</td>
</tr>
</tbody>
</table>

* p<0.05; PA: tender point (dolorimeter); VAS: visual analog scale; TT: tenderness threshold; VAS: anallogic visual scale; TST: total sleep time.
Conclusions: This preliminary study suggests that physical therapy using combined therapy with interventional analgic current and pulsed ultrasound can be effective in the treatment of sleep and pain manifestation in fibromyalgia patients.

References:

670.P

Sleep Spindles During Slow Wave Sleep in Fibromyalgia

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Introduction: Sleep spindles had been considered as a sleep protecting mechanism by inhibiting or attenuating potentially arousing stimuli. Since auditory stimulation was not able to induce increase in sleep spindles, it was claimed that these effects appear to be restricted to endogenously generated stimuli. Considering that pain, an endogenous stimulation mechanism of awakening might play a role in fibromyalgia, we hypothesized that an increase in sigma activity and sleep spindles count could occur in this clinical condition.

Methods: Together with all-night polysomnography, digital electroencephalogram of twenty fibromyalgia female patients (45 ± 7 years), with pain complaints at the occasion of the study and of 18 female healthy controls (42 ± 8 years), were studied. Sample selection was performed during slow wave sleep of the first and second sleep cycles, taking 50 consecutive 2-second epochs from the beginning onwards, excluding artifacts. The spectral analysis was performed by Fast Fourier Transformation on F3, F4, C3, C4, P3 and P4 electrodes and sigma activity band was considered between 12.5 and 15.5 Hz. Visual count of sleep spindles on the same samples was also performed and sleep spindles density calculated.

Results: Significant increases in sigma activity and in sleep spindles density in all studied brain topographies was obtained in fibromyalgia patients, during both first and second cycles.

Figure 1

571.P

Alpha-EEG Sleep and Chronic Pain: Challenges to the Alpha-EEG Sleep as a Pain Specific Sleep Anomaly

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Introduction: The alpha-EEG sleep anomaly has been associated with chronic benign pain syndromes such as fibromyalgia and rheumatoid arthritis, and believed by some to be an important biologic correlate of these painful conditions. Alpha-EEG sleep may be experimentally induced in normal individuals through stage 4 sleep deprivation with auditory or other noxious stimuli, in some cases resulting in subsequent complaints of myalgia, fatigue, and mood disturbance. Thus, it has been postulated that the alpha-EEG sleep pattern may be the mechanism through which psychological factors influence pain. This study examined the sleep and psychological factors of chronic pain patients who underwent evaluation at a sleep disorders center over a five-year period. Sleep parameters and psychological characteristics of the chronic pain patients were compared with pain-free psychiatric and medical patients who were also found to exhibit the alpha-EEG sleep anomaly.

Methods: Patients participated in nocturnal polysomnography (PSG), underwent testing of daytime sleepiness with the multiple sleep latency test (MSLT), and completed psychological questionnaires. Alpha-EEG sleep was identified in 5% of adult patients (54 of 1,076 patients), including patients with a concurrent diagnoses of: chronic pain (n = 18), psychiatric disorder (n = 15), or non-painful medical or other sleep disorder (n = 18). These three diagnostic groups did not differ on age (M age = 43 years) or gender composition (52% male).

Results: All groups evidenced significant disturbance in sleep architecture (i.e., increased tonic alpha and beta activity, decreased slowwave or delta sleep). The groups did not differ on other PSG features (i.e., Apnea/Hypopnea Index, nadir SaO2, arousal index, period limb movements, heart rate). The chronic pain and psychiatric patients exhibited less total sleep time than did the general medical patients (50 – 60 minutes less on average) with poorer sleep efficiency (pain patients M = 79%; psychiatric = 77%; and medical = 90%; F = 4.75, p ≤ .05). However, excessive daytime sleepiness was demonstrated with the MSLT in medical patients only (F = 15.6, p ≤ .001). Psychological testing with
Conclusions: This study finds that chronic pain patients exhibited a significant alpha-EEG sleep disturbance similar to that observed in some pain-free medical and psychiatric patients. Findings challenge the notion that alpha-EEG sleep is of direct etiological significance in producing the pain complaint, since the alpha-EEG sleep was not a necessary or sufficient condition for pain. Furthermore, sleep disturbance was not accounted for by psychological symptoms. Results suggest instead that a variety of noxious stimuli (physiologic, psychologic, and environmental), may precipitate the alpha-EEG sleep pattern.

672.P

Sleep and Quality of Life in Women With Breast Cancer: Preliminary Results


Methods: Six women (mean age 51 yrs, SD 9.3; range 40-65 yrs) with breast cancer were referred to the UCSD Sleep Clinic prior to the onset of chemotherapy. All women were recently diagnosed with stage I-IIIA breast cancer were scheduled for four cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy at the UCSD Cancer Center. Each woman wore an Actilume (Ambulatory Monitoring Inc, Ardsley, NY) for three consecutive 24-hour periods and completed questionnaires on fatigue, quality of life, sleep and mood. Data from the Pittsburgh Sleep Quality Index (PSQI) were associated with lower quality of life scores on the FOSQ (r = -.52). Furthermore, subjective reports of poor sleep on the PSQI were associated with increases in WASO (r = -.97) and decreases in TST (r = .68). This relationship was also seen with decreases in FACT-B total scores being associated with decreases in TST (r = .68) and increases in number of nighttime awakenings (r = -.76). This relationship was also seen with decreases in FACT-B total scores being associated with decreases in TST (r = .68) and increases in number of nighttime awakenings (r = -.76). This relationship was also seen with decreases in FACT-B total scores being associated with decreases in TST (r = .68) and increases in number of nighttime awakenings (r = -.76).

Results: Mean scores (SD) on QOL, mood, and sleep variables were: QOL: FACT-B 97.8 (15.7), PSQI 8.3 (3.1), TST 7.6 hrs (0.5), WASO 63.8 (38.3), number of nighttime awakenings 11.0 (7.3). Due to the small sample size (n=6) at this phase of the study, only effect size statistics are reported here; more through analyses will be reported in future. Correlations suggest increases in depression are associated with decreases in TST (r = -.52) and increases in WASO (r = -.64). Reductions in QOL as measured by the PSQI were associated with increases in WASO (r = -.97) and number of nighttime awakenings (r = -.76). This relationship was also seen with decreases in FACT-B total scores being associated with decreases in TST (r = .68) and increases in number of nighttime awakenings (r = -.52). Furthermore, subjective reports of poor sleep on the PSQI were associated with lower quality of life scores on the FOSQ (r = -.90).

Conclusions: These preliminary results indicate women with breast cancer are suffering from sleep disruption which may be related to their depressed mood and reductions in quality of life. This sample’s reduction in quality of life and increases in depression are associated with objective measures of poor sleep, as well as self-report of poor sleep. As the study progresses, larger sample size will help us further explore the relationships between sleep, quality of life, and mood in this population.

References:

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673.P

Effects of Total Hip Replacement on Subjective and Actigraphic Measures of Sleep

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Methods: Forty-eight patients with primary or secondary osteoarthritis (26 women, 22 men, average age 66 years) were recruited consecutively from orthopaedic waiting lists of three metropolitan public hospitals in New Zealand, between April and July 1999. Participants completed a sleep questionnaire and were monitored (actigraphy and sleep diaries) for 4-5 nights at least four weeks prior to surgery, and again three months after surgery. Sleep duration and sleep quality measures were estimated using the custom software (“SleepWatch”) provided with the actigraphs (Mini-Mitter, Oregon). Changes in subjective measures pre- and post-surgery were assessed by McNemar tests. Changes in actigraphic measures of sleep, and comparisons of changes in subjective versus actigraphic measures of sleep, were assessed by mixed-model analysis of variance.

Results: Sleep duration (estimated from questionnaires and from actigraphy) did not change post-surgery. However, participants averaged 23 minutes less time in bed, with reduced activity during sleep, improved sleep efficiency, and reduced sleep fragmentation. There were no measurable changes post-surgery in the use of sleeping pills, napping behavior, or daytime sleepiness (Epworth sleepiness score; Johns, 1994). The majority of patients (75%) reported a marked reduction in sleep disturbance due to hip pain, with the rest reporting no change. About 40% of patients reported an improvement in how often they got enough sleep, woke feeling refreshed, had their sleep disturbed by other pain, and the extent to which inadequate sleep affected their day-to-day functioning. More than half of the participants (56%) considered that they had a sleep problem prior to surgery, but this fell to 21% post-surgery. Participants’
Sleep, Daytime Sleepiness and Wakefulness in Patients with Retinitis Pigmentosa

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Introduction: Sleep disturbances and the failure to entrain circadian rhythms to the 24-hour day have been reported in a high proportion (48.7%) of blind individuals, supporting the idea that photic input from the retina to the suprachiasmatic nucleus (SCN) is the main “zeitgeber” or time-giver, synchronizing endogenous circadian rhythms in mammals. Retinitis pigmentosa (RP) includes a group of hereditary progressive retinal dystrophies caused by a primary degeneration of rod and secondary of cone photoreceptors. The disease is typically characterized by night blindness, bone spicule-like pigmentary retinal changes, and progressive loss of peripheral field. The loss of rods could disturb retinal input to the SCN and thus, affect the circadian rhythms. The aim of the study was to examine sleep, daytime sleepiness and the ability to stay awake during the day in subjects with RP compared to normally sighted controls. We hypothesized that visually impaired patients affected with RP would have more subjective sleep complaints, sleep disturbances and daytime sleepiness when compared to a control population.

Methods: Twelve individuals diagnosed with RP (40±8 yr.) and twelve normally sighted healthy individuals (39±7 yr.) matched for age, body mass index (BMI) and sex were selected for the study. Participants had their sleep recorded on two consecutive nights and two days. On the first day, their ability to stay awake and on the second, their sleep propensity were examined using the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT) respectively. Self-report measures were obtained using the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Toronto Hospital Alertness Test (THAT).

Results: Daytime sleepiness (ESS: 9±5 vs 6±4; p=0.053) and sleep propensity (MSLT: 10±5 vs 17±3 min; p=0.000) were significantly higher in RP patients than controls, whilst their alertness (THAT: 29±9 vs 38±7; p=0.016) and ability to stay awake (MWT: 21±9 vs 29±2 min; p=0.006) were reduced. Nighttime sleep in the RP patients tended to be disturbed, with more awakenings (arousal index: 14±8 vs 8±6/h; p=0.062), and less REM sleep (19±5 vs 22±3 %; p=0.094).

Conclusions: Patients with RP have more disturbed nighttime sleep of poorer quality than controls, with increased daytime sleepiness and reduced alertness/wakefulness.

References:
(1) Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. Sleep, 1994, 17: 703-710.
(3) Wicklund I. and Romanos. A comparison of quality of life before, 6 weeks, and 6 months after total hip replacement surgery. J. Driver HS, Loyola University Medical Center

Introduction: Lung transplant recipients are at high risk for developing sleep disturbances secondary to their post-transplant medications, weight gain, and recurrent medical complications. These sleep disturbances are likely to lead to further psychological and physiological problems which can affect the patient’s quality of life. Unfortunately, the incidence of sleep disorders in lung transplant recipients has not been well defined.

Methods: We asked 23 lung transplant recipients to fill out a sleep questionnaire and an Epworth Sleepiness Scale (ESS) in order to determine the effects of transplantation on sleep.

Results: The group consisted of 16 women and 7 men, mean age of 47±12 years, and 1160±1028 days post transplantation. The underlying diseases were emphysema (8), cystic fibrosis (7), sarcoidosis (3), pulmonary fibrosis (2), and pulmonary hypertension (3). Fifty two percent (12) of the patients felt that they had a sleeping problem. Of these, 6 stated that the problem developed after transplantation, 2 that it worsened after transplantation, and 4 that it was the same before and after transplantation. 48% complained that their sleeping difficulties affected their activities of daily living, 78% complained of being tired, and 41% stated that they felt sleepy during the day, 50% felt that they did not get enough sleep and 41% of patients had taken sleeping pills at some point after their transplant. 65% of patients were habitual snorers and 57% complained of “restless legs”. 17% of patients had been told by their bed partners that they stopped breathing during sleep. The average ESS score was 7±4.

Conclusions: Sleep disturbances are a common and significant cause of morbidity after lung transplantation and are detrimental to the patient’s quality of life. Based upon this data all lung transplant recipients should undergo a thorough sleep evaluation and further interventions should be instituted to improve quality of life.

Sleep Disturbances in Lung Transplant Recipients

Villanueva J, Khurshid A, Bhorade SM, Garrity ER

Lung transplant recipients are at high risk for developing sleep disturbances secondary to their post-transplant medications, weight gain, and recurrent medical complications. These sleep disturbances are likely to lead to further psychological and physiological problems which can affect the patient’s quality of life. Unfortunately, the incidence of sleep disorders in lung transplant recipients has not been well defined.

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Conclusions: Sleep disturbances are a common and significant cause of morbidity after lung transplantation and are detrimental to the patient’s quality of life. Based upon this data all lung transplant recipients should undergo a thorough sleep evaluation and further interventions should be instituted to improve quality of life.

Cold Feet: Can’t get to Sleep? Sleep Onset Disturbances in Vasospastic Syndrome

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Introduction: A relationship between thermoregulatory processes and the initiation of sleep has long been implicated. Recent studies have shown that the degree of dilation of blood vessels in the skin of hands and feet, which increases heat loss at these extremities, is the best predictor for the rapid onset of sleep (1). It has also been proposed that some sleep disorders might be secondary to problems in distal vasodilation.
(1). Persons with a so-called vasospastic syndrome often suffer from cold hands and cold feet (2), and sometimes also from systemic hypotension, Raynaud’s phenomenon, migraine, and tinnitus (3). These persons respond to stimuli like coldness or even emotional stress with inadequate constriction or insufficient dilation in the microcirculation (2). We used a questionnaire to elucidate whether this group of persons had sleep disturbances which might be related to their impaired ability to initiate distal vasodilation.

Methods: Thirty-two carefully diagnosed vasospastic persons (M:F= 3:29; age 46y±3 SD), of whom fourteen suffered from normal-tension glaucoma, were evaluated with a detailed sleep questionnaire and compared with an age- and sex- matched non-vasospastic control group (N=31; M:F= 4:27; age 43y±3) without any general or ocular disease. The BMI did differ (22.9±0.5 vs. 21.4±0.6*).

Results: Differences between the groups are shown in the Table. In comparison with the control group, vasospastic persons showed a significantly prolonged sleep-onset latency not only before nocturnal sleep but also after a nocturnal sleep interruption. Furthermore, they complained significantly more often about difficulty falling asleep due to cold feet. No significant difference in circadian phase position of sleep or its duration was documented.

Table 1

<table>
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</table>

Conclusions: Vasospastic persons have a selective sleep disturbance of prolonged sleep-onset latency that may be related to an impaired nocturnal distal vasodilation.

References:

### A Sleep Therapy Program for Cancer Patients with Insomnia

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Introduction: Approximately one third of cancer patients report trouble sleeping that interferes with their daytime functioning (1). This study describes, and examines the efficacy of, a sleep therapy program developed for cancer patients with insomnia. Two previous studies of non-pharmacologic approaches to insomnia treatment for cancer patients have been reported. In a randomized controlled study, Cannici et al. (2) found that relaxation training was effective for sleep-onset insomnia, and Stam and Bultz (3) reported a case study of successful use of relaxation and imagery training for insomnia in one patient. The current treatment was specifically developed to address the types of insomnia identified by cancer centre patients—trouble sleeping (predominantly multiple awakenings) associated with thoughts, concerns, pain and discomfort (1). Therefore the program aimed to consolidate sleep and reduce interference with sleep due to cognitive-emotional arousal and pain. It was predicted that the sleep therapy program would lead to improvements in the sleep, mood, and functioning of cancer patients with insomnia.

Methods: The 12 final participants were patients of a regional cancer centre who had insomnia; mean age 54.7 years (SD 10.4); median time from cancer diagnosis 33.6 months; all were fully ambulatory. The program was a six-session group program; and three groups (4-6 patients in each) were conducted. The main components were: sleep education, stimulus control therapy, worry time, and relaxation practice. Participants kept daily sleep diaries. In addition, the following self-report instruments were used to measure mood, functioning, and perceived severity of sleep problems: Sleep Impairment Index (SII; Morin, 1993); Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) and the EORTC Quality of Life Questionnaire-Cancer 30 (QLQ-C30) version 3 (Aaronson et al., 1993). From the QLQ-C30, the five functioning scales, the fatigue and pain scales, and the insomnia item were examined. One-way repeated measures analysis of variance was used to compare outcome measures at baseline, week 4 and week 8.

Results: Significant improvement over baseline was observed at weeks 4 and 8 in mean: number of awakenings, time awake after sleep onset, sleep efficiency, sleep quality ratings, the SII, and scores on the QLQ-C30 Role Functioning and Insomnia (all p<.05). Total sleep time and fatigue were significantly improved at week 8 only. Mean mood scores indicated that patients were generally non-distressed at baseline, and these scores did not change significantly at weeks 4 and 8.

Conclusions: The sleep therapy program led to improved sleep, reduced fatigue, and enhanced ability to perform activities, in relatively well individuals attending a cancer centre. This is preliminary evidence of the efficacy of the program. Further research is required to determine which aspects of the program account for its efficacy, and to examine its suitability for a wider range of people with cancer.

References:
Judith Davidson is a Research Student of the National Cancer Institute of Canada supported with funds provided by the Canadian Cancer Society

678.P

Pain Reduces Nocturnal Sleep Duration In Medical Oncology Patients

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Introduction: Pain in cancer patients is both a common and important problem. Nocturnal sleep disturbances are also prevalent in this group. However, little research has been conducted to examine the relationship between pain intensity and nocturnal sleep duration in medical oncology patients. We believe that this project is the first to quantify this relationship.

Methods: We performed secondary analyses of data from a study on pain and sleep in 99 patients. These patients had a documented cancer diagnosis, excluding local skin cancers, for which they received care between March 1999 and June 2000 at the Atlanta Veterans Affairs Medical Center. We used the ordinary least squares (OLS) model to estimate the effect that pain intensity has on sleep duration, holding constant other sleep-related variables. The regression model is as follows:

Sleep = X.B + e; 1

The parameter X is a vector of patient specific characteristics, B is a vector of coefficients, and e is a random error term. The dependent variable was sleep duration, measured as the number of self-reported hours of sleep per night (Buysse et al., 1989). The key independent variable of interest, pain intensity, was measured using the pain intensity composite score from the Brief Pain Inventory (Cleeland & Ryan, 1994). In addition, we included control variables for daytime dysfunction (Buysse et al., 1989), opioid use, patient disposition, and patient demographic characteristics (age, race, and marital status).

Results: The regression results from OLS estimation indicated that pain intensity was inversely related to hours of sleep per night (p<0.01). The results suggested that each one-unit increase in pain intensity reduced nighttime sleep by approximately 14.5 minutes. Daytime dysfunction was also inversely related to hours of sleep per night (p<.05). Patients reporting daytime dysfunction slept, on average, 39 minutes less each night than patients who did not report daytime dysfunction.

Conclusions: Our results indicate that sleep duration is significantly shorter in those patients who experience pain of greater intensity. In addition, patients who report shorter sleep duration are more likely to experience daytime dysfunction. Based on our findings, sleep disturbances are yet another reason why pain should be aggressively treated in cancer patients.

References:

This study was supported by a grant from the Atlanta Research and Education Foundation (AREF).

679.P

Sleep Predicts Psychological Adjustment and Mortality in Cancer Patients

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Introduction: Emerging evidence suggests that sleep is an important correlate of mental and physical health. Disturbed sleep is associated with the onset and maintenance of psychiatric disorders, as well as decrements in physical health including health care utilization, absenteeism, illness severity, and immune function. Fewer studies have evaluated sleep as a predictor, or mediator, of subsequent health outcomes. In the present study, we sought to evaluate the impact of subjective sleep complaints on subsequent mental and physical health outcomes in a sample of newly diagnosed cancer patients.

Methods: We evaluated prospective relationships among sleep and health outcomes in a sample of 42 patients (6 female, 36 male; mean age of 56.5 years + 10.4) with newly diagnosed stage IV renal cell carcinoma who were recruited prior to participating in a phase II immunotherapy trial. Patients completed the Pittsburgh Sleep Quality Index, the Brief Symptom Inventory (BSI), the CES-D, and the SF-36 at baseline, prior to vaccination, and 24 patients completed the same measures at a follow-up session 8 weeks later.

Results: Regression analyses revealed that poorer sleep quality was subsequently associated with elevated symptoms of distress on the BSI (Beta =.43, p<.02) and depression on the CES-D (Beta =.56, p<.006), after controlling for disease status and these measures at baseline. Among the 42 patients who completed the baseline assessment, logistic regression analyses revealed that sleep quality was a significant predictor of mortality during a 6-15 month follow-up period (p<.02), after adjusting for indicators of medical prognosis, bodily pain, or other indices of quality of life at baseline.

Conclusions: These data suggest that sleep is an important predictor of subsequent mental and physical health outcomes in cancer patients. In this sample, sleep was a stronger predictor of mortality than were traditional indices of disease severity including number and site of metastases. The nature of the relationship between sleep quality and health outcomes remains to be addressed. It will be important to determine whether sleep acts to signal vulnerability to, or plays a direct causal role in, adverse health outcomes. Pathways to outcomes may also differ depending on the outcome; for example, sleep-immune relationships may be especially important to mortality in cancer patients. Finally, relationships between laboratory-observed sleep and subsequent health outcomes need to be determined as well.

Research supported by MH01554, MH24652, MH30915, RR00056, & M.D. Anderson University Cancer Foundation

680.P

Heart Rate Fluctuations of Successive Non-REM/REM Transitions in IBS Patients

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Thomas N. Lynn Institute for Healthcare Research

Introduction: Recent studies from our laboratory have described significant differences in sympatho-vagal balance during REM sleep in patients with irritable bowel syndrome (Orr, et. al., 2000). Heart rate is
an easily recorded measure of the autonomic functioning shown to decline overnight in young healthy males during each successive non-REM/REM period (Cajochen et al., 1994). Heart rate typically increases with the onset of each REM period due to vagal withdrawal as well as increased sympathetic activity (Baust, 1969). This study investigated heart rate changes before and after each REM period for IBS patients in order to determine specific differences which exist in this group with regard to cardiac regulation during sleep. The goal of the study was to perform a quantitative analysis of heart rate during sleep in IBS patients focusing on a global trend over the entire sleep interval and also specific changes related to each non-REM/REM transition.

Methods: Seventeen female (M = 32) IBS patients and 14 healthy women (M = 37) underwent one night of polysomnographic recording and ECG monitoring. Five minutes of digitized ECG signal was used to calculate heart rate (HR) utilizing the computer software Toolbox for MATLAB, the Math Works Inc, Natick, Massachusetts. Five minute segments were calculated before, during, and after each of the first three REM periods.

Results: HR was higher for IBS patients during each non-REM/REM transition (see Figure 1). Patients had significantly (p < .01) higher HRs prior, during, and after the 1st non-REM/REM than controls. IBS patients revealed a significant (p = .03) decrease in overall HR over the night of sleep (Mean = 4.09) compared to controls (Mean = 13). The mean HR during the non-REM intervals was significantly higher (Mean = 70) for IBS patients (Mean = 63) than controls.

Conclusions: 1) The marked changes in HR over the course of sleep reveals differential patterns in IBS women. 2) IBS patients show a decrease in HR decrease throughout the night and specifically are higher than controls during non-REM periods. 3) The decreasing heart rate observed in the IBS patients over the course of the night indicates increased vagal tone with an eventual return of heart rate similar of healthy controls. Even though heart rate changes in IBS patients during each non-REM transition was similar to controls, increased HR during non-REM sleep and significant decline over the sleep interval confirms autonomic dysfunction during sleep in IBS patients.

References:

681.P

Behavioral and Physiological Sleep Characteristics in IBS Symptom Subgroups

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Introduction: Although subjective sleep complaints are well-documented in patients with IBS, the presence of objective sleep abnormalities remains controversial. It also remains unclear whether sleep dysfunction is related to patients gastrointestinal (GI) symptoms and/or to psychological factors. The goal of this study was to investigate sleep characteristics in IBS symptom subgroups.

Methods: 31 female IBS patients were stratified into 15 patients with only bowel symptoms (IBS+L) and 16 patients with both lower and upper dyspeptic-like symptoms (IBS+D). 21 healthy females served as controls. For 4 consecutive days subjective sleep quality, insomnia symptoms, alertness, state anxiety, stress levels, and daytime and nighttime GI symptoms were assessed. Saliva samples were collected for cortisol analysis. On night 4, subjects underwent polysomnographic (PSG) monitoring for an objective assessment of sleep quality including arousals and respiratory parameters.

Results: Compared to both IBS-L and controls, IBS+D reported greater difficulties falling asleep, and showed a greater global Pittsburgh Sleep Quality Index (PSQI) score indicating greater overall sleep problems (all p<.05). A greater percentage of IBS+D patients reported night time GI symptoms (73.5 vs. 38.2%, p<.01). Compared to both controls and IBS+L, IBS+D reported greater depression and morning anxiety across the 4 study days (all p<.05). Both patient groups felt less rested and showed decreased levels of daytime alertness on all 4 days compared to controls (all p<.01). Both patient groups showed normal circadian changes in salivary cortisol (evening: 4.2± 2.01 ng/ml for controls; 4.4+ 2.6 for patients; morning: 14.9 + 5.3 for controls; 12.9+ 5.3 for patients), and did not report increased stress levels. There were no objective abnormalities in sleep architecture as measured with PSG in either patient group: sleep stage distribution, number of arousals were no different from controls.

Conclusions: (1) IBS patients with dyspeptic symptoms report more severe and widespread GI symptoms, but also more extraintestinal symptoms including increased sleep problems and greater psychopathology. (2) In the absence of objective sleep abnormalities, IBS patients do have sleep-related GI complaints. (3) Sleep complaints are not related to abnormal circadian changes in cortisol secretion or increased stress levels in any IBS subgroup. Instead, increased sleep complaints may be attributable to a misperception of and/or a reporting bias regarding sleep quality.

682.P

Self-reported Disturbed Sleep in Patients with Postherpetic Neuralgia

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(1) Pfizer, (2) UCLA Division of General Internal Medicine and Health Services Research

Introduction: Patients with postherpetic neuralgia (PHN) often report accompanying sleep problems. This study ascertained the level of sleep disturbance in this patient population as measured by the Medical Outcomes Study (MOS) Sleep Scale.
Methods: The MOS-Sleep Scale is a 12-item, patient-completed questionnaire that yields seven 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 sleep problem index. The MOS-Sleep Scale is scored such that higher scores indicate more of the individual domain being measured. For example, a higher score on the sleep adequacy subscale indicates a positive sleep attribute, while a higher score on the somnolence subscale indicates more somnolence, or a negative sleep attribute. The subscales and index scores range from 0-100 except for optimal sleep, which is scored dichotomously (1 = 7 or 8 hours of sleep a night; 0 = otherwise). This measure was administered to 173 patients with a diagnosis of PHN, the average age of the population was 72, 53% were female and 95% of the population was white. The subscale and index scores of the PHN sample were compared to previously reported results from 3,445 patients in the MOS. The individuals in the MOS had at least one of the following medical conditions: congestive heart failure, myocardial infarction, diabetes, hypertension, or major depression. The average age of the MOS sample was 54, 63% of the sample was female and 76% of the sample was white. Differences in sleep scores between the two samples were assessed univariately by t-tests and in multivariate regression models, controlling for age, gender and race.

Results: Patients with PHN had more sleep problems than those in the MOS in terms of sleep disturbance (46 vs. 29), sleep adequacy (50 vs. 60), somnolence (34 vs. 26), quantity of sleep (6.3 hours vs. 6.9 hours), optimal sleep (37% reporting optimal sleep vs. 54%) and by the 9-item sleep problems index (41 vs. 29). Each of these univariate results was significant at the p<0.01 level (see Figures 1 & 2). There were no significant differences between samples in snoring (30 vs. 31) and awakening short of breath or with a headache (14 vs. 13). However, in the multivariate analyses, patients with PHN were significantly more likely than MOS patients to report awakening short of breath or with a headache (p<0.05). All other univariate results were confirmed in the multivariate models.

Conclusions: Patients with PHN appear to have more sleep problems than a patient population comprised of at least one chronic medical condition. Further work is underway to compare these findings to a sample from the general population. However, these initial results demonstrate that sleep problems are prevalent in persons with PHN.

References:

Research supported by Pfizer Global Research and Development

Evaluation of Quality of Sleep in Patients with Cystic Fibrosis

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University of North Carolina at Chapel Hill

Introduction: Cystic Fibrosis (CF) is associated with progressive decline in pulmonary function. Sleep studies in CF patients have focused on nocturnal pulmonary gas exchange. Little research has been directed towards other potential sleep disturbances. Our aim was to examine self-reported sleep hygiene, subjective attitudes toward sleep, and symptoms related to pathophysiological abnormalities in CF which may have an impact on sleep.

Methods: A standardized 66-item survey including the Epworth Sleepiness Scale (ESS) was administered to 10 CF patients (9 outpatients and 1 hospitalized). Questions focused on symptoms of sleep disordered breathing, daytime sleepiness or fatigue, sleep hygiene, nocturnal coughing/wheezeing, anxiety and depression as well as a self-rating of sleep quality. Patients rated the frequency of symptoms as none, occasional, or frequent.

Results: Data collection is continuing with 10 patients having completed the survey to date. Patients ranged in age from 20 to 60 years with FEVI’s ranging from 19% to 77% of predicted. Four patients were on oxygen and none was using bilevel continuous positive airway pressure. The average number of hours slept was 8.1 on weeknights and 8.2 on weekends. Five patients reported napping approximately 1 hour daily. Symptoms compatible with obstructive sleep apnea were reported in only 3 patients. However, 8 patients reported dry mouth (4 frequently) and 9 complained of blocked nasal passages (3 frequently) in the morning. Although 9 patients complained of nocturnal cough/wheezeing, only 1 reported this as occurring frequently. Seven patients reported experiencing fatigue and decreased energy while 9 reported feeling unre-
freshe(d 3 frequently) regardless of the amount of time slept. Excessive daytime sleepiness affecting work or school performance was reported by only one subject while four felt their performance was not optimal because of excessive sleepiness. On a scale of 1 (poor) to 10 (excellent), 8 rated their sleep quality as 5 or greater. None of the subjects reported awakening with feelings of anxiety and only 2 reported occasional feelings of depression. Seven had ESS scores of 9 or higher.

Conclusions: Low energy, fatigue and feeling unrefreshed regardless of sleep duration were frequent complaints of these CF patients. The ESS scores indicated the majority were sleepier than normal, but few reported decreased performance at work or school and few rated the quality of their sleep to be below average. Nine patients reported awakening with cough/wheezing, but only 1 reported it as occurring frequently. However, a larger proportion reported frequent symptoms consistent with nasal obstruction, which could be associated with sleep disordered breathing. Anxiety and depression did not seem to be significant factors affecting sleep or contributing to fatigue. We feel these findings suggest patients may be attributing fatigue to chronic infection and misperceiving their sleep quality. As a result, physicians caring for CF patients may not be aware of potentially treatable sleep disturbances. If our initial findings are confirmed by additional data, polysonmographic evaluation of CF patients with subtle symptoms suggestive of sleep disturbance may be indicated. Appropriate intervention for specific causes of sleep disturbance could be important to improve quality of life.

Research supported by NIH Sleep Academic Award K07 HL03897

684.P

Sleep Problems in Dialysis Patients with and without Restless Legs Syndrome

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Introduction: Sleep disturbance is very common in renal dialysis patients, and restless legs syndrome (RLS) has been reported to be one of specific causative factors of sleep complaints. However, in the previous reports, the definition of RLS itself implied sleep disturbance, and the existence of sleep disturbance was determined usually by questionnaire with dichotomized questions, which might lead to overestimation of the prevalence of sleep problems in dialysis patients with RLS. In this study, we firstly aimed at estimating the prevalence of RLS in dialysis patients in a local hospital in Japan according to the standardized diagnostic criteria for RLS, and comparing the prevalence and content of sleep problems, taking its quantitative aspects into consideration, in dialysis patients with and without RLS.

Methods: Consecutive sixty-eight patients were interviewed who received hemodialysis from 1st to 16th June, 2000 at an outpatient dialysis unit, Shizuoka City Hospital. We used modified Basic Nordic Sleep Questionnaire (mBNSQ) for assessing sleep disturbance and the four minimal criteria by the International RLS Study Group for the diagnosis of RLS. Patients who fulfilled all four minimal diagnostic criteria during the last three months were classified into definite RLS, and patients with three of the four criteria including motor restlessness were defined as possible RLS. Only patients who negated motor restlessness or any kind of sensory discomfort or pain with no history suggestive of RLS in the past were categorized as asymptomatic patients. As most parts of mBNSQ were answered on an ordered five-point scale, scale 4 (on 3-5 nights per week) and 5 (every night or almost every night) were considered positive for disturbed sleep.

Results: Sixty-two patients (65.7 ± 11.4 years) responded the interview and completed the questionnaire. Nine patients (14.5%) fulfilled the diagnostic criteria for definite RLS and eight (12.9%) for possible RLS. There were 18 (29.0%) asymptomatic patients. Sleep disturbance was reported by 38/62 patients (61.3%). Patients demographics of the two groups (Definite & possible RLS vs Asymptomatics) and the content of sleep problems are shown in Table. There was no significant difference between two groups about the demographic characteristics, and patients with definite and possible RLS did not report statistically more sleep problems than asymptomatics, but two-thirds of definite and possible RLS group attributed their sleep disturbance to RLS symptoms.

Table 1

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<td>64.4±11.4 (range 42-81)</td>
<td>70.8±11.4 (range 47-89)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>6.1±3.1 (range 13.7-28.0)</td>
<td>20.3±2.7 (range 16.0-23.1)</td>
</tr>
<tr>
<td>HD duration (month)</td>
<td>32.7±42.8 (range 0.5-174.0)</td>
<td>37.3±31.2 (range 0.5-98.0)</td>
</tr>
<tr>
<td>Self-claimed TST (hour)</td>
<td>6.1±1.9 (range 3-10)</td>
<td>6.6±1.4 (range 4-10)</td>
</tr>
<tr>
<td>Disturbed sleep (No.)</td>
<td>12 (70.6%)</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>Difficulty of initial sleep</td>
<td>8 (47.0%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Frequent awakening</td>
<td>9 (52.9%)</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>Early awakening</td>
<td>2 (11.8%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Unrefreshed sleep</td>
<td>6 (35.3%)</td>
<td>5 (26.9%)</td>
</tr>
<tr>
<td>Use of sleeping Medication</td>
<td>4 (23.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Disturbed sleep due to discomfort / restlessness</td>
<td>8 out of 12 (66.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>No sleep problems (No.)</td>
<td>5 (29.4%)</td>
<td>10 (55.6%)</td>
</tr>
</tbody>
</table>

BMI: body mass index, HD: hemodialysis, TST: total sleep time.

Conclusions: RLS is commonly seen in dialysis patients and high percentage of dialysis patients experienced sleep disturbance. However, even in patients without RLS or isolated motor/sensory symptoms, sleep disturbance is commonly reported, which suggests that overall sleep problems of dialysis patients may be multi-factorial and not always be caused by RLS.

References:
(2) The international Restless legs syndrome Study Group; Walters AS, Group Organizer and Correspondent. Toward a better definition of the restless legs syndrome. Mov Disord 1995: 10: 634-642.

685.P

The OSA - Diabetes Interaction Model in African-American Women

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Introduction: Type 2 diabetes mellitus (DM) disproportionately affects 1 out of 4 African-Americans over age 65 years. Obstructive sleep apnea (OSA) increases the risk of hypertension, coronary artery disease, and stroke. The incidence of diabetes was 2.4 fold higher among African-American women residing in the Deep South than Caucasian women who did not reside in the South1. Potentially modifiable lifestyle factors, such as diet and exercise were used to explain nearly half of the excess risk of diabetes in women. However, the decreased physical activity reported in African-American women with Type 2 DM may be related to excessive daytime sleepiness (EDS), the daytime symptom of OSA. The OSA - Diabetes Interaction Model is derived from the work of Strohl and colleagues2 and describes how OSA and diabetes exacerbate one other through several mechanisms.

Methods: This descriptive, correlation study examined OSA symptoms
and glucose control in African-American women. An adaptation of the Douglass Sleep Disorders Questionnaire\(^3\) was used to measure symptoms of OSA, sleep quality, and EDS. Subjects also reported health, nocturia, and diabetic status. Blood was drawn for HbA1c levels. Volunteers were recruited by mail and also at health fairs at African-American churches in an urban Southeast US city.

**Results:** The convenience sample of African-American women (n = 53) included many with Type 2 DM (36%) and many who were obese (55% with BMI > 30). The mean age was 64 years (range = 50-87 years). Moderately strong associations were found between the following: poor sleep quality and nocturia (r = .40, p = .003); poor sleep quality and EDS (r = .45, p = .001); OSA symptoms and self-rated health (r = -.37, p = .007); and BMI and HbA1c level (r = .48, p = .001). Subjects with Type 2 DM had more nocturia (p = .047) and more OSA symptoms (p = .07). Stepwise regression of obese women (BMI > 30, n = 30) showed elevated HbA1c as a predictor for OSA while BMI and age were excluded from the model.

**Conclusions:** These findings suggest that many obese African-American women with Type 2 DM may also have OSA. However, these women may be not be screened or referred for treatment if we attribute diabetes to "lifestyle" alone. Therefore, aggressive screening for OSA and targeted treatment programs for African-American women with Type 2 DM is warranted.

**References:**

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686.P

**The Polyuria - Sleep Disordered Breathing Model: Case Studies Across the Lifespan**

**Umlauf MG, Wells JA, Chasens ER:**
(1) University of Alabama School of Nursing, (2) Wayne State University School of Nursing

**Introduction:** Although we consider nocturia a significant problem for older adults, this same behavior among young children is viewed very differently. As a rule, parents look forward to the day that children gain continence and bedwetting is no longer observed. However, like nocturia in adults, bedwetting is also one of the common symptoms associated with obstructive sleep apnea (OSA) in children.(1) The most widely held urological explanation for enuresis is that some children are just neurologically immature and fail to wake when their bladder has reached capacity. These children are said to sleep through normal sensations of urge to void. As first line treatment, parents are instructed to treat bedwetting behaviorally at home by withholding fluids several hours before bedtime, eliminating caffeine from the child's diet (cola drinks, chocolate), toileting the child just prior to going to bed, and then waking the child to toilet again one hour after sleep onset. This second toileting event is said to be crucial to bedwetting management because most children who wet the bed do so 1-2 hours after sleep onset. Although this has been standard practice, it does not resolve bedwetting - even when practiced faithfully. By contrast, pharmacologic treatment is very effective using administration of vasopressin (DDAVP) by intranasal spray just prior to bedtime. However, the medication is relatively expensive (approximately $1/day) and urologists often advise parents later to withdraw the drug and resume behavioral treatments. In the end, parents are advised to be patient and wait until the child matures neurologically. The purpose of this paper is to provide case studies of nocturia/enuresis combined with OSA in children and adults to illustrate the Polyuria - Sleep Disordered Breathing Model.(2)

**Methods:** Based on parent/patient interviews and clinical reports, selected patients will be profiled regarding the presentation of nocturnal polyuria.

**Results:** Evaluations and treatments offered for enuresis/nocturia prior to referral for a sleep evaluation will be described in full. Data from polysomnography will be summarized and treatment outcomes will be presented for each case.

**Figure 1**

"Polyuria – Sleep Disordered Breathing Model"
Conclusions: In older adults we explain away nocturia by referring to benign prostatic hypertrophy or poor pelvic floor function. In children, more often we ask parent and child to wait for the child to outgrow bed-wetting and praise nocturia. In both cases we may be observing a failure to screen for OSA, which results in a delay of appropriate treatment and a subsequent increase in morbidity in children. (3)

References:

687.P

The Relation of Insomnia and Pain to Mood Variables in a Randomized Sample

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(1) The University of Memphis, Memphis, TN, (2) The University of Tennessee, Memphis, TN

Introduction: The current literature supports a substantial relation between pain, insomnia, and mood (in particular depression and anxiety.) Chronic pain patients often have elevated scores on the BDI, STAI, as well as self-reports of insomnia. Despite this, studies examining secondary insomnia have been limited, often controlling for variables such as mood disturbance in pain patients. Many studies have hypothesized that pain, sleep, and mood have reciprocal effects, but very few studies have examined this relation closely. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diary and daytime functioning data. This paper will focus on the relation of sleep and pain to depression and anxiety among these individuals.

Methods: We used random-digit dialing to collect data from 772 participants from 20 to 98 years old in the metropolitan Memphis (TN) area. Participants completed sleep diaries and questionnaires evaluating health, mood, and daytime functioning, including sleepiness and fatigue. Participants who self-reported a complaint of chronic pain (arthritis, back pain, and headache) were classified as people with chronic pain (PCP). Participants were classified as people with insomnia (PWI) if they complained of a sleep problem related to insomnia for at least 6 months.

Results: There were 236 PWI and 206 PCP. Of the PCP, 104 (50.5%) complained of insomnia, and 102 did not (49.5%). Of the PWI, 104 (44.1%) complained of chronic pain, and 132 (55.9%) did not. We examined the interaction of the complaint of chronic pain and the complaint of insomnia on the two measures of mood (STAI and BDI) in this sample. We performed a 2 x 2 MANOVA comparing the two pain groups (present vs. absent) and the two insomnia groups (complaining vs. non-complaining) on the BDI and STAI. The MANOVA was nonsignificant for the pain x insomnia interaction. There was a significant main effect for both PWI and PCP. Post hoc t-tests showed that insomnia complainers had worse BDI and STAI scores than noncomplainers. Chronic pain complainers had worse BDI and STAI scores than noncomplainers. Mood impairment in these individuals was clinically significant with BDI and STAI scores in the mild to moderate range of depression and anxiety. Considering there was no interaction, there was little difference between mood scores in PWI, irrespective of a complaint of pain.

Conclusions: Based upon sleep diaries in this randomized sample, these results find that (1) there is a high prevalence of chronic pain complaints in PWI, with almost half of the insomniacs reporting chronic pain, (2) there is a high prevalence of insomnia complaints in PCP, with over half of the PCP complaining of insomnia, and (3) when insomnia is present, the addition of chronic pain does not contribute significantly more to increased anxiety or depression.

Research supported by National Institute on Aging grants AG12136 and AG14738

688.P

Evaluation of Sleepiness in Patients with Chronic Medical Disease: Unreliability of the Epworth Sleepiness Scale

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Sleep Unit -Dpt of Neurology, S.Orsola-Malpighi Hospital, University of Bologna, Italy

Introduction: The Epworth Sleepiness Scale (ESS) is considered a reliable method for assessing excessive daytime sleepiness (EDS) in patients with sleep disorders. However there are few data on usefulness of ESS in pts affected by chronic medical disorders complaining of EDS and/or fatigue. The scale rates the chances of dozing off in eight different situations of daily life with a score ranging from 0 to 3 in each situation.; a final score greater than 10 is considered indication of EDS. If a subject has never experienced one or more of the proposed situations, it is suggested to imagine it. We evaluated the reliability of ESS in pts with chronic medical diseases whose daily activities are affected by the pathology.

Methods: Patients: We administered the ESS and the Basic Nordic Sleep Questionnaire (BNSQ) to 342 pts affected by chronic metabolic disease: 172 pts with hepatic cirrhosis and 170 pts with renal failure on chronic haemodialysis. Among cirrhotics, females were 38.2%, males 60.3%, mean age was 52 years, mean Child-Pugh was 8.3. Among uremics, females were 35.3%, males 64.7%, mean age was 64.7 years, mean duration of dialysis was 57.5 months. Both ESS and BNSQ were administered by a physician in order to obtain better collaboration. According BNSQ we considered affected by EDS patients who reported “daytime sleepiness more than three time per week”.

Results: ESS was correctly filled up by 197 pts but could not be completed by 145 subjects (42.3%), because one or more of the proposed situations did not occur recently and the pts were not able to imagine how they could behave in those situations. Eighty two subjects (24%) answered 7 questions; 49 subjects (14%) answered 6 questions; 9 subjects (2.7%) answered 5 questions; 5 subjects (1.3%) answered 4 questions. The situations that more frequently went unanswered were: “in a car, while stopped for a few minutes in the traffic” (85 subjects didn’t answer, 21.8%), “sitting inactive in a public place” (76 subjects didn’t answer, 19.5%), “sitting and reading” (37 subjects didn’t answer, 9.5%). The ESS was not completed by 30.8% of cirrhotics and 55.9% of the uremics. The pts who did not complete the scale were older (62.7 years vs 53.3 years, p<0.0001) and more often females (57.2% vs 33.3%, p<0.0001). Among the cirrhotics those who did not complete the scale had higher Child-Pugh (9.2 vs 7.9, p=0.003). Among the uremics there were no significant differences in duration of haemodialysis between those who completed the scale and those who did not. On the basis of BNSQ we found 56% of the pts with ESD: 52.9 % of cirrhotics, 61.7 % of uremics (p=0.002). ESS identified only 10 % of the sleepy pts, 16.3% of cirrhotics, 3.5% of uremics.

Conclusions: The ESS does not seem suitable for assessment of EDS in patients with chronic medical diseases, when the disease affects daily.
activities and the patient might have not experienced situations proposed by the scale in recent time. Some correction factors for unanswered questions could be useful in this cases.

689.P

Sleep Complaints and Effects of Dialysis Schedules in Patients with Renal Failure

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(1) Sleep Unit - Dpt of Neurology, S.Orsola-Malpighi Hospital, University of Bologna, (2) Dpt of Nephrology, S.Orsola-Malpighi Hospital, University of Bologna, (3) Dpt of Nephrology, Infermi Hospital, Rimini, Italy

Introduction: Sleep disorders, mainly restless legs syndrome (RLS) and insomnia, have been reported to be common in uremic patients on chronic haemodialysis. Moreover, there are many evidences of relationships between dialysis schedule and sleep complaints. Aim of our study was to assess the prevalence of sleep disturbances and daytime sleepiness among haemodialysis pts and to verify the impact of different dialysis schedules on sleep and alertness.

Methods: We considered 170 patients referring to the Haemodialysis Units of the S.Orsola-Malpighi Hospital in Bologna and of the Infermi Hospital in Rimini; males were 64.7% of the sample, females were 35.3%, mean age was 64.8 years, mean duration of dialysis was 57.7 months. A physician administered to all patients a subjective questionnaire, the Basic Nordic Sleep Questionnaire (BNSQ), focused on sleep habits and disturbances, modified with two supplementary questions on sleepiness. In addition, patients were asked several questions on night sleep quality after dialysis session. Restless Legs Syndrome was diagnosed according to the ICSD criteria. Seventy-one pts were scheduled on morning session (7a.m. - 12 a.m.) (Group 1), 69 pts on afternoon session (1p.m.-6 p.m.) (Group 2) and 30 pts on evening session (7 p.m.-11 p.m.) (Group 3). Among the three groups there were no significant differences regarding sex, aetiology of uraemia, duration of dialysis, while a significant difference was found in terms of age between group 1 and group 3 (67years vs 60.3 , p=0.05).

Results: On the total sample almost 20% complained of poor sleep, and 29% used hypnotic drugs three times per week or more. Among the symptoms of insomnia the most common was “more than 1 awakening per night” referred by almost 50% of the pts. Sixty-two per cent of the pts complained of some degree of daytime sleepiness (DS) mild in 34.4% of the pts, moderate in 15.7% and severe in 12%. Napping habit was referred by 63% of the patients. Twenty-eight per cent suffered of RLS and 37% snored three times per week or more. The table shows the prevalence of subjective sleep complaints defined by BNSQ in the total sample and in the three groups. Comparing the three groups we found in group 2 and 3 an higher prevalence of RLS, a greater difficulty in falling asleep and a more common use of hypnotics. The night following the dialysis session 61.1% of pts slept the same than the other nights: 72.9% in group 1, 54% in group 2 and 48.3% in group 3. Twenty-five percent reported they slept worse: 15.7% in group 1, 30.1% in group 2 and 37.9% in group 3.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tr>
<td>Insomnia (%)</td>
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<td>24.6</td>
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<td>Difficulty Falling Asleep (%)</td>
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<td>25.7</td>
<td>39.1</td>
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<tr>
<td>&gt;1Awakening/night (%)</td>
<td>46.7</td>
<td>52</td>
<td>39.7</td>
<td>50</td>
<td>0.05</td>
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<tr>
<td>Early Awakening (%)</td>
<td>20.8</td>
<td>24.6</td>
<td>17.4</td>
<td>20</td>
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<td>Hypnotics(%)</td>
<td>28.8</td>
<td>22.5</td>
<td>34.8</td>
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<tr>
<td>Total SleepTime (min)</td>
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<td>364</td>
<td>414</td>
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<td>Bed time (min)</td>
<td>22.36</td>
<td>22.12</td>
<td>22.36</td>
<td>23.24</td>
<td>0.001</td>
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<tr>
<td>Get up time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RLS (%)</td>
<td>28</td>
<td>21.4</td>
<td>30.9</td>
<td>36.7</td>
<td>ns</td>
</tr>
<tr>
<td>Snoring (%)</td>
<td>37.1</td>
<td>43.8</td>
<td>28.8</td>
<td>41.7</td>
<td>ns</td>
</tr>
<tr>
<td>Nap (min)</td>
<td>63.5</td>
<td>77.5</td>
<td>49.3</td>
<td>63.3</td>
<td>0.002</td>
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<tr>
<td>Daytime Sleepiness (%)</td>
<td>62.1</td>
<td>71.8</td>
<td>50</td>
<td>75</td>
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</tr>
</tbody>
</table>

Conclusions: Haemodialysis patients complained more often of daytime sleepiness than poor nocturnal sleep. Dialysis schedule influences sleep quality: patients on afternoon and evening schedules presented more often difficulty in falling asleep and RLS.

690.Q

The Sleep of Patients with Schizophrenia: A Meta-analysis

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Introduction: Despite numerous efforts, inconsistencies remain regarding the characteristics of sleep in patients with schizophrenia,(1,2) The goal of the present study was to integrate the results of published articles having compared the sleep of patients with schizophrenia to that of healthy participants.

Methods: To be included in the analysis, the studies had to meet a set of criteria, including the presence of a control group made of healthy participants and the formal presentation of descriptive statistical data corresponding to a set of predetermined dependant variables. A total of 14 studies met the criteria, including an average of 14.6 /pm 6.7 patients and 15.0 /pm 5.7 healthy participants. These studies were included in a statistical meta-analysis, using the method of Hunter and Schmidt.(3) Data was subjected to common metric “t-tests” and the average “T” was calculated for each sleep variable.

Results: The following variables showed a significant difference between patients with schizophrenia and healthy participants: sleep latency, total sleep time, number of awakenings, sleep efficiency and REM sleep latency. The other variables did not show significant differences (Table 1). Moderator variables: Moderator analysis showed that the variance between studies decreased when these were grouped according to treatment: never treated (G1, n=5 studies), interruption of treatment for more than 2 weeks (G2, n=4), interruption of treatment for 2 weeks or less (G3, n=5). The three groups of patients were significantly different from healthy participants on sleep latency, total sleep time, number of awakenings and sleep efficiency. T values increased from G1 to G3 (Figure 1). Stage 4 (%) and REM sleep latency reached significantly only when subjects from G2 and G3 studies were grouped (T = -2.27; p<0.05 and T = -3.28; p<0.05, respectively).Abbreviations for Table 1 and Figure 1: SP = REM sleep; SLP = Slow wave sleep.
Introduction: Seasonal affective disorder (SAD) is a form of major depression characterized by a regular occurrence of symptoms in fall or winter and full remission (or hypomania) in spring or summer. Clinical trials have found that response of SAD patients to fluoxetine were better than to placebo. Fluoxetine has a significant sleep disturbing effects in patients with schizophrenia and healthy participants.

Methods: Ms. T is a 44-year-old nurse who was diagnosed with SAD in 1996. The diagnosis was based on the clinical assessment according to DSM-III-R criteria. The values of her SPAQ (Seasonal Patterns Assessment Questionnaire), HDRS-SAD (a 29-item Hamilton Depression Rating Scale for Seasonal Affective Disorder), BDI (Beck Depression Inventory, a 21-item self assessment questionnaire for depression) and CES-D (a 20-item questionnaire for self assessment of depression) were 12, 38, 33 and 47, respectively. These results indicate that she was suffering from a moderate to severe SAD. She started taking fluoxetine (20 mg daily) on November 11, 1996 and received 3 PSG assessments: before treatment (baseline, W0), by the end of week 4 (W4) and week 8 (W8). In October 1997 Ms. T repeated the same procedure on fluoxetine (20 mg daily) taking and PSG recording. Her depression was improved but her sleep disturbance was such that she was unable to continue on fluoxetine. She stopped taking fluoxetine and started taking nefazodone at doses of 100 mg, 200 mg, 300 mg and 400 mg in week 1, week 2, week 3 and weeks 4-8, respectively. PSG recordings were done at baseline (W0), by the end of weeks 2 (W2), 4 (W4), 6 (W6) and 8 (W8).

Results: The results of the first episode on fluoxetine at W0, W4 and W8 were: sleep efficiency (SE, %), 86.8, 55.4, 46.3; total sleep time (TST, min), 411.5, 239.5, 195; REM latency (RL, min), 92, 243.5, 276; wake (W, %), 7, 8, 36.6; slow wave sleep (SWS, %), 34.4, 30, 22.2; REM sleep (S5, %), 20.4, 2.4, 6.7, respectively. The results of the second episode at W0, W4 and W8 were: SE (%), 93.7, 64.2, 54; TST (min), 504, 316, 230.5; RL (min), 73, 110.5, 166; S0 (%), 3.3, 30.2, 41; SWS (%), 25.2, 22.5, 14; S5 (%), 20.7, 10.9, 4, respectively. The results of the patient on nefazodone at W0, W2, W4, W6 and W8 were: SE (%), 65.4, 83, 87.2, 85.3, 93.4; TST (min), 322, 428.5, 467.5, 471, 437; RL (min), 167, 211.5, 67.5, 120.5, 78.5; S0 (%), 24, 13.8, 9.8, 22.5, 4.1; SWS (%), 22.6, 28.2, 29, 23.9, 15.6; S5, 16.4, 13.6, 14.4, 20.2, 27.7, respectively. The PSG profiles on nefazodone in the two episodes were quite similar. However, they were different from those on nefazodone. Fluoxetine seems to disturb the patient’s sleep while nefazodone had no sleep disturbing effect. This case vignette is relevant in that nefazodone is often thought of as sedating drug but was helpful in this case. A formal study is required.

Conclusions: The PSG profiles on fluoxetine in the two episodes were quite similar. However, they were different from those on nefazodone. Fluoxetine seems to disturb the patient’s sleep while nefazodone had no sleep disturbing effect. This case vignette is relevant in that nefazodone is often thought of as sedating drug but was helpful in this case. A formal study is required.

References:

Different Effects of Fluoxetine and Nefazodone on Polysomnographic Sleep of Seasonal Affective Disorder Patient - A Case Report
Shen J, Shapiro CM
Sleep Research Unit, Toronto Western Hospital, University Health Network, University of Toronto

Introduction: Seasonal affective disorder (SAD) is a form of major depression characterized by a regular occurrence of symptoms in fall or winter and full remission (or hypomania) in spring or summer. Clinical trials have found that response of SAD patients to fluoxetine were better than to placebo. Fluoxetine has a significant sleep disturbing effects in major depression. This has led researchers to try to find other antidepressants to treat SAD and to monitor their polysomnographic (PSG) effect. The purpose of this report is to highlight the different PSG effects of fluoxetine from those of nefazodone in a single SAD patient.

Methods: Ms. T is a 44-year-old nurse who was diagnosed with SAD in 1996. The diagnosis was based on the clinical assessment according to DSM-III-R criteria. The values of her SPAQ (Seasonal Patterns Assessment Questionnaire), HDRS-SAD (a 29-item Hamilton Depression Rating Scale for Seasonal Affective Disorder), BDI (Beck Depression Inventory, a 21-item self assessment questionnaire for depression) and CES-D (a 20-item questionnaire for self assessment of depression) were 12, 38, 33 and 47, respectively. These results indicate that she was suffering from a moderate to severe SAD. She started taking fluoxetine (20 mg daily) on November 11, 1996 and received 3 PSG assessments: before treatment (baseline, W0), by the end of week 4 (W4) and week 8 (W8). In October 1997 Ms. T repeated the same procedure on fluoxetine (20 mg daily) taking and PSG recording. Her depression was improved but her sleep disturbance was such that she was unable to continue on fluoxetine. She stopped taking fluoxetine and started taking nefazodone at doses of 100 mg, 200 mg, 300 mg and 400 mg in week 1, week 2, week 3 and weeks 4-8, respectively. PSG recordings were done at baseline (W0), by the end of weeks 2 (W2), 4 (W4), 6 (W6) and 8 (W8).

Results: The results of the first episode on fluoxetine at W0, W4 and W8 were: sleep efficiency (SE, %), 86.8, 55.4, 46.3; total sleep time (TST, min), 411.5, 239.5, 195; REM latency (RL, min), 92, 243.5, 276; wake (W, %), 7, 8, 36.6; slow wave sleep (SWS, %), 34.4, 30, 22.2; REM sleep (S5, %), 20.4, 2.4, 6.7, respectively. The results of the second episode at W0, W4 and W8 were: SE (%), 93.7, 64.2, 54; TST (min), 504, 316, 230.5; RL (min), 73, 110.5, 166; S0 (%), 3.3, 30.2, 41; SWS (%), 25.2, 22.5, 14; S5 (%), 20.7, 10.9, 4, respectively. The results of the patient on nefazodone at W0, W2, W4, W6 and W8 were: SE (%), 65.4, 83, 87.2, 85.3, 93.4; TST (min), 322, 428.5, 467.5, 471, 437; RL (min), 167, 211.5, 67.5, 120.5, 78.5; S0 (%), 24, 13.8, 9.8, 22.5, 4.1; SWS (%), 22.6, 28.2, 29, 23.9, 15.6; S5, 16.4, 13.6, 14.4, 20.2, 27.7, respectively.

Conclusions: The PSG profiles on fluoxetine in the two episodes were quite similar. However, they were different from those on nefazodone. Fluoxetine seems to disturb the patient’s sleep while nefazodone had no sleep disturbing effect. This case vignette is relevant in that nefazodone is often thought of as sedating drug but was helpful in this case. A formal study is required.

References:

692Q
REM Sleep EEG Beta Activity Correlates with Positive and Negative Symptoms in Drug-naive Patients with Schizophrenia
Poulin J,1,2,4 Stip E,1,2,3,4 Godbout R1,2,3,4
(1) Centre de recherche Fernand-Seguin, (2) Hospital Louis-H.-Lafontaine, (3) Departement de psychiatrie, (4) Universite de Montreal

Introduction: Previous studies have shown a relationship between sleep organization and clinical status in patients with schizophrenia, particularly with REM sleep. Recently, we have shown an increase in REM sleep EEG Beta activity in the bilateral prefrontal and right temporal cortical regions in drug-naive patients with schizophrenia (1), regions that are known to be involved in the pathophysiology of this disease. We verified whether REM sleep EEG Beta activity also correlates with clinical symptoms in drug-naive patients with schizophrenia.

Methods: Six acute patients never exposed to neuroleptics (4 M, 2 F, mean age = 35.0 ± 19.3) were individually recorded for two consecutive nights in the sleep laboratory during the first week of their hospitalization. According to DSM-IV criteria, the final diagnosis was confirmed within six months. At the time of recording, clinical symptoms were assessed by the Brief Psychiatric Rating Scale (BPRS) and three symp-
Results: REM sleep relative Beta power amplitude was positively correlated with negative symptoms on bilateral frontal cortical sites (Fp1, Fp2, F7 and F8) and negatively correlated with positive symptoms on bilateral frontal (Fp1, Fp2, F7 and F8) and right central and temporal cortical sites (C4, T4 and T6). There were no significant correlation with the global severity of symptoms factor (see Table 1).

Table 1

<table>
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<tr>
<th>Neg. Sx</th>
<th>Pos. Sx</th>
<th>Global Sx</th>
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<tr>
<td>Fp1</td>
<td>.83*</td>
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<tr>
<td>F7</td>
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</tr>
<tr>
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<td>-.15</td>
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<tr>
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</tr>
<tr>
<td>O2</td>
<td>.43</td>
<td>-.64</td>
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</tbody>
</table>

*: p < 0.05

Conclusions: The dissociation between positive and negative symptoms relative to REM sleep Beta EEG activity emphasizes the anatomical and functional dissociation between these two categories of symptoms in schizophrenia (2). The suggestion that EEG Beta activity reflect REM- on neuronal activity (3) together with the present results further substantiate the hypothesis of a possible link between over-active REM sleep neuronal substrates and symptoms of schizophrenia.

References:


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694.Q

Epworth Sleepiness Scale: Measuring Daytime Sleepiness in Depressed Patients

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Introduction: Epworth Sleepiness Scale (ESS) is a validated self-administered questionnaire, which is shown to provide a measurement of the subject’s general level of daytime sleepiness. Approximately 85-90% of patients with major depression have disturbed nocturnal sleep and 20% of these patients complain of excessive daytime sleepiness. The aim of this study was to assess subjective daytime sleepiness in non-medicated and treated with antidepressants patients with major depression.

Methods: One hundred patients, 55 females and 45 males, aged 45.1 ± 11.0 years, with an established diagnosis of major depression constituted the study sample. Patients were referred to the sleep clinic with the complaints of chronic insomnia. Whole sample of the participants had high scores on the CES-Depression Scale (27.8±8.4) All patients underwent two consecutive overnight polysomnographic studies. The polysomnograms were scored blind according to standard criteria. Patients who were found to have primary sleep disorders (sleep apnea, periodic limb movement disorder) were excluded from the study. Thirty six patients were taking antidepressants at the time of the sleep studies (Group I). Sixty four non-medicated depressed patients were assigned to Group II. Each group was divided into two sub-groups based on the gender (24 females and 12 males in Group I and 31 females and 33 males in Group II). Prior to the sleep studies patients completed the ESS and Stanford Sleepiness Scale (SSS). Statistical analysis was performed using SPSS and included two-tailed t-test.

Results: The mean global ESS score in Group I was 7.3±5.0 and in Group II it was 7.9±4.8. The difference between ESS scores in treated with antidepressants and non-medicated depressed patients was not significant (p>0.05). Males in Group I scored significantly higher than females (9.0±5.1 vs 6.2±4.8, p<.04). There were no significant differences between ESS scores in non-medicated depressed males and females (8.0±4.7 and 7.1±5.1, p>0.05). The mean global score on the SSS in Group I was 3.7±1.4 and in Group II it was 2.9±1.7 (p<.05). There were no significant differences between females’ and males’ SSS scores in Group I and Group II (3.7±1.5 and 3.7±1.2; 2.9±1.9 and 2.9±1.5, respectively, p>0.05).

Conclusions: Non-medicated and treated with antidepressants patients with major depression showed mild daytime sleepiness as judged by the ESS. Males on antidepressant therapy were sleepier than females. Antidepressant therapy did not change scores on the SSS.

References:


693.Q

Subjective Reports of Nighttime Sleep in Older Schizophrenia Patients and Normal Comparison Subjects: A 2-year Follow-up

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Introduction: Patients with schizophrenia often complain of disturbed sleep at night, and studies suggest the frequency of these complaints is higher than what is expected in normal adults. Few studies, however, have included older patients in these comparisons. The current study examined the differences between older patients with schizophrenia and normal comparison subjects (NCs) in reports of sleep. Data are presented on questionnaires conducted at 2-year intervals. We expected that patients would have more sleep complaints than controls, and that changes over a 2-year time period would be associated with changes in...
Methods: As part of a larger study on late-life psychosis, 41 schizophrenia patients (27 men, 14 women; mean age=60, sd=8.6, range=45-79 years) and 34 NCs from the same age range (15 men, 19 women; mean age=62, sd=8.4, range=45-79 years) completed questionnaires about sleep at visits to the UCSD Center for Psychosis in Older Adults. Data are reported for questionnaires completed at 2-year intervals. The Structured Clinical Interview for DSM-III-R (SCID) was administered to all participants. Information about sleep satisfaction and sleep schedule were analyzed using split-plot ANOVAs across diagnosis (SCZ vs. NCs), and from time 1 (initial interview) to time 2 (2-years later). For variables with significantly skewed distributions, normal scores transformations were used in analyses. For omnibus tests, α=.05. Bonferroni corrections were used in all follow up tests.

Results: Schizophrenia patients and NCs were not statistically different in gender distribution (p=.059) or age (p=.30). There was a significant time x diagnosis interaction for wake after sleep onset (WASO; F(1,66)=6.27, p=.015). There was a significant main effect for diagnosis at time 1 (t(69)=2.82, p=.006; SCZ>NCs), but not at time 2 (t(70)=0.264, p=.79). There were significant main effects in reported sleep satisfaction (F(1,73)=8.03, p=.006; SCZ<NCs), and in gender distribution (p=.059) or age (p=.30). There was a significant time x diagnosis interaction for wake after sleep onset (WASO; F(1,66)=6.27, p=.015). There was a significant simple main effect for diagnosis at time 1 (t(69)=2.82, p=.006; SCZ>NCs), but not at time 2 (t(70)=0.264, p=.79). There were no other significant main effects or interactions.

Conclusions: These results confirm other reports that patients with schizophrenia report poorer sleep quality than NCs. These differences appear fairly stable over time. We found a significant time x diagnosis interaction, which appears to be due to an improvement in the median WASO in the SCZ patients (15 minutes at time 1 to 5 minutes at 2-year follow-up). This change may be accounted for by the fact that 9 SCZ patients showed a reduction in WASO of 60 minutes or more over 2 years. These changes could not be accounted for by changes in medications (6/9 had no change over the 2 years) or changes in symptoms (mean BPRS score change = 0.5). This change may reflect increased variation over time in sleep in schizophrenia relative to NCs or to simple regression to the mean over time. Understanding what may improve subjective sleep quality in schizophrenia patients has important clinical and quality of life implications, and warrants further exploration.

Supported by: AG02711, AG08415, CA85264, MH45131, MH43693; VA VISN-22 MIRECC, Research Service of VASDHS

696.Q

Sleep Studies in Pregnancy and Postpartum Depression
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Introduction: Sleep disturbances characterize a major depressive episode (MDE) and may predict a therapeutic response to critically timed sleep deprivation or “wake therapy.” A majority of patients with a MDE, in distinct contrast to healthy control subjects, have a marked improvement in mood, often within 24 h, in response to critically timed sleep deprivation. Critically timed sleep deprivation may offer an alternative treatment, effective within one day, for women with pregnancy or postpartum depression who are not candidates for pharmacological or psychotherapeutic interventions. The aim of this study was to assess the efficacy of critically timed sleep deprivation in MDEs occurring during pregnancy or postpartum and to test the hypothesis that improvement in mood would be associated with improvement in sleep quality, as measured by polysomnography (PSG), during recovery vs. baseline nights of sleep.

Methods: Ten women who met DSM-IV criteria for a MDE with onset during pregnancy or within one year postpartum underwent a trial of either early-night sleep deprivation (ESD), in which they were sleep deprived in the early part of one night and slept from 03:00-07:00 hours (h), or late-night sleep deprivation (LSD), in which they were deprived of sleep in the latter part of one night and slept from 21:00-01:00 h. Mood and PSG were assessed before, during and after the night of sleep deprivation.

Results: More patients responded to LSD (9 of 11 trials: 82%) compared with ESD (2 of 6 trials: 33%) and they responded more after a night of recovery sleep (9 of 11 nights: 82%) than after a night of sleep deprivation (6 of 11 nights: 55%). Pregnant women were the only responders to ESD and the only nonresponders to LSD. Compared with baseline nights, during recovery nights of sleep in women undergoing LSD, measures of sleep quality improved: total sleep time, sleep efficiency, and delta sleep increased, whereas sleep latency and wake after sleep onset decreased. In contrast, after ESD, during recovery vs. baseline nights of sleep, there was an increase in wake after sleep onset, a shorter REM latency and a decrease in total sleep time, sleep efficiency, and delta sleep-sleep architecture changes that are more characteristic of depression.

Conclusions: Although the findings are preliminary, the results suggest that with further study, critically timed sleep deprivation interventions may benefit women with pregnancy or postpartum mood disorders and potentially provide a viable alternative treatment modality for those women who are not candidates for pharmacological or psychotherapeutic interventions. Such interventions are needed to help prevent the devastating effects of depression during pregnancy and the postpartum period on the mother, infant, her family and society. As Papousek (1975) hypothesizes, depression is associated with disturbed or desynchronized rhythms and sleep deprivation resynchronizes these rhythms. Although the mechanism by which sleep deprivation exerts its antidepressant effects is unknown, one possibility is that by altering internal phase relationships and restoring sleep quality, it thereby improves mood at least in some patients who may respond after recovery nights of sleep (day 2 responders).

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696.Q

Sleep Parameters in Identical Twins Discordant for Schizophrenia
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Introduction: Studies in twins and in inbred mice strains proved a strong genetic determination in particular on non-REM sleep parameters (Linkowski 1994, Franken 1999). A very recent investigation using quantitative EEG analysis showed a reduced amplitude of the slow wave activity in patients with schizophrenia (Hoffmann et al., 2000). In order to further clarify the influence of the disease or neuroleptic medication we recorded the sleep EEG in monogygotic twins discordant for schizophrenia (n=5). All subjects underwent laboratory, physical and psychiatric examination as well as wake EEG and ECG before the first night in the sleep laboratory.

Methods: Polysomnographic recordings were visually analyzed according to standard criteria. In addition, we submitted the digitized EEG data to a serial spectral analysis (EEG power spectrum from 0.39 - 19.1 Hz; frequency resolution 0.39 Hz). The EEG power spectra were cumulated across the delta (0.8-4.3 Hz), theta (4.3-7.8 Hz), alpha (7.8-11.7 Hz),

SLEEP, Vol. 24, Abstract Supplement 2001
Effects of Aerobic Exercise on Cognition and Sleep in Alzheimer's Disease

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(1) Department of Neurology, Northwestern University, (2) Cognitive Neurology and Alzheimer's Disease Center, Northwestern University, (3) Rehabilitation Institute of Chicago, Northwestern University

Introduction: It is known that exercise has a beneficial effect on cognition and sleep in the normal elderly. However, less is known about the effects of exercise on sleep and cognition in patients with Alzheimer’s Disease (AD). This study was conducted in order to test the hypothesis that aerobic exercise will attenuate cognitive decline, increase physical functioning capabilities, and improve sleep quality in AD patients.

Methods: Nine subjects with probable or possible AD according to the NINCDS-ADRDA (5M, 4F; 77 ± 7.5 years) and five age-matched normal controls (3F, 2M; 72.2 ± 6.4 years) were recruited from the Alzheimer’s Disease Center at Northwestern University. All AD subjects scored at least 19 on the Mini-Mental State Examination. Subjects were divided into three groups: (1) an aerobic exercise group with probable or possible AD, (2) an aerobic exercise group of elderly subjects with normal cognition, and (3) a non-exercise group with possible or probable AD. Informed consent for participation was obtained from participants and caregivers, and for the exercise groups, their primary care physician. Exercise consisted of two 30-minute exercise sessions per week for 8 weeks. The exercises included walking on a track or treadmill and cycling on a stationary bicycle. Participants rated their exertion on the Borg Perceived Exertion Scale. Heart rate was recorded before, during, and after each exercise session, with a target heart rate of 55-75 percent of the estimated maximal heart rate (220-age). Cognitive and neuropsychological performance tests were administered at baseline, and at the end of 4 weeks and 8 weeks of exercise. Certain selected tests were also administered immediately after the second exercise session. Written neuropsychological performance tests included semantic fluency, letter fluency, the digit symbol test, and logical memory, delay, recall, and recognition. Computerized performance tests included d2, naming, stroop, sternberg, and figure memory and delay tests. Activity and sleep were measured throughout the study by actigraphy, physical activity logs, and daily sleep logs.

Results: The normal exercise group performed significantly better in all of the neuropsychological performance tests than the AD exercise group (p<0.01). Analysis of the results shows improvement at 8 weeks on the stroop and digit symbol test that did not reach statistical significance with the current sample. Activity and sleep data are currently being analyzed.

Conclusions: Our results clearly demonstrate the high genetic influence on the spectral profiles of both non-REM and REM sleep in humans. In contrast, the effects of a current neuroleptic medication or psychiatric symptoms on the quantitative sleep EEG parameters appeared to be comparably weak.

References:
Conclusions: These preliminary results indicate that aerobic exercise may lead to an improvement in neuropsychological performance in patients with AD. Previous studies have shown cognitive decline in patients with AD over the same time interval. Thus, we expect performance might also decline in the AD non-exercise group in the present study. Comparison of the exercise and non-exercise AD groups will help us determine whether exercise may be helpful for attenuating the cognitive decline that naturally occurs in AD.

Research supported by R01 AG11412

Electroencephalographic Sleep Profiles in Response to Tryptophan Depletion after Cognitive Behavioral Therapy for Depression

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Introduction: Depression has been associated with a cluster of sleep abnormalities, including reduced latency to rapid eye movement (REM) sleep, increased REM sleep duration, and REM density. The role of serotonin in these sleep abnormalities has not been explicaded; however, research has found that selective serotonin reuptake inhibitors (SSRIs) suppress these REM sleep measures in depressed and non-depressed subjects. One paradigm particularly useful for studying the role of serotonin is the rapid tryptophan depletion (RTD) challenge; this methodology operates by reducing the free and total plasma levels of tryptophan, the biosynthetic precursor of serotonin. Preliminary work has suggested that RTPD produces “depressed” sleep in medicated remitted subjects and normal controls, even without a change in depressive symptoms. To date, the findings have been mixed with regard to impact of empirically-supported psychotherapy treatments, such as cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT), on traditionally scored electroencephalographic (EEG) sleep measures. Few studies have examined the biological substrates of depression in people partially remitted from depression with cognitive behavior therapy (CBT), and none of which we are aware has used a tryptophan depletion challenge. This study examines the hypothesis that a tryptophan-free amino acid drink will produce temporary disturbances in EEG sleep profile in ten unmedicated, partially remitted patients who have been treated for depression with group CBT for approximately 8 weeks.

Methods: Ten subjects enrolled in group CBT participated in the RTD challenge as soon as they achieved partial recovery or better from depression (defined by a Hamilton Depression Rating Scale, HDRS, score of <10 or >50% reduction). Each subject then participated in two, randomly-ordered challenges (one experimental, one control) conducted score of <10 or >50% reduction). Each subject then participated in two, randomly-ordered challenges (one experimental, one control) conducted

Results: Consistent with the hypothesis, comparisons to a sham drink indicated statistically significant trends (p <.10) for the RTD to reduce REM latency and increase REM density; however, no depressive relapse was evident in either condition. Interestingly, there was a trend indicating better sleep quality (i.e. sleep efficiency and wakenings after sleep onset) in the RTD than in the sham condition.

Conclusions: These findings tentatively suggest that the efficacy of CBT may depend on a subtle change in biologic systems that may operate via different mechanisms than pharmacotherapy.
breathing complaints in these firestorm survivors ought not to preclude a work-up for SDB—a disorder which we predict will ultimately prove to be a premorbid risk factor for chronic PTSD in some traumatized individuals.

References:

Research support NIMH 63477 (Rapid Mechanism)

700.R

Oscillations in Peripheral Arterial Tone in CHF Patients: A New Marker for Cheyne-Stokes Breathing

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Introduction: Cheyne-Stokes breathing (CSB) is a form of periodic breathing typically seen in patients with advanced heart failure during sleep saturation which was reported to be related to poor prognosis. Its' typical pattern is that of central apneas or hypopneas alternating with hyperpneas, having a crescendo-decrescendo pattern. CSB is detected by monitoring breathing effort, oral-nasal airflow and arterial oxygen saturation. Using a newly developed finger plethysmographic technology, we showed that peripheral arterial tone (PAT) is a sensitive marker of breathing disorders in sleep. Here, we demonstrate that the PAT is a sensitive indicator of CSB in patients with advanced heart failure as well.

Methods: We studied 20 congestive heart failure patients (6 men, age: 58.6±15.1; weight: 77.9±19.5, height: 170.3±8.5, New York Heart Association score stage 3-4 and mean ejection fraction 22.8±6.3%). Sleep recordings: Patients were studied in the Technion Sleep Disorders Center with conventional polysomnographic and PAT recordings. The PAT device was described in detail elsewhere (1). A single finger probe was used from one hand. Each sleep record was divided into 3-min epochs and was scored twice for CSB. First, based only on the effort and airflow respiratory signals, and second, based only on the PAT signal after removing all polysomnographic channels. In both conditions, the scorer assigned a score of 1 if CSB was visually identified in at least 2 of the 3-min epochs, and 0 if not. The total number of 3 min epochs that were True Positives, True Negatives, False Positives and False negatives were assigned a score of 1 if CSB was visually identified in at least 2 of the 3-min epochs, and 0 if not. The total number of 3 min epochs that were True Positives, True Negatives, False Positives and False negatives were determined for the entire record, as well as to segments defined as NON-REM and REM sleep and wake. Segments contaminated by technical or body movement artifacts were removed before the analysis.

Results: A total of 3156 three-min epochs were available for analysis. Whenever CSB appeared, it was accompanied by clearly visible oscillations in PAT amplitude during both sleep and wake periods. Overall, the sensitivity and specificity of the PAT to detect CSB were 91% and 86%, which were similar to those obtained for NONREM sleep, 90% and 87%. A relatively lower sensitivity (74%) with very high specificity (97%) was found for Wake periods, and a relatively lower specificity (71%) and high sensitivity (94%) for REM sleep.

Conclusions: Our present results show that the PAT signal is a sensitive and specific marker of CSB. In view of the recognition of the prognostic value of CSB in CHF patients and its amendment by effective treatment, screening CHF patients for periodic breathing may become a routine clinical practice. The accessibility of the fingers, and the benign and non-intrusive nature of the PAT, make it a convenient tool for screening and monitoring CSB.

References:

701.R

Evaluating Light Recordings at the Wrist-Level: A Prerequisite Study for Future Shuttle-Based Investigations

Brown EL, Jewett ME, Barger LK
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Introduction: We have developed a mathematical model of the effects of light on the human circadian pacemaker that, given an individual’s eye-level light exposure (measured using an IL-1400 meter) as an input, can accurately predict changes in that person’s circadian phase and amplitude. This model has great potential for the prescription of appropriate, non-pharmaceutical countermeasures (e.g. light exposure) to the circadian misalignment and associated impairments in sleep quality and waking performance that frequently occur in space. However, before this model can be employed, light recordings from the Actiwatch-L device to be worn by individual astronauts in future space missions must be transformed into appropriate input values to the light model. Therefore, we have completed a study comparing the light values recorded by the Actiwatch-L with those recorded by the IL-1400 meter across a wide range of light levels. This has allowed us to distinguish and omit from study improperly-calibrated Actiwatch-Ls, as well as to develop an adjustment function to equate Actiwatch-L readings to those of the IL-1400. Our findings from this study, along with another ongoing study comparing light levels at the wrist to light levels at the eye, will allow us to directly input light values recorded on the wrist-worn Actiwatch-L into our light model to predict an individual astronaut’s circadian phase and amplitude and to suggest appropriate countermeasures to any predicted circadian misalignment.

Methods: Six AW-Ls and three IL-1400 light meters were tested at nine light levels ranging from very dim (~ 1 lux) to very bright (~10,000 lux). A template was constructed with specifically labeled positions for the AW-Ls and IL-1400s. We first recorded the light intensity at each of the different positions on the template with each of the IL-1400 meters to insure that there were no differences in the lighting intensity across the different positions. The AW-Ls were then uncovered for a period of ten minutes for light exposure recording. To ensure that the lighting intensity in the room did not fluctuate during the testing session, readings were taken from the three IL-1400 light meters at the beginning, middle and at the end of the ten-minute period. This procedure was repeated at nine different light levels, ranging from 5 lux to 10,000 lux. A series of one-way analysis of variance (ANOVA) procedures were used to determine if there were any differences in light intensity between positions on the template, between IL-1400 readings, and/or between AW-L readings.

Results: Our statistical analysis demonstrated that no significant differences existed between light meter readings taken at the different positions on our template. Likewise, we found no significant differences between the readings of the three IL-1400 light meters at any of the light levels. However, significant differences were found between the six AW-Ls at many light levels (Figure 1). AW-L3 was a clear outlier at low light levels.
levels (Figure 1, panels a–c) while AW-L 10 was a clear outlier at higher light levels (Figure 1, panels c–e,g). Across all light levels, there was a significant difference between the AW-L and the target readings measured by the IL-1400s with the AW-Ls consistently recording values that were lower than the target values (p < 0.05). When plotted on a log-log scale, there was a significant linear relationship (p < 0.0001) between the AW-L readings and the target IL-1400 values, so a linear regression was fit to the data (Figure 4, solid blue line, R² = 0.997). The slope ± s.d. of this line was 0.99 ± 0.0085, and the intercept ± s.d. was 0.35 ± 0.2. Thus, a function was formulated to adjust the AW-L readings so that they were approximately equivalent to those of the IL-1400s. When this function was applied to the AW-L data, the adjusted AW-L readings (adjAW-L, Figure 2, red circles) fell along the line of identity (Figure 2, dashed black line) that marks when the adjAW-L recordings are equivalent to the target light levels recorded by the IL-1400 meters. Thus, this function is able to accurately adjust AW-L readings so that they are approximately equivalent to IL-1400 readings across a wide range of light levels.

Conclusions: The data obtained from this study (Study A) demonstrate that even after manufacturer calibration, some AW-Ls do not give readings consistent with other AW-Ls at all light levels (Figure 1). The protocol developed for Study A appears to be a valid procedure for evaluating the AW-L, and we recommend that all AW-Ls be utilized in the upcoming space missions should be subjected to this protocol. However, considering the small population of AW-Ls examined in this pilot study, we suggest that this study be repeated in a larger population of manufacture-calibrated AW-Ls. We have also developed an adjustment function that is able to accurately transform AW-L readings so that they are approximately equivalent to IL-1400 readings across a wide range of light levels. Once this function has been validated using another data set, it will allow AW-L data to be input into the light model rather than being limited to data from an IL-1400. The final result of Study A is that we have established two stable populations of AW-Ls and IL-1400s from which a function relating IL-1400 and Actiwatch-L readings was derived. Additionally, these validated AW-Ls and IL-1400s were deemed acceptable to be used in the next prerequisite study, in which the relationship between wrist recordings and eye-level recordings will be examined.

702.R Validation of the SleepStrip™ in Three Independent Studies

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Introduction: The SleepStrip™ is a disposable apnea/hypopnea-screening device designed for home use (1). This single-unit device monitors breathing using oral and nasal thermistors and real time analysis hardware and software. Following a night of at least 5 hours of recording, a score is displayed, which represents the number of respiratory events per hour of recording. To evaluate the reliability of the SleepStrip™ score (Score) against the Respiratory Disturbance Index (RDI) obtained by traditional polysomnographic (PSG) recordings, three validation studies were conducted independently in Belgium, Germany, and Israel.

Methods: Four hundred and two patients (303 from Israel, 50 from Belgium and 49 from Germany) suspected of sleep apnea underwent full overnight PSG monitoring concomitantly with the use of the SleepStrip™. Age ranged between 18-86, BMI ranged between 18-59. Results from 372 patients were available for analysis (289 from Israel, 39 from Belgium and 44 from Germany). Pearson correlations were computed between PSG determined RDI and Sscores obtained by the SleepStrip™. Sensitivity and specificity values of the Sscores were assessed against “gold standard” RDI using three thresholds (RDI/Sscore > 10, >20, >40).

Results: Table 1 shows that significant correlations (corr) were found for each population (Ger = Germany, Bel = Belgium, Isr = Israel) and for all populations combined (r = 0.64-0.86, p < 0.001). Sensitivity (sens) and specificity (spec) values ranged between 0.85-0.88 and 0.48-0.91 respectively for a threshold >10; 0.70-0.85 and 0.58-0.86 respectively for a threshold > 20; and 0.75-0.88 and 0.81-0.94 respectively for a threshold > 40.

Table 1

<table>
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<tr>
<th></th>
<th>Ger  n=44</th>
<th>Bel n=39</th>
<th>Isr n=289</th>
<th>All n=372</th>
</tr>
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<td>Corr(p&lt;0.001)</td>
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<td>0.81</td>
<td>0.64</td>
<td>0.68</td>
</tr>
<tr>
<td>&gt;10 sens/spec</td>
<td>0.85/91</td>
<td>0.86/97</td>
<td>0.88/78</td>
<td>0.85/72</td>
</tr>
<tr>
<td>&gt;20 sens/spec</td>
<td>0.78/86</td>
<td>0.85/84</td>
<td>0.82/58</td>
<td>0.80/62</td>
</tr>
<tr>
<td>&gt;40 sens/spec</td>
<td>0.88/94</td>
<td>0.75/81</td>
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<td>0.77/82</td>
</tr>
</tbody>
</table>

Conclusions: The SleepStrip™ is a reliable tool for the initial assessment of sleep apnea in high-risk populations. The Score is strongly correlated with traditional RDI. For the detection of apnea from the mild to the severe range, sensitivity values remain high albeit a slight decline, while specificity values increase substantially with apnea severity.

References:

703.R The BiteStrip: A Novel Screener for Sleep Bruxism

Hadas N, Shochat T, Molotsky A, Lavie P
Scientific Laboratory Products, Ltd., Tel Aviv, Israel

Introduction: Sleep Bruxism is characterized by the involuntary grinding and clenching of teeth during sleep. Symptoms include tooth wear, temporomandibular joint (TMJ) dysfunction, chewing difficulties, headaches and daytime sleepiness. Based on a large survey, the prevalence of bruxism in the adult population is estimated at 8% (1), however, as many individuals may be unaware of this condition, the prevalence is most likely to be higher. Bruxism is diagnosed based on clinical examination of the teeth, complaints of jaw and masticatory pain, and reports by the bed partner of the grinding noise. Patients suspected of bruxism are not routinely referred to the sleep laboratory. Thus, clinical and experimental data is scarce, and there is no widely accepted “gold standard” for a definitive, objective diagnosis. We present a novel home monitoring device for the detection of bruxism.

Methods: The BiteStrip is a miniature single-use electronic device designed as a front line screener for bruxism (figure 1). It is comprised of three EMG electrodes and an amplifier to acquire masticatory muscle signals, a CPU with real time software, which detects and analyses EMG patterns, a permanent chemical display which presents the outcome in the morning, a light emitting diode (LED) and a lithium battery. All elements are integrated on a single flexible substrate. At bedtime, patients are instructed to attach the device to the cheek over the mandible, to activate it and to perform a series of maximal strength clenching and grinding activities, in order to establish an individual threshold for the nighttime monitoring. The device must be worn for at least 3 hours of sleep. In the morning, patients deactivate the device, and wait for approxi-
mately 20 minutes for the bruxism index (number of bruxing events per hour of recording) to be displayed. We present the preliminary testing of the device with comparison to masticatory muscle EMG recorded concomitantly on either cheek in the sleep laboratory.

Results: Figure 2 displays a segment of the recordings. Output of the BiteStrip is displayed above the masticatory muscle EMG. Note that the BiteStrip detects only those EMG bursts, which exceed the individually predetermined threshold.

Figure 1

![LED, CPU, Battery, Display, Flexible Film]

Figure 2

BiteStrip output

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
</table>

Conclusions: The BiteStrip is a viable, promising device for the detection of bruxism. Further testing and validation on a large population of bruxers is underway.

References:

704.R

A Prototype of a Sensorized and Electrically Actuated Bed for Snoring and Sleep Apnea Relief

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Introduction: The main goal of this project was to design a sensorized and electrically actuated bed for eliminating or, at least, reducing the problem of snoring and Sleep Apnea.

Methods: As it is commonly known and it has been described in many articles, the supine sleeping position during sleep facilitates the coming up of this disorder. Usually the negative effects of this most undesirable problem improve once the person changes position and turns to his/her side. Many anti-snoring devices are commercially available. Most of them make the sleeping person avoiding the supine position by holding a cumbersome object on the sleepers back and they are therefore quite uncomfortable. This new device is able to detect the laying position on the mattress and also whether he/she is lying on the side or back or front. The sound produced by the person is acquired and analyzed by a computer program able to recognize snoring. The frame is longitudinally divided, so in case of snoring or Sleep Apnea, the computer orders the actuators to incline quietly and slowly the parts where he/she is lying on, in order to stimulate him/her - during sleep – to turn to the side. This “invitation” to turn happens gently enough to avoid the weakening up of the sleeper or at least is so smooth to allow him/her to fall again asleep soon. In order to design this robot-bed, first some indicative data have been collected by constructing a bed-frame divided in 2 parts, one of which could be inclined. Some test subjects have been asked to lie on the mattress, to lift a part and to give information about the preferred configuration that they thought would make them turn on their side during sleep. After these data have been analyzed, a frame divided in 4 parts and electrically actuated has been designed and constructed. Once the sensorized sheet has been put on the mattress and connected to the control system that drives the motors, the bed was ready for some preliminary tests concerning snoring.

Results: The results were quite encouraging. During these sleep tests on the actuated bed, the unpleasant sound was significantly reduced though the movement of the lifting parts did not decrease the subjective quality of sleep. Moreover, with increasing number of nights spent, the need for the lifting mechanism seemed to decrease, so that a “on the side sleep” training effect could be supposed.

Conclusions: In future, more accurate tests will have to be performed, in order to improve the device and to study the medical backgrounds of snoring reduction and also the positive effects on Sleep Apnea.

705.R

Repeatability of Pupil Outcome Measures

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Introduction: Data about the repeatability of infrared video pupillometry outcomes are limited(1) even though clinical measurement of pupil diameter over time has potential as a measure of an individual’s state of alertness. Pupil size in darkness is estimated to be highly reproducible while size and dynamic responses can vary considerably with environmental light and the intensity of light stimuli(2). The purpose of this study was to determine if pupil diameter and oscillation pattern of individuals with consistent weekday sleep-wake-activity patterns were repeatable across 5 consecutive days of recordings.

Methods: Normal subjects (9F, 3M, mean age = 28.75±8.1) without any complaints or clinical evidence of a sleep disorder participated in the Alertness Level Test (ALT). Testing was conducted between 8:30 AM and 12:30 PM with the Mayo pupillometer across five weekdays (M-F) at the same time of day for each subject. Subjects slept their usual number of hours (average = 5 - 7.75) each weekday night, denied taking any medications that could affect pupil behavior or alertness, maintained their usual caffeine intake of 0-2 cups of coffee upon awakening, and maintained their usual daytime activity pattern between testing periods. During the ALT (1 minute of pupil diameter recording in light, 14 minutes in a quiet, dark room) subjects are seated comfortably with instructions to try to stay awake while not doing anything special to do so, and to try to minimize blinking while staring straight at a red spot of light. Pupil diameters are extracted from the video signal of infrared video cameras, digitized and downloaded to a microprocessor that calculates the horizontal diameter for each eye at a rate of 64 Hz. Data are cleaned off line of eye blink and closure artifact, and then down sampled to 8 Hz before further processing.
Results: Quantitative analyses for the 3.6-11.6 minute period of the ALT for each day were conducted. A repeated measures ANOVA revealed no significant differences in mean pupil diameter between days for the fifth minute of recording, the period when a stable diameter (dark adaptation) has been achieved [F (4) = 1.07, p .383]. The pupillary unrest index (PUI), a measure of spontaneous pupil oscillation with higher values indicating greater levels of sleepiness, was calculated for each individual’s pupil diameter data for each day. A repeated measures ANOVA for the PUI between days was nonsignificant [F (4) = 1.95, p .119].

Conclusions: Individuals who maintain a stable weekday wake-activity-sleep pattern demonstrate a consistent pupil diameter and pattern of oscillation that is repeatable between days when data are collected in a quiet dark environment over a 15 minute test period.

References:

Research supported by Mr. J. A. Piscopo.

706.R

Scoring Maintenance of Wakefulness Test with Adaptive Epoch Length

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Introduction: The most common tests for Excessive Daytime Sleepiness (EDS) are Epworth Sleepiness Scale (ESS), Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT). MWT is assumed to measure wake tendency, the ability to stay awake under soporific circumstances (1) and thus it is often applied in traffic safety studies. Recent Visual Adaptive Scoring System (VASS) describes microstructure in sleep and in sleep onset. In VASS epoch durations are adaptive and more stage categories are used compared to standard scoring system (2). In this preliminary report we used Adaptive Epoch Length (AEL) and traditional sleep categories in scoring MWT.

Methods: We analyzed 29 MWT recordings from 29 subjects using Rechtschaffen and Kales’ (RK) (1) and Adaptive Epoch Length (AEL) scoring. The sleep categories scored in AEL were wake (S0), movement artefact (MT), slow eye movements (SEM) and S1. For this report MT and SEM were treated as S0. Duration of the shortest epoch was two seconds for AEL and 30 seconds for RK. For both RK and AEL analysis the data was treated in the way that various latencies, cumulative latencies and Sleep Onset Moment (SOM) could be calculated even if no sleep existed within the first 40 minutes. We defined SOM as sleep latency with weight given to the relative position of S1 epochs.

Results: Sixteen subjects had normal ability to maintain wakefulness with S1 (RK) sleep latency being longer than 12.9 min (1). Thirteen subjects had impaired ability to maintain wakefulness with S1 (RK) sleep latency being shorter than 12.9 min (1). We compared AEL parameters between these groups, Table 1 and Table 2. For these groups SOM was 38.1±7.7 min versus 8.2±2.5 min with RK and 35.7±8.1 min versus 7.4±2.2 min with AEL. To test the sensitivity of AEL parameters we recalculated Lat10 (10 seconds of continuous sleep) for both RK and AEL for the first 5 minutes of MWT. Specificity of Lat10<5 min criteria was 100% for both RK and AEL and sensitivity was 38 % for RK and 62% for AEL.

Table 1: Mean AEL latencies (±SD min) for 3, 10, 15 and 20 seconds of continuous sleep.

<table>
<thead>
<tr>
<th>Lat3</th>
<th>Lat10</th>
<th>Lat15</th>
<th>Lat20</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1(RK)&lt;12.9 min, n=16</td>
<td>22.4±14.9</td>
<td>31.9±10.5</td>
<td>35.2±9.3</td>
</tr>
<tr>
<td>S1(RK)&gt;12.9 min, n=13</td>
<td>3.1±1.8</td>
<td>3.6±2.0</td>
<td>5.3±3.1</td>
</tr>
</tbody>
</table>

Table 2: Mean AEL latencies (±SD min) for 5, 10, 15 and 20 seconds of cumulative sleep.

<table>
<thead>
<tr>
<th>Cum5</th>
<th>Cum10</th>
<th>Cum15</th>
<th>Cum20</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1(RK)&lt;12.9 min, n=16</td>
<td>24.6±13.9</td>
<td>28.7±13.2</td>
<td>30.5±12.5</td>
</tr>
<tr>
<td>S1(RK)&gt;12.9 min, n=13</td>
<td>3.2±1.9</td>
<td>3.5±1.8</td>
<td>4.1±1.9</td>
</tr>
</tbody>
</table>

Conclusions: The use of Adaptive Epoch Length (AEL) can increase the sensitivity of MWT with short test duration. Similar results have been obtained for MSLT with 5-second microsleep scoring (3). The new latency parameter, Sleep Onset Moment (SOM), has to be evaluated further.

References:

707.R

Collective Modes in Whole-Head MEG Sleep Signals

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Introduction: NA

Methods: We analyzed 61-channel, whole-head MEG recordings during sleep(1). A limited dataset was obtained from three subjects, only one of whom (Subject A) sustained the deep slow-wave phase. The others, Subjects B and C, slept lightly. None reached REM. The records for each subject were separated into segments of 5.12 sec which were subsequently grouped according to sleep phase, ranging from waking-drowsiness to deep slow-wave sleep. These groups were then subjected to spectral decomposition and collective modes sought. A collective mode is defined as a narrow frequency range at which all or nearly all detectors does not necessarily imply that the corresponding oscillation appear simultaneously in all channels but merely that it is important in all channels during the epochs analyzed.

Results: By far the most prevalent collective mode appeared in the two lowest frequency bins, at 0.49 and 0.98 Hz, respectively. This mode was extremely strong in all subjects and for all phases of true sleep. In fact,
we found it even for waking-drowsiness, although low-frequency artifacts were somewhat competitive at this phase. As sleep progressed, power in the two lowest bins grew rapidly, until, in the deepest slow-wave phase, these frequencies totally dominated the spectrum. In addition to the low-frequency mode just discussed, two other, less comprehensive, collective modes were also discerned: 1) in Subject A, a “spindle” mode near 13 Hz, present during light and deepening sleep but virtually disappearing in the deep slow-wave phase; and 2) in Subject C, a mode near 10 Hz, powerful in waking-drowsiness, then receding substantially as true sleep was established.

Conclusions: The ubiquitous low-frequency collective mode, also discerned in the records of the only previous whole-head MEG sleep study(2), probably corresponds to the “slow oscillation” first described by Steriade, et al.(3). If, as suspected by many authors, shared oscillation corresponds to the strengthening of certain selected neuronal connections, then the presence of a given mode in detectors all over the head hints that the same frequency is involved in the establishment of many different pathways of neural connectivity. On the other hand, while the low-frequency mode was important in all our subjects, additional modes appeared in some subjects but not in others. This brings up the question of how functions which might be associated with given oscillations are performed in subjects whose sleep records lack the corresponding modes. Clearly, much more work needs to be done before the functionality of the collective modes can be deduced and inter-subject differences elucidated.

References:

708.R

Sleep/Wake Detection Using an Active Security Device

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Introduction: Polysomnography (PSG) is considered as a gold standard in sleep research, but it is not applicable in long-term and large-scale studies. Wrist actigraphy is a widely applied, low cost, unobtrusive but less accurate alternative to PSG in sleep/wake analysis. In this study, a preliminary validation of a new approach for sleep/wake identification was made using an active security device (ASD) designed originally for health monitoring. The device continually sends information to a base unit by using radio transmission and automatically signals for help, if anything out of the ordinary occurs. The device, carried on a person’s wrist, provides an activity signal, which is constructed using a method that combines pulse, skin conductivity, temperature and movement measurements. The detection of sleep/wake states is only a by-product for the system.

Methods: Ten subjects (9 females and 1 male with mean age=60 years) were studied. Data were collected simultaneously over one night using WristCare (International Security Technology Oy), ActiWatch (Cambridge Neurotechnology, AW4) and PSG. The PSG was scored using the standard Rechtschaffen and Kales (R&K) criteria. Sleep/wake detection for ASD and actigraphy signals was made using a simple thresholding technique and then applying post-processing [1]. In post-processing, the periods shorter than 3 minutes scored as wake were rescored as sleep. Agreement percents in epoch-by-epoch basis (60 s epochs) were computed between ASD and PSG as well as between actigraphy and PSG. The optimization of the threshold was based on the agreement percents. In addition, the method based on discriminant analysis was applied for comparison [2].

Results: The ASD, actigraphy and PSG signals from one subject are visualized in Fig. 1. The agreement percents for all subjects were 79% and 78% for ASD and actigraphy data, respectively, when the thresholding technique without post-processing was used. As post-processing was applied, the corresponding values increased to 85% and 85%. The lowest value of 54% for ASD appeared for the subject who stayed long time awake in the bed without movements. The optimal thresholds found were 0.95 (ASD) and 13 (actigraphy). For comparison, the agreement values were 77% for ASD and 77% for actigraphy data using the discriminant analysis without post-processing. If the total sleep times are compared using the algorithm in [1] with optimization based on the absolute difference in the total sleep time, the mean absolute differences were 33 and 52 minutes for ASD and actigraphy data, respectively.

Conclusions: The active security device tested provided equal agreement rates compared to the results produced by actigraphy. However, a larger set of subjects is needed before any final statements about the use of the low cost ASD in sleep studies can be given.

References:

Research supported by the National Technology Agency, Finland.
Divided Attention Steering Simulator (DASS) in Subjects Without Sleep Disorders: A Pilot Study

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Introduction: The Divided Attention Steering Simulator (DASS) is one type of driving simulator that has been used in assessing functional deficits in sleep disorders but the data on subjects without sleep disorders (especially women) and its test-retest reliability is minimal. The aims of this pilot study are: 1) to investigate the performance of a group of subjects without sleep disorders; 2) to assess the effect of repeated measurement; 3) to determine whether the sequence of testing sessions (either am/pm or pm/am) and sex of subject affected performance.

Methods: Ten drivers, without a history or symptoms of sleep disorders, and an Epworth Sleepiness Scale (ESS) score <10 (median score of 4.5, range 1 to 9) completed the DASS on two separate occasions (one morning and one afternoon session). Five participants were male and 5 female with a median age of 53 yrs (43 to 61) and 56 years (46 to 64) respectively. The DASS is described in detail elsewhere (Juniper et al., 2000; Hack et al., 2000) and takes 30 minutes to complete. The version chosen here displays the road in its entirety. The primary outcome measures were: standard deviation (SD) of steering position, number of off-road events per hour, length of drive before “crashing” (off the road for 15 seconds or more), and the average reaction time (RT) to peripheral targets.

Results: Wilcoxon Signed Ranks tests were used to compare the participants’ performance on the simulator at test and retest (see Table 1). The Mann-Whitney test found no significant difference between sexes on any of the measures investigated on either visit (see Table 2). An analysis of performance on visit 2 and visit 1 revealed that the afternoon session lead to slightly better reaction times regardless of whether the subject started with an afternoon session or not ($\chi^2 = 3.987, df = 1, p = 0.046$).

Table 1

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Median Visit 1 (Range)</th>
<th>Median Visit 2 (Range)</th>
<th>$p$ value</th>
<th>Median for controls in Juniper et al.</th>
<th>Median for patients with OSA in Juniper et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD of steering position</td>
<td>0.26 (0.13 to 0.95)</td>
<td>0.23 (0.11 to 0.98)</td>
<td>0.44</td>
<td>0.11 (0.09 to 0.25)</td>
<td>0.23 (0.12 to 0.9)</td>
</tr>
<tr>
<td>Off-road events (no./h)</td>
<td>8.0 (0 to 134)</td>
<td>3.0 (0 to 96)</td>
<td>0.024</td>
<td>0.0 (0.0 to 3.6)</td>
<td>5.2 (0.0 to 118)</td>
</tr>
<tr>
<td>Length of drive (min)</td>
<td>30.0 (30 to 30)</td>
<td>28.9 (19.9 to 30)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average RT (s)</td>
<td>2.07 (1.61 to 3.69)</td>
<td>1.96 (1.43 to 3.14)</td>
<td>0.092</td>
<td>1.8 (1.3 to 2.4)</td>
<td>2.6 (1.4 to 4.9)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>U value Visit 1 (N1=5; N2=5)</th>
<th>$p$ value Visit 1</th>
<th>U value Visit 2 (N1=5; N2=5)</th>
<th>$p$ value Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD of steering position</td>
<td>10.0</td>
<td>0.602</td>
<td>10.0</td>
<td>0.602</td>
</tr>
<tr>
<td>Off-road events (no./h)</td>
<td>5.0</td>
<td>0.113</td>
<td>6.5</td>
<td>0.196</td>
</tr>
<tr>
<td>Length of drive (min)</td>
<td>12.5</td>
<td>1.000</td>
<td>10.0</td>
<td>0.317</td>
</tr>
<tr>
<td>Average RT (s)</td>
<td>11.0</td>
<td>0.753</td>
<td>10.0</td>
<td>0.602</td>
</tr>
</tbody>
</table>

Conclusions: Performance on the DASS is largely reproducible at retest, with no significant difference between visits in the SD of position on road, average RT, or length of drive. However, the number of off-road events is significantly lower at retest. Our subjects performed worse than the healthy subjects described in Juniper et al. (2000) on all measures and, surprisingly, at visit 1 worse than untreated patients with Obstructive Sleep Apnoea (OSA) on the SD of the steering position and number of off-road events. Further data are required but our findings bring into question the use of this test as a measure of the impact of sleep disorders.

References:

Signal-Validation Pilot Study of the KickStrip: A Novel Screener for Periodic Limb Movements in Sleep (PLMS)

Shochat T, Molotsky A, Hadas N, Lavie P
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Introduction: The KickStrip is a novel periodic limb movement (PLM) screener developed by SLP Ltd., Israel. It is a disposable, noninvasive device designed for the initial screening of patients suspected by their physician or sleep specialist to have PLMS. The screener is a miniature electronic device comprised of a strain gauge flex sensor, a CPU with real time software, and a chemical display that presents a score in the morning, and a lithium battery (figure 1). The sensor is placed along the bottom front of the leg and extends down to the center of the foot, to detect the leg movements. It is activated when a small gel patch is attached to it at bedtime. The software collects the data, identifies each PLM episode, counts the number of PLMs and following at least 3 hours of continuous recording computes the number of PLMs per hour of recording. In the morning, the device is removed from the leg and the sensor is detached. The score on the display may be read after 20 minutes.

Methods: Four subjects (1 woman, 3 men, ages 21-80), who were suspected of PLMS and referred to the sleep clinic for overnight PSG recording participated in the pilot study. The KickStrip software provides two types of signals: one for the detection of an isolated leg movement (non-PLM), and another for the detection of a sequence of leg movements defined as periodic (PLMs). To validate the KickStrip signals, traditional anterior tibialis EMG and KickStrip signals were recorded simultaneously during full overnight PSG recordings in the sleep clinic. Recordings were scored by experienced scorers using standard criteria. Isolated leg movements as well as PLMs detected by EMG and by KickStrip signals were counted separately.

Results: Two out of four subjects had PLMS. The number of isolated movements and PLMs detected by EMG (Non-PLM EMG and PLMs EMG) and by KickStrip (Non-PLM KickStrip and PLMs KickStrip), as well as percentages of KickStrip signal detection are presented in the table. KickStrip detection of isolated movements was high (89%-95%), as was KickStrip detection of PLMs for the two patients with PLMS (72%-85%).
Conclusions: This preliminary study shows that the KickStrip may be a reliable and efficient screener for PLMs. Due to its simple self-administered home-use design and its low cost, the KickStrip has great potential as an initial home screener for PLMS.

711.R

REM-ß: A New Parameter to Describe Circadian Functionality from the Hypnogram?

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Introduction: Although human sleep-wake regulation is substantially under circadian control, no parameter derived from standard polysomnography exists that describes circadian functionality. REM sleep appearance is ultradian generated, but circadian modulated. REM sleep propensity is highest at the nadir of core body temperature (a reliable phase-marker of the circadian timing system - CTS), in the entrained individual REM sleep duration is longer at the end of nighttime sleep, and a lesioning of the suprachiasmatic nucleus (SCN) leads to a reduction in REM sleep continuity (1). The aim of the study was to develop a parameter, which represents a measure for circadian rhythmicity, in addition to standard parameters describing human sleep by means of polysomnography (PSG).

Methods: Part one: For the development of method we used PSG recordings of 18 out of 34 healthy drugfree subjects (12 females, 6 males; mean-age=51.6±19yrs., range=22-77yrs.). For entrainment, subject were asked to keep good sleep hygiene for 8 consecutive days (actigraphy control) including initiating bedtime between 10 and 12p.m.. As an approximation to an entrainment measure we calculated the sum of changes of time sleep, and a lesioning of the suprachiasmatic nucleus (SCN) leads to a reduction in REM sleep continuity (1). The aim of the study was to develop a parameter, which represents a measure for circadian rhythmicity, in addition to standard parameters describing human sleep by means of polysomnography (PSG).

Part two: The sum of changes in Tc was significantly and negatively associated to REM-ß (Pearson’s r=-0.384, p<0.05, one-tailed).

Conclusions: Results show that the change in REM sleep episode duration in the course of the night is correlated to a circadian parameter (night time core body temperature changes under at least partly unmasked condition). Thus, results suggest that REM sleep episode length in the course of the night is a circadian influenced parameter. If results can be confirmed by constant-routine or forced desynchrony protocols REM-ß may prove to be an easy applicable and quantifiable parameter for the description of circadian functionality to be derived from the hypnogram.

References:

Work was funded by the European Commission BMH4-CT97-2040 (DG12 - SSMI)

712.R

Telemetry for Naturalistic Sleep Recording: Results in Inbred and Hybrid Mice

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(1) Eastern Virginia Medical School, (2) University of Pennsylvania, (3) Philadelphia Veterans Affairs Medical Center

Introduction: Differences among inbred strains of mice suggest that the duration of NREM and REM, total sleep, and the circadian rhythm of sleep have genetic bases (Franken et al. 1999; Friedmann, 1974; Valatx et al., 1972), and there has been a surge in interest in recording sleep in mice in order to take advantage of the their strengths as genetic models. Their small size can produce recording concerns not found in larger animals. Cable systems can limit movement, are difficult to adequately counterweight and may require the cable to be permanently affixed to the skull. Telemetry eliminates these concerns, may reduce potential stress associated with cable recording and also holds the promise of a more naturally behaving animal. However, current commercially available transmitters that are of a size applicable to mice are limited in the number and types of recording channels, particularly for electrophysiological variables. We assessed the utility of telemetric recorded EEG and motor activity for determining sleep and wakefulness in freely moving mice.

Methods: Mice from three inbred strains (C57BL/6J, n=12; BALB/cJ, n=12; DBA/2J, n=8) and one hybrid strain (CB6F1/J (C57BL/6J x BALB/cJ) n=8) were intraperitoneally implanted with transmitters (DataSciences ETA10F20). Leads from the transmitter were routed sub-
cutaneously to the head and attached to screw electrodes for recording EEG. The receivers (DataSciences RPC1) were configured to record gross locomotor activity. After recovery, EEG and activity were recorded continuously for three consecutive days. Behavioral state (wakefulness, NREM and REM) was visually scored (10 sec epochs) based on EEG and activity.

Results: During the light period, BALB/cJ and CB6F1/J mice exhibited less NREM than other two strains (P < 0.01); BALB/cJ strain showed less REM sleep than the other three strains (p < .01). During the dark period, DBA/2J strain showed less NREM sleep than the other three strains (P < 0.01); CB6F1/J and BALB/cJ strains displayed more REM sleep than the other two strains (P < .001). Table 1 and 2 show the percentages of wakefulness, NREM and REM for the light and dark periods averaged across 3 recording days.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Light period sleep/wakefulness percentages across strains (M±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C57BL/6J</td>
</tr>
<tr>
<td>% W</td>
<td>42.2±1.3</td>
</tr>
<tr>
<td>% NREM</td>
<td>52.5±1.3</td>
</tr>
<tr>
<td>% REM</td>
<td>5.4±0.3</td>
</tr>
<tr>
<td>% REM/TS</td>
<td>9.3±0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Dark period sleep/wakefulness percentages across strains (M±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C57BL/6J</td>
</tr>
<tr>
<td>% W</td>
<td>62.0±2.0</td>
</tr>
<tr>
<td>% NREM</td>
<td>35.0±1.8</td>
</tr>
<tr>
<td>% REM</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>% REM/TS</td>
<td>8.0±0.4</td>
</tr>
</tbody>
</table>

Conclusions: We describe sleep recorded by telemetry in four strains of mice. Telemetry allows relatively more natural behavior and activity (e.g., climbing on cage bars) than cable systems, and after recovery the animals can be handled much as before implantation. Clear, discriminable EEG signals and gross motor activity produce easily scored sleep records in mice. Telemetry may be most desirable for experimental protocols in which animals need to be regularly handled and sleep recorded over relatively long periods of time.

References:

Research supported by Supported by MH61716.

713.R

Comparison of a Wearable Polysomnograph With Standard Laboratory Polysomnographic Equipment

Hayee GD,1 Seifert GJ,1 Gibson PL,1 Mulrooney T2
(1) Advanced Medical Electronics Corp., (2) MN Sleep Institute

Introduction: Existing methods to conduct sleep studies require the subject to be tethered to a pin jack box or a portable recorder that is placed next to the bed. The approach tested here removes the need for cables to run off the body by transmitting the polysomnograph data. A wearable polysomnograph was designed for use in a body worn package, 6.6” x 3.15” x 0.84” in size. It was worn on the upper chest of the sleeping patient. Sixteen sensor channels including built-in SpO2 are processed for up to 15 hours using two AA alkaline batteries. A built in radio frequency (RF) transmitter sent the digitized data off the sleeping patient in real-time. Three receiver modalities collect data were tested. These include a PC, a battery powered solid-state recorder, and the Internet. Comparison tests were performed that compared the quality of the wearable polysomnograph data to the data simultaneously recorded by a standard laboratory polysomnograph. The National Institutes of Health provided funding for the development of the wearable polysomnograph and the human testing.

Methods: The wearable polysomnograph tested was capable of 16 data channels, including: Pulse Oximetry and Heart Rate, EEG (4 channels), EOG (2 channels), EMG (2 channels), EKG, Chest Effort (2 channels), Airflow (thermoregulatory or based pressure), Body Position, Snore Sensor. The wearable polysomnograph used a low power 900MHz RF transmitter to send a noise-free digital data stream. It transmits a unique digital protocol developed by Advanced Medical Electronics for this application at 50 kbps. A RF receiver receives the signal and sends the digital data over a cable to the monitoring room. Safety connectors provided interconnect for all the common sensors used in sleep studies. Comparison testing using human subjects was done at the sleep Diagnostic center of St. Joseph’s hospital in St. Paul, Minnesota an AASM accredited facility. In these tests the data transmitted by the wearable polysomnograph was received and recorded in two different methods. One method used a RF receiver connected to the serial port of a PC that both recorded and displayed the data. The other method used a battery powered portable recorder that received the signal and save the data on a flash PCMCIA card. In these two overnight tests, a subject diagnosed independently as having a sleep disorder, was wired with both the wearable polysomnograph and a Nellcor Puritan Bennett Sandman polysomnograph concurrently. While the additional wiring and sensors made for a busy looking patient, it did not affect the quality of data recorded by either system during the study. The complete electrical isolation of the wearable polysomnograph allowed it to float to the bias levels of the wired standard laboratory polysomnograph without affecting data collection.

Results: The data recorded by the polysomnographs were scored by the same technician (on different days) to reduce the effects of scoring style in the comparisons. Each epoch was scored as awake, stage 1, stage 2, stage 3, stage 4, or REM sleep. Manual scoring of the two tests comparing the wearable polysomnograph to the standard laboratory polysomnograph resulted in a sleep-stage scoring agreement in the range of 86 to 93%.

Conclusions: The wearable polysomnograph system performed well during all testing was found to be in satisfactory agreement with standard laboratory polysomnographic equipment.

714.R

Abnormal EEG’s in Patients Presenting for Polysomnography

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(1) University Services, Philadelphia, PA, (2) Philadelphia College of Osteopathic Medicine, Philadelphia PA

Introduction: The EEG channels of a Polysomnogram provide some of its most important information. Proper interpretation requires knowledge of the expected patterns in sleep. However, a patient with an
abnormal baseline EEG can show unusual or unexpected EEG patterns on the polysomnographic EEG. The following study looked at the number of abnormal EEG’s in patients presenting for polysomnography.

**Methods:** The first 143 patients presenting to our sleep laboratories had an eight or ten channel routine waking EEG prior to their polysomnograms. Each EEG was interpreted by a trained neurologist and classified as normal (NML) or abnormal (ABN). An abnormal EEG was one showing epileptiform transients, ictal events, excessive slowing or focal slowing. A neurologic history was obtained from each patient. The neurologic histories were grouped by: no history of neurologic disease or insult (NEG), a history of headaches (HA) or a positive history of neurologic disease or insult (POS). The last included histories of stroke, head trauma, seizures, dementia, etc.

**Results:** See table

**Table 1**

<table>
<thead>
<tr>
<th>EEG results versus Neurologic history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic History</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>EEG</td>
</tr>
<tr>
<td>NML</td>
</tr>
<tr>
<td>ABN</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

P < .05 Chi-squared

**Conclusions:** There is an obvious difference in the frequency of finding abnormal EEG’s in patients with a positive Neurologic history as opposed to patients without a Neurologic history. This is an expected result. However, 10 of 102 (9.8%) of patients without a neurologic history had abnormal EEG’s. Six patients showed abnormal slow activity and four showed unexpected epileptiform activity: sharp waves, spikes or spike and wave activity. The abnormal slowing could confuse the scoring of sleep stages especially sleep onset. The epileptic activity could easily be missed on a thirty second EEG window. This activity could indicate the presence of sub-clinical seizures mistakenly described as micro-sleeps or cause sleep disruption due to seizures. This data suggests that a routine EEG could be quite helpful in patients with known neurologic histories and raises the question whether or not routine EEG’s should be part of a sleep evaluation.

**715.R**

Is there a First Night Effect with Ambulatory Polysomnography (PSG)?

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The Cleveland Clinic Foundation, Sleep Disorders Center

**Introduction:** First night effect (FNE) is a well-known limitation of conventional PSG. The purpose of our study was to determine whether FNE is present to a significant extent on PSG performed in the home.

**Methods:** 11 patients with focal epilepsy, who were part of a larger study addressing the effects of the antiepileptic drug lamotrigine on sleep were the subjects of this study. Patients with sleep disorder symptoms other than primary snoring were excluded. All subjects underwent two consecutive PSGs in the home using the Digitrace SleepScan. This system incorporates 4 EEG channels (C3, C4, O1, O2), 2 channels of EOG (right and left outer canthus), chin and anterior tibialis EMG, EKG, airflow, respiratory effort (thoracic and abdominal), oxygen saturation, body position, and snoring. Subjects were entirely seizure free (including auras) for at least 48 hours prior to each PSG. Polysomnographic variables from the two nights were compared using the Wilcoxon sign-rank test.

**Results:** Polysomnographic variables are shown in the following tables.

**Table 1**

<table>
<thead>
<tr>
<th>N=11</th>
<th>Night 1</th>
<th>Night 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recording time (min)</td>
<td>489.6</td>
<td>433.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>383.5</td>
<td>387.6</td>
<td>0.80</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>78.9</td>
<td>88.9</td>
<td>.001</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>33.6</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>92.5</td>
<td>64.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>N=11</th>
<th>Night 1</th>
<th>Night 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% stage 1</td>
<td>15.0</td>
<td>7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% stage 2</td>
<td>49.6</td>
<td>51.3</td>
<td>0.80</td>
</tr>
<tr>
<td>% stage 3/4</td>
<td>17.1</td>
<td>19.5</td>
<td>0.40</td>
</tr>
<tr>
<td>% REM</td>
<td>23.2</td>
<td>22.2</td>
<td>0.80</td>
</tr>
<tr>
<td>REM periods</td>
<td>3.5</td>
<td>3.5</td>
<td>-</td>
</tr>
<tr>
<td>Stage shifts</td>
<td>77.5</td>
<td>68.4</td>
<td>0.40</td>
</tr>
<tr>
<td>Arousal index</td>
<td>7.3</td>
<td>6.4</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Conclusions:** Total recording time was nearly one hour longer on night 1. We believe this was due to subject activation of the recording mechanism earlier than they typically go to bed on night one, perhaps related to anticipation. This finding led to other differences between the two nights, including longer sleep latency and REM latency and lower sleep efficiency. However, these changes did not appear to affect sleep architecture as relatively normal percentages of SWS and REM sleep were recorded in both nights and the number of REM periods was identical between the two nights. Therefore, we believe that ambulatory PSG can be performed in the home without adversely affecting sleep architecture.

We would like to thank Glaxo Wellcome and Digitrace for support for this study.

**716.R**

Pilot Evaluation of an Ambulatory, Wrist-Worn Oximeter with Identification of Movement Artifact

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(1) Johns Hopkins University, Zanvyl-Krieger School of Arts and Sciences, Department of Psychology, (2) Sleep Medicine Associates of Texas, P.A., (3) Johns Hopkins Bayview Medical Center, Department of Neurology, (4) IM Systems, Inc., Baltimore, MD

**Introduction:** A number of pulse oximeters are available for overnight recording of oxygen saturation in the blood (SpO2) outside of the sleep lab setting. However, these units are less than optimal for use in unattended settings, such as the home, for several reasons. First, while portable, these are rather large units placed on a table or nightstand and

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are not designed for use with an ambulatory patient. Second, many of these units require some level of patient training on how to use such a device on their own. Finally, these monitors typically have only enough memory to record data for up to 24 hours before being reset. The OxiTrac (IM Systems, Baltimore, MD) was designed to overcome these limitations by allowing for SpO2 data to be collected for up to several days in a miniature, wrist-worn unit which can be easily placed and removed by the patient. In addition, the OxiTrac also includes an accelerometer assembly designed to identify movement artifacts, a capability which no other existing oximeters possess. The current pilot study was designed to provide an initial validation of the OxiTrac as compared to standard methods for the recording of SpO2 data.

Methods: 13 sleep apnea patients (ranging in severity from minimal to severe) and 10 control subjects were each admitted for a standard, overnight PSG evaluation. Each subject had an OxiTrac monitor placed on one hand with the unit’s sensor on the index finger and the sensor for the sleep lab’s standard oximeter placed on the ring finger. The SpO2 data for each 4-second interval of the sleep period of the recording was compared to those from the OxiTrac and the standard oximeter. In addition, 6 of the subjects were asked to wear the OxiTrac at home for one night to evaluate patient comfort and ease of use in an unattended environment.

Results: Point-to-point comparisons of SpO2 data for the OxiTrac and the standard oximeters yielded a mean, absolute difference of 0.45% with a standard deviation of 0.85%. Additionally, the correlation between the OxiTrac and the standard oximeter readings of SpO2 throughout the sleep periods was observed to be 0.93; while the regression line did not differ significantly from the identity line, there were a few series of points with lower OxiTrac readings when compared to the standard oximeter. Further investigation indicated that these appeared to correspond to mild, 30-60 second hypopnea events associated with patient movement. Those subjects who wore the OxiTrac at home stated that the device did not interfere with their sleep and rated the unit as being comfortable to wear, and easy to apply and remove.

Conclusions: The results of this pilot study are encouraging, indicating that the miniature, ambulatory OxiTrac provides an accurate means recording SpO2 data. The OxiTrac compares very well with standard measures of SpO2 identification. The next stage of research with the OxiTrac will be to conduct larger-scale, more in-depth studies with this equipment and to evaluate multiple-evening recordings in a home environment.

Research supported by DHHS Grant # 1R43HL62077

717.R

Peripheral Arterial Tonometry (PAT) is a Sensitive Indicator of Acute Arousal Responses to Obstructive Sleep Apnea (OSA)

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Division of Pulmonary and Critical Care Medicine, Johns Hopkins Medical School

Introduction: OSA is associated with repetitive periods of intermittent hypoxia and arousal from sleep, both of which augment autonomic activity in a canine model of OSA.1 Recently, a non-invasive PAT device has been developed to assess changes in autonomic activity.2 We evaluated the PAT response to arousal induced by airway obstruction in OSA patients.

Methods: Short periods of airway obstruction were induced either with or without an arousal, as previously described in the canine OSA model.3 Ten OSA patients (2 F/8 M; age, 44.8 ± 3.7 years, BMI, 3 8.6 ± 3.7 kg/m², NREM apnea-hypopnea index, 66.5 ± 8.3 events/hr, mean ± SE) were monitored polysomnographically. PAT was monitored with a finger plethysmographic device (Itamar Ltd., Caesaria, Israel). Patients were placed on therapeutic nasal continuous positive airway pressure (CPAP) at 13.1 ± 1.1 cm H₂O. In each patient, nasal pressure (Pn) was abruptly lowered for 3-5 breaths over a range from 9.3 ± 1.3 to 1.9 ± 1.3 cm H₂O, leading to increasing airway obstruction and decreasing levels of inspiratory airflow from 361 ± 45 to 97 ± 5.9 ml/min. ASDA criteria were used to determine whether each drop in Pn was associated with arousal. The amplitude of the PAT signal was determined for 10 cardiac cycles (1) immediately prior to the drop in Pn (P1), (2) immediately prior to restoring Pn (P2), and (3) immediately after Pn was restored (P3), as shown in figure.

Results: A step reduction in Pn from 18.0 to 5.4 cm H₂O during NREM sleep led to a marked decrease in tidal airflow, augmenting esophageal pressure swings, and arousal from sleep (see figure). The PAT signal remained stable during the period of reduced Pn (P2 vs. P1), but attenuated markedly during the arousal from sleep (P3). In pooled data from ten patients, the normalized PAT amplitude did not change significantly between periods P1 to P2, but decreased markedly from periods P1 to P3 in the presence of arousal (1.00 to 0.80 ± 0.16 arb. Units; P<0.005). In the absence of arousal, however, the normalized PAT amplitude showed a small, non-significant, decrease between periods P1 and P3 (1.00 to 0.95 ± 0.13 arb. Units).

Figure 1

Conclusions: The PAT signal is a sensitive indicator of arousal induced by acute periods of airflow obstruction. Our findings imply that peripheral arterial tone increases following periods of upper airway obstruction during sleep that are terminated with arousal.

References:
718.R

FFT and Coherence Analysis of the Sleep Onset Period as a Function of Hori’s 9 Stages

Lazic SE, Williams BR, Ogilvie RD
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Introduction: The purpose of this study was to perform a detailed examination of changes in EEG coherence and power spectral (FFT) analysis during the sleep onset period (SOP). Others (1,2) have examined coherence and FFT in a broader fashion—for example, as a function of standard R & K stages. However, there are many distinct changes in EEG from waking through the onset of sleep, ending when stage 2 is established (2,3). Many of these systematic processes are conflated when R & K stages are used. Therefore, in order to provide a much finer analysis of the SOP, a slightly modified version of Hori’s 9-stage system (3) was used. These nine stages correspond to the standard stages of awake to stage 2.

Methods: Participants consisted of 9 individuals with mild traumatic brain injury (MTBI) and 9 matched controls with mean ages of M = 21.4 (SD = 2.4) and M = 20.7 (SD = 2.1), respectively. Participants spent 3 nights in the lab, the first two serving as adaptation nights. On the third night, participants were woken without interruptions, and PSG data were recorded. Analysis: Frequencies bins used were: delta, theta, alpha-1, alpha-2, alpha-3, sigma, beta-1, and beta-2. Interhemispheric coherence channel pairs used were: C3-C4, O1-O2, P3-P4, T3-T4, T5-T6, F3-F4, F7-F8, and Fp1-Fp2. And sites for FFT analysis were Cz, Pz, O2, and T4.

Results: BETWEEN SUBJECTS DIFFERENCES: FFT and coherence values between the MTBI and control groups were very similar, and the coherence during sleep and wakefulness in left- and right-handed subjects. FFT RESULTS: Gener Values between the MTBI and control groups were very similar, and the coherence during sleep and wakefulness in left- and right-handed subjects.


Research supported by Grant from the Natural Sciences and Engineering Research Council of Canada

719.R

Actigraphic Detection of Periodic Leg Movements; A Validation Study

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Introduction: Periodic limb movements of sleep (PLMS) may be a significant and readily treatable cause of fragmented sleep. In this study, we determined the sensitivity and specificity of the Actiwatch® actigraphic monitor (Mini Mitter Co., Inc., Bend, OR) attached to the feet, comparing it to polysomnography (PSG), considered the assessment standard.

Methods: The subjects were patients undergoing one night of clinical PSG evaluation in the OHSU sleep disorders program (N = 30; 8 women and 22 men). Most of the patients were being studied for suspected sleep-disordered breathing. After the patients had provided informed consent, an Actiwatch® was attached to the dorsum of each foot as part of the PSG recording procedure. PLMS were hand-scored from the PSG recordings using conventional criteria. PLMS were auto-scored from the actigraphic recording using software developed by Cambridge Neurotechnology Ltd; data from the two feet were combined (for each time point, data from the most active foot was used). A PLMS index (PLMS per hour of sleep) was determined by both the PSG and actigraphic methods.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>True Positive</td>
<td>a 7</td>
</tr>
<tr>
<td>False Positive</td>
<td>b 3</td>
</tr>
<tr>
<td>False Negative</td>
<td>c 1</td>
</tr>
<tr>
<td>True Negative</td>
<td>d 19</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>a/(a+c) 0.88</td>
</tr>
<tr>
<td>Specificity</td>
<td>d/(b+d) 0.86</td>
</tr>
<tr>
<td>False neg. rate</td>
<td>c/(a+c) 0.13</td>
</tr>
<tr>
<td>False pos. rate</td>
<td>b/(b+d) 0.14</td>
</tr>
<tr>
<td>Pos. predictive value</td>
<td>a/(a+b) 0.70</td>
</tr>
<tr>
<td>Neg. predictive value</td>
<td>d/(c+d) 0.95</td>
</tr>
<tr>
<td>Overall accuracy</td>
<td>(a+d)/(a+b+c+d) 0.87</td>
</tr>
</tbody>
</table>

Results: Overall, it appeared that the actigraphic method detected about 30 to 50% fewer PLMS than PSG [consistent with prior studies (1)]. Therefore, the cutoff for a positive actigraphic PLMS index was set at 5 while the cutoff for a positive PSG PLMS index was set at 10. Using these cut-offs, sensitivity and specificity calculations were made (see Table below). The three false positive actigraphic studies appeared to be related to rhythmic movements caused by recurrent apneic or snoring episodes. The one false negative may have been caused by faulty placement of the sensor.

Conclusions: Actiwatches® attached to the feet provide a sensitive and specific method of screening for PLMS. Follow-up PSG recordings may be needed to confirm the diagnosis and (more importantly) to determine the frequency of PLMS related arousals. Rhythmic movements from
apnea or snoring can mimic PLMS; consequently, the accuracy of actigraphy might be higher in patients who do not have sleep-disordered breathing. Because of the simplicity of the procedure, actigraphy might also be a useful method for the longitudinal monitoring of treatment response.

References:

720.R
Prediction of Drowsiness Based on the Study of the Autonomic Nervous System

Bader G
Department of Clinical Neuroscience

Introduction: Detection of drowsiness is a concern in many professional activities. The transition from wakefulness to sleep is accompanied by physiological and behavioural modifications and significant changes in the autonomic nervous system (ANS) occur just before sleep onset (SO). The golden standard to study sleepiness remains the EEG which, with a resolution of 20 s poorly represents the progressive process of drowsiness. We have previously presented a method of staging EEG with higher temporal resolution reflecting drowsiness adequately. The aim of the following study was to develop a method predicting drowsiness based on parameters from the ANS.

Methods: Eighteen healthy subjects were investigating with standard paper polysomnography (EEG, EOG, ECG, airflow, movements...) and video recorded. Subjects reported sleepiness on analogue visual scales. Multiple Sleep Latency Test (MSLT) was used for studying ability to fall asleep, Maintenance of Wakefulness Test (MWT), for ability to maintain alertness. For both tests 5 recording sessions of 25 min and 45 min apart, were performed. Each MSLT-MWT record (total 60) was visually scored according to Rechtshaffen and Kales based on a 20 s period and “micro”-scored with a 2 s period according to a previously reported method. Heart rate (T-R interval), amplitude and interval of respiratory movements were calculated from the paper chart using a digitizer. Body movements and eye blinking were also analysed.

Results: Changes in the R-R intervals (R-R) were significant when comparing R-R during wakefulness at the beginning of the record, and at sleep onset SO as defined by the EEG (t-test, P< 0.02), and when comparing R-R during wakefulness at the beginning of the record, and when EEG arousals led the EEG profile. Plot of variance of R-R related to time showed a progressive increase of R-R up to SO. This R-R profile most of the time paralleled the EEG profile. Plot of variance of R-R related to time showed a great variability at the beginning of the records, and when EEG arousals were observed than after SO. Correlation between R-R and EEG in the entire record was r=0.76 SD 0.13. Analysis of R-R in only selected upward (increased drowsiness) and downward (increased alertness) segments of the EEG profile had a correlation r=0.82 SD 0.19. Respiration amplitude most often decreased during drowsiness while intervals could increase. The interval had higher correlation to EEG than amplitude. Body movements presented alternation of periods with low and high activity prior to SO and activity following arousal. In most of the records, the number of eye blinks decreased when the R-R increased although it could also increase reflecting the subject struggle against drowsiness. For each peak of drowsiness in the EEG corresponded a peak in the regression plot of the blinks.

Conclusions: In conclusion, physiological parameters mainly reflecting the activity of the ANS can be used as indicator of drowsiness.

721.R
The Effects of Motion and Hypoxemia upon the Accuracy of 20 Pulse Oximeters in Human Volunteers

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Department of Anesthesiology, University of Arizona College of Medicine

Introduction: Patient motion is a well-known source of error in pulse oximetry, and can occur in patients most in need of accurate SpO2 readings. In previous studies, we have developed a laboratory protocol using human volunteers to determine the effects of controlled hand motions upon pulse oximeter accuracy during hypoxemia.1,2 Results of our laboratory studies have been supported by recent clinical studies.3 In the current study, we compare 20 pulse oximeters in terms of accuracy during motion as well as sensitivity and specificity for the detection of hypoxemia.

Methods: Seventy healthy volunteers participated in this study, which was approved by the University Human Subjects Committee. Each volunteer was instrumented with six pulse oximeter finger sensors: three on the moving “test” hand, and three on the stationary “control” hand. The Masimo SET was compared with two other instruments on the test hand of each subject. A motorized motion table produced controlled finger tapping and rubbing motions at frequencies between 1 and 3 Hz. Both SpO2 and pulse rate values from all oximeters were recorded continuously. Measurements were made while subjects breathed room air, and also during rapid hypoxic events with arterial saturations falling to 75%. Hypoxemia was accomplished using an anesthesia machine modified to provide FiO2 values as low as 9%. The room temperature was held at 16-18°C, to reduce peripheral perfusion and better simulate actual patients. Data were analyzed using bias (mean error), precision (std dev of error), and dropout rate (%-time no SpO2 displayed). “Performance indices” are defined as SpO2 PI = %-time an SpO2 is displayed that is within 7% of the average of the controls, and PR PI = %-time a pulse rate is displayed that is within 10% of controls. Sensitivity and specificity for detection of hypoxic events were also calculated, using a SpO2 value of 90% as the threshold for hypoxemia.

Results: The statistical results of the 20-oximeter comparison are summarized in the table below. The performance of the Masimo SET was superior in every measured parameter, including a saturation PI value of 94%. The closest competitor was the Hewlett-Packard (Agilent) Viridia 24C, with a PI value of 84%.

Table 1

<table>
<thead>
<tr>
<th>Pulse Oximeter</th>
<th>Missed Events</th>
<th>False Alarms</th>
<th>SpO2 Sensitivity</th>
<th>SpO2 Specificity</th>
<th>SpO2 PI</th>
<th>PR PI</th>
<th>drop-out %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximo SET</td>
<td>0/40</td>
<td>7/30</td>
<td>99</td>
<td>93</td>
<td>94</td>
<td>93</td>
<td>1.6</td>
</tr>
<tr>
<td>HP Viridia 24C Res II</td>
<td>9/40</td>
<td>6/40</td>
<td>78</td>
<td>90</td>
<td>84</td>
<td>75</td>
<td>1.6</td>
</tr>
<tr>
<td>HP CMS 15/40</td>
<td>15/40</td>
<td>25/40</td>
<td>57</td>
<td>43</td>
<td>60</td>
<td>45</td>
<td>3.2</td>
</tr>
<tr>
<td>Datex-Ohmeda 3740</td>
<td>13/40</td>
<td>15/40</td>
<td>68</td>
<td>40</td>
<td>80</td>
<td>10</td>
<td>0.0</td>
</tr>
<tr>
<td>Datex-Ohmeda 3760</td>
<td>15/40</td>
<td>18/40</td>
<td>60</td>
<td>40</td>
<td>60</td>
<td>9</td>
<td>0.0</td>
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<tr>
<td>Datex-Ohmeda AS3</td>
<td>17/40</td>
<td>17/40</td>
<td>65</td>
<td>45</td>
<td>67</td>
<td>61</td>
<td>1.2</td>
</tr>
<tr>
<td>Nellcor N-955</td>
<td>23/40</td>
<td>25/40</td>
<td>67</td>
<td>40</td>
<td>76</td>
<td>10</td>
<td>0.0</td>
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<tr>
<td>Datex-Ohmeda 3900</td>
<td>26/40</td>
<td>26/40</td>
<td>70</td>
<td>50</td>
<td>67</td>
<td>10</td>
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</tr>
<tr>
<td>Noramtec MARKS</td>
<td>24/40</td>
<td>30/40</td>
<td>66</td>
<td>52</td>
<td>64</td>
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<td>HP CMS 15/40</td>
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<td>25/40</td>
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<td>35</td>
<td>51</td>
<td>33</td>
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<td>26/40</td>
<td>28/40</td>
<td>55</td>
<td>40</td>
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<td>77</td>
<td>2.4</td>
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<tr>
<td>Nellcor N-200</td>
<td>30/40</td>
<td>32/40</td>
<td>55</td>
<td>35</td>
<td>82</td>
<td>67</td>
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</tr>
<tr>
<td>Nellcor N-180</td>
<td>26/40</td>
<td>28/40</td>
<td>55</td>
<td>35</td>
<td>82</td>
<td>67</td>
<td>1.2</td>
</tr>
<tr>
<td>Nellcor NPB-550</td>
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<td>28/40</td>
<td>55</td>
<td>35</td>
<td>82</td>
<td>67</td>
<td>1.2</td>
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<tr>
<td>Nellcor NPB-600</td>
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<td>28/40</td>
<td>55</td>
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<td>Nellcor NPB-190</td>
<td>21/40</td>
<td>24/40</td>
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<td>CSI 5040</td>
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<td>25/40</td>
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<td>20</td>
<td>65</td>
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<td>1.1</td>
</tr>
</tbody>
</table>

Effects of Motion and Lower Perfusion on the Performance of Twenty Pulse Oximeters

SLEEP, Vol. 24, Abstract Supplement 2001
Conclusions: Our motion protocol is challenging, and caused failures of all instruments at various times. However, the incidence of failure to provide an accurate SpO2 value during motion was much lower in the Masimo SET than in the other 19 instruments. The sensitivity and specificity values show that the Masimo provides more certain detection of hypoxemia while at the same time yielding a lower false alarm rate. Although the performance for pulse rate was inferior to that for saturation in all oximeters, the pulse rate values from the Masimo were more accurate (PR-PI = 83%) than those of the other instruments.

References:

722.R

A Comparison Between the Effects of Repeated Practice and Prolonged Wakefulness on Simulated Driving Performance

Thiele K, Davies DR, Gaasbeek K, Dawson CM, MacLean AW
Department of Psychology, Queen's University, Kingston, Ontario, Canada

Introduction: An important issue to consider when examining the influence of sleep loss on any behavioural task is that performance may be influenced by practice or repeated exposure to that task. Improvements due to practice may mask decrements attributable to factors such as sleep loss. The objective of the present research is to examine the influence of repeated practice on simulated driving performance and to compare the size of these effects to those observed under conditions of prolonged wakefulness.

Methods: Data for this comparison were obtained from two separate experiments investigating performance on the York Driving Simulator. In one study, 28 subjects (mean age = 24.8 years) completed four 20-minute daytime driving sessions over the course of a week in which they maintained their usual sleep-wake schedules. In the second, 32 subjects (mean age = 18.9 years) completed four 30-minute sessions at 2230, 0100, 0330, and 0600 during one night of prolonged wakefulness. In both studies, subjects were required to “drive” along a monotonous stretch of 4-lane highway whilst staying as close to the posted speed limits and centre of their lane as possible.

Results: For both samples, performance on the following variables was examined: Mean Road Position, Mean Speed Deviation, Road Position Variability, and Speed Deviation Variability. Effect sizes (Glass’ Delta) were calculated for comparisons between baseline and sessions 2, 3, and 4, respectively, within each sample. These effect sizes are presented in the figures below. In general, repeated practice improved driving performance notably within the first three sessions and had limited benefits thereafter. Sleep loss, on the other hand, clearly lead to a significant deterioration in performance that was maximal in the final session.

Conclusions: Improvements in performance due to repeated practice are of substantial concern - particularly in applied settings where appropriate experimental control is not readily available. In studies where performance deterioration is likely to occur, effects are likely to be found but underestimated. Conversely, interventions aimed at improving performance or counteracting the detrimental effects of sleep loss may be overestimated. Researchers should either ensure that sufficient practice sessions are included or that appropriate designs are used to control the influence of practice effects.

We gratefully acknowledge the support of DuPont Canada Inc. and a special research grant from Queen’s University.
Cognitive Testing in the FMRI Environment Increases Subjective Sleepiness

Drummond S.1,2 Goldin PR.1,2 Eyler Zorrilla LT.1,4 Tapert SF.1,3 Brown GG.1,3,4 Gillin JC.1,2
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Introduction: Periods of cognitive performance as short as 35 minutes can increase subjective sleepiness post-performance compared to pre-performance. This effect may not emerge, however, until after 16 hours of wake time. We recently reported increased sleepiness following total sleep deprivation (TSD) is associated with characteristic increases in cerebral activation as measured with functional magnetic resonance imaging (FMRI).1 The FMRI environment is potentially conducive to promoting sleepiness as subjects are typically lying supine in a dimly-lit or dark room for as long as 120 minutes. Given this, it is possible that increased sleepiness may occur during cognitive performance even in the diurnal period. If significant increases in sleepiness occur simply as a function of the environment, it may influence the results of studies using FMRI to examine cognitive performance. Here we report subjective sleepiness data pre- and post-FMRI sessions involving cognitive performance.

Methods: Subjects (N=72; mean age = 37.8 ±16 years) came from 4 different studies using several different cognitive tasks and subject populations. Each subject completed the Stanford Sleepiness Scale (SSS) just prior to scanning. The post-testing SSS scores here did not reach pathological levels, and this may be due to the fact most of them occurred before core body temperatures likely started to drop. Given our recent findings1 of sleepiness-related effects on brain activation, though, researchers should be mindful of potential effects of increased sleepiness on cognitive performance and brain imaging data during FMRI studies, especially during late evening or very long sessions. We suggest all FMRI studies include measures of subjective sleepiness pre- and post-scanning.

Results: 1. Overall, subjects reported increased sleepiness following cognitive testing inside the FMRI scanner compared to prior to testing (Table 1). 2. Time-of-day did not significantly affect SSS scores, nor did it interact with the cognitive testing effects. However, the effect size for the pre/post testing effect was larger for evening scans (eta² = 0.437) vs. earlier scans (0.176). 3. Group membership did not significantly affect SSS scores, but there was a trend for a group X testing interaction (p=0.067).

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>SSS pre-scan</th>
<th>SSS post-scan</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n=72)</td>
<td>1.9 ±1.0</td>
<td>2.7 ±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Scan time ≤16:00</td>
<td>1.9 ±1.1</td>
<td>2.5 ±1.4</td>
<td>0.007</td>
</tr>
<tr>
<td>(n=39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scan time 16:30-21:00</td>
<td>1.9 ±1.0</td>
<td>2.8 ±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=33)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=46)</td>
<td>1.8 ±0.9</td>
<td>2.6 ±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social Phobia (n=13)</td>
<td>1.5 ±0.7</td>
<td>2.6 ±1.4</td>
<td>0.008</td>
</tr>
<tr>
<td>Alcohol Dependence (n=8)</td>
<td>2.2 ±1.0</td>
<td>3.2 ±1.3</td>
<td>0.050</td>
</tr>
<tr>
<td>Schizophrenia (n=5)</td>
<td>2.6 ±2.1</td>
<td>2.0 ±1.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Conclusions: Cognitive testing of at least 35 minutes in the FMRI environment increases subjective sleepiness, even during the diurnal period after a normal night of sleep and even during the Wake Maintenance Zone. Additionally, certain populations may be more susceptible to increased sleepiness (Table 1). The post-testing SSS scores here did not reach pathological levels, and this may be due to the fact most of them occurred before core body temperatures likely started to drop. Given our recent findings1 of sleepiness-related effects on brain activation, though, researchers should be mindful of potential effects of increased sleepiness on cognitive performance and brain imaging data during FMRI studies, especially during late evening or very long sessions. We suggest all FMRI studies include measures of subjective sleepiness pre- and post-scanning.

References:

Research supported by F31MH11452:SPAD, 5P30MH30914;JCG, M01RR00827, R01AA09033, T32MH18399, VA MIRECC(VISN22)

Initial Findings from a Multi-Site Evaluation of an Unattended Monitoring System for Automatic Detection of Sleep Disordered Breathing Events

(1) Johns Hopkins University, Zanvyl-Krieger School of Arts and Sciences, Department of Psychology, (2) Samaritan and University of Kentucky Hospitals, Lexington, KY, (3) Johns Hopkins Bayview Medical Center, Department of Neurology, (4) IM Systems, Inc., Baltimore, MD

Introduction: There are a number of portable recording systems used to identify sleep disordered breathing events (SDBEs) in a patient’s home environment using measures of airflow and respiratory effort. However, these devices are less than optimal for home recording for several reasons. First, they are not designed for unattended use and require a trained technician to set up and disconnect the system. Secondly, while they are portable, they are not ambulatory, as patients are required to wear an array of tethered electrodes and sensors connected to bulky body–worn monitors or table–top consoles. Finally, most require analysis of the data by trained professionals and do not provide for automatic identification of SDBEs. The Ambulatory Site-Specific Recorder system (ASSR; IM Systems, Baltimore, MD) was designed to overcome these limitations by allowing for data to be collected in miniature, self-contained recorders which could be easily placed and removed by the patient. The data is downloaded to a computer and automatically scored for identification of SDBEs. Pilot data has demonstrated that the ASSR system accurately identifies and records SDBEs during sleep; the current study was designed as a larger-scale validation of the system.

Methods: 8 sleep apnea patients (with a range of symptom severity), 4 patients with suspected sleep apnea and 12 non-apnea patients were admitted for a standard, overnight PSG evaluation and were simultaneously outfitted with the ASSR system, which includes thoracic and abdominal respiration recorders, a body position recorder, an actigraphy monitor, and a nasal and oral airflow sensor. PSG data was independently scored for number and duration of SDBEs and compared with the automatic scoring of SDBEs from the ASSR. Each patient was then asked to wear the ASSR system at home for one night in order to assess the device’s comfort and ease of self-attachment and unattended use.

Results: Comparison of the ASSR and PSG scoring of SDBEs per night showed an excellent agreement, with an overall correlation of 0.97. The mean absolute difference between the two measures was observed to be 14.12 (std. dev. = 10.62) and was not statistically significant (t(46) = 0.05, p > 0.05). The ASSR system, as compared to PSG data, was

SLEEP, Vol. 24, Abstract Supplement 2001
observed to slightly underestimate the number of total SDBEs per night in persons with severe apnea and slightly overestimated the number of events in those non-apnea subjects who demonstrated a very small number of events (0-3 per hour) during their sleep period. In addition, subjects who wore the ASSR system at home stated that the device was only mildly uncomfortable, relatively easy to use and did not significantly interfere with their sleep.

Conclusions: The results of the current study support previous pilot research which indicates that the miniaturized, ambulatory ASSR system provides an accurate means of identifying and recording SDBEs during sleep. This device would be useful for unattended monitoring of such events outside of the lab environment for successive, multiple-night recordings. Future research should include studies to assess the ASSR system’s ability to accurately distinguish between the various types of SDBEs.

Research supported by NIH Grant #N44-NS-8-2328 and NIH Grant #5-K07-HL.03637-03

725.R

A Comparison of Obstructive and Central Respiratory Events using a Respiratory Thermistor, a Pressure Transducer or Both for Scoring.

Benderhausman NJ, Scherr JE, Trudeau SK, Sandok
Marshfield Clinic Sleep Disorders Center, Marshfield, WI

Introduction: Following the introduction of nasal cannula/pressure transducers for use in detecting apneas/hypopneas, many sleep laboratories began using this technology in place of, or in addition to respiratory thermistors. Data directly comparing the possible differences in the ability of trained sleep technologists to identify both central apneas, obstructive apneas and hypopneas using either of these technologies alone or in combination has not previously been reported. This information is important, particularly when respiratory disturbance indexes (RDI’s) from more recent studies using alternative indirect methods of measuring respiratory airflow are compared with older data.

Methods: Seven full night polysomnogram recordings were randomly selected. The patients had all been evaluated in the sleep disorders clinic for possible sleep disordered breathing. The polysomnograms were run using standard EEG, EOG, EMG limb monitors, ECG, oximetry, snore, and position channels. Four respiratory channels were used. These included two flow channels (oral/nasal thermistor and nasal pressure transducer) a chest and abdominal channel (piezo crystal belts). For each study the first technologist scored using all channels, the second technologist scored while blinded to the thermistor channel, and the third technologist scored while blinded to the pressure transducer channel. Five different technologists (RPGST) were rotated as the first, second and third technologists to score the studies. Standard AASM guidelines were followed in scoring central, obstructive and mixed apneas. Hypopneas were defined as a clear reduction in airflow (as determined by the thermistor, pressure transducer or both) associated with a 3% oxygen desaturation or an arousal. The number of the various respiratory events, as well as the overall RDI’s obtained by each technologist were compared using the Wilcoxon Signed Ranks Test.

Results: Statistically significant differences (p < 0.05) were found in the number of obstructive apneas and the RDI when the studies scored without the pressure transducer were compared to the same studies scored with both a thermistor and a pressure transducer. The use of both airflow channels resulted in a larger number of obstructive apneas being identified and a larger overall RDI. There was also a trend when scores obtained without the use of the pressure transducer were compared to scores obtained without the use of the pressure transducer, for a larger number of apneas but fewer hypopneas to be identified when using the pressure transducer alone. This may suggest that some events identified as hypopneas with the thermistor, were scored as obstructive apneas when using the pressure transducer. The severity of sleep disordered breathing in the patients used for this study varied widely with the RDI ranging from 2 to 120 per hour. None of the patients had a significant number of central apneas (<2 on any study).

Conclusions: While this study is limited due to the small number of patients, it does demonstrate a significant difference in the number of obstructive apneas scored and the RDI obtained, depending on whether thermistors alone are used as an indirect measure of airflow or whether a combination of a thermistor and a nasal cannula/pressure transducer is used. The combination of both methods of airflow detection appears to be more sensitive in detecting apneas. Our data also lead us to suspect that there may be times when what is scored as a hypopnea using a thermistor, may appear as an obstructive apnea when using the pressure transducer. Further study of these differences using a larger number of patients is planned.

726.R

Reduction of Artifacts in PSG Data by Independent Component Analysis.

Stewart C, Pal I
Bio-logic Systems Corp.

Introduction: Artifacts due to mixing of potential fields from multiple sources are a common annoyance in PSG recordings. Potentials from other sources, e.g. eye movements, eye blinks, EKG, appear on EEG channels and obscure waveforms from neural generators. Here we address the issue how Independent Component Analysis (ICA) can be used to reduce artifacts. ICA [1] is an established method to construct statistically independent components from a set of signals. Statistical independence in ICA is not limited to first order covariance, as is the case with Principle Component Analysis. We applied a correction strategy based on ICA to a representative sample of PSG data, and calculated a measure of its effectiveness. Although the method is applicable to many artifacts, the data presented here is focused on removal of eye movement artifacts from EEG channels.

Methods: 15 full night PSG records were analyzed. The standard patient calibration protocol consisted of 60-120 seconds of eye movements, eye blinks, closed eye alpha EEG activity, chewing, and various breathing patterns. The pre-sleep calibration section was used to estimate the ICA mixing matrix. 15 channels (9 EEG, 2 EOG, submental EMG, EKG, airflow, and respiratory effort) were input to ICA. The mixing matrix was fit to the PSG signals by maximizing the statistical independence of the resulting components. Each ICA component was classified according to its apparent origin (neural, ocular, EKG, muscle, respiratory). The EEG and EOG channels were reconstructed using only the appropriate components. Four ICA components were identified as eye movement and blink components by having the largest contribution (sum of squared elements in the mixing matrix) from the EEG channels. EOG was reconstructed from these 4 ocular components. Artifact corrected EEG was reconstructed from the components of neural origin. The same ICA matrix was used to reconstruct EEG and eye components on the rest of each record, including post-sleep patient calibration. To assess the effectiveness of artifact removal, correlation coefficients were calculated between EEG and EOG channels. When EOG contamination of EEG is removed correlation EEG to EOG is lower. Average correlation was calculated for each record separately for pre and post sleep calibration and each sleep stage.
Results: The Figure shows an example of calibration data before and after ICA correction, corresponding to horizontal eye movements (45-50 s) and eye blinks (52-55 s). Most, but not all, eye activity is removed from the EEG channels. The Table shows the correlation between EEG and EOG signals before and after ICA correction, averaged over all 15 PSG records. Pre and post sleep calibrations show similar drops in correlation after artifact correction, indicating stability of the ICA mixing matrix over the night. During REM and Wake, when eye movements and associated EEG artifacts are most common, there is a bigger drop in correlation after correction than in other stages.

Figure 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>DATA</th>
<th>RAW</th>
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<tr>
<td>Stage Wake</td>
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<td>0.28</td>
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</tr>
<tr>
<td>Stage 1</td>
<td>0.28</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>0.32</td>
<td>0.34</td>
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<tr>
<td>Stage 3</td>
<td>0.28</td>
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<td>Stage 4</td>
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<tr>
<td>Stage REM</td>
<td>0.34</td>
<td>0.16</td>
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<tr>
<td>Post-sleep Calibration</td>
<td>0.36</td>
<td>0.24</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: This study demonstrates the feasibility of ICA based artifact removal for PSG display or for waveform detection algorithms.

References:

Supported by NIH grant 1R43MH61044-01

727.R

Non-Invasive Phenotyping of Sleep in Mice

Ward S,1 Seburn K,2 Galante RJ,1 Pack AI1
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Introduction: One of the barriers to examining whether a mutant mouse has an abnormal sleep phenotype and to high-throughput phenotyping for sleep is the relative complexity of measuring sleep and wakefulness by traditional means, i.e., electroencephalogram, electromyogram, etc. New approaches are needed that utilize technology more suitable for high-throughput screening of sleep phenotypes. These technologies need not be totally accurate, because a second stage screen utilizing EEG, etc. can be employed in those mice detected to be abnormal on the first stage screen.

Methods: One component of such high-throughput technology is likely to be in-depth rest/activity monitoring. We have utilized a new rest/activity system from Columbus Instruments (Opto-Varimex-Minor) that uses three photocell arrays on the X, Y, and Z axes. The photocells in the Z axis are arranged to detect rearing activity and the photocells in the X and Y axes monitor movement in the horizontal plane. All photocells are spaced at one-inch on-center intervals. The instrument provides three counts of activity in fixed epochs that can be short. In our studies we have used 1 minute epochs. These counts are (a) horizontal-total beam breaks in any direction on basic plane of movement; (b) ambulatory-total number of times mouse breaks beams in sequential fashion; and (c) vertical-total number of beam breaks caused by mouse rearing and cutting upper level of beams.

Results: We assessed, using this system, rest/activity of 8 C57BL/6J mice over two sequential days in 12 hr L:D cycles. We examined magnitude of error over all data points (1 minute epochs) in all mice comparing published data about sleep/wakefulness in this strain [1] with calculated durations of sleep/wakefulness where sleep was defined as being less than a particular threshold for one of the counts and wakefulness greater than that threshold. Our analysis showed that ambulatory and vertical counts had less information than the horizontal counts. The optimal threshold to distinguish sleep from wake was a horizontal count/minute of 9. With this threshold we found the following:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Published data (Franken et al, 1999) (Mean±SD)</th>
<th>Calculated from rest/activity (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Wakefulness over 24 Hours (%)</td>
<td>59.4 ± 4.8</td>
<td>57.2 ± 4.1</td>
</tr>
<tr>
<td>Total Wakefulness in Light Period (%)</td>
<td>43.6 ± 3.7</td>
<td>43.4 ± 4.6</td>
</tr>
<tr>
<td>Total Wakefulness in Dark Period (%)</td>
<td>75.3 ± 6.3</td>
<td>71.0 ± 7.0</td>
</tr>
</tbody>
</table>

Conclusions: While this approach seems promising, further studies are needed to validate this in a sample of mice with simultaneous measurement of rest/activity and recording of sleep/wakefulness by EEG/EMG.

References:

Research supported by NIH grants HL-60287 and HL-66611.

728.R

Development of a Sleep Hygiene Scale

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(1) Jacksonville State University, (2) University of Arkansas at Little Rock

Introduction: Sleep hygiene may be conceptualized as practices relating to sleep routine, stimulus-control, health, environmental, and cognitive/affective variables that impact the quality and quantity of sleep. Sleep hygiene is thought to play a role as a mediating variable with regard to the effects of sleep disorders and may be seen as an integral component of treatment. (1) This study describes the construction and empirical validation of the Sleep Hygiene Scale (SHS), a questionnaire intended to provide an assessment of an individual’s current sleep hygiene status.

Methods: Data were collected from 261 college students (132 male, and 129 female) whose ages ranged from 17 to 51 years (mean=22.7, SD=6.3). All subjects denied any diagnosis of sleep disorders. Each subject completed a battery of questionnaires that included the SHS, the Epworth Sleepiness Scale (ESS), the Blake-Gomez Sleep Hygiene Self-
The Sleep Hygiene Scale (SHS) is a self-administered paper and pencil questionnaire containing 33 rationally derived items scored on a 5-point Likert scale. Item scores were summed providing a global assessment of sleep hygiene. Higher scores are indicative of a more adaptive sleep hygiene status. Summing relevant individual sets of items yielded the subscale scores of routine, stimulus-control, health, environmental, and cognitive/affective.

Results: Support for inter-item consistency of the SHS was provided by a Cronbach’s alpha (α) value of 0.73. Split-half reliability analysis resulted in a value of 0.68. Item-total correlation coefficients ranged from 0.12 for question 3 (I exercise) to 0.49 for question 22 (I go to bed feeling stressed). The five subscale scores of the SHS had an overall α of 0.56. The subscale-total correlation coefficients ranged from 0.51 for the routine subscale to 0.72 for the health subscale. As expected, a significant negative correlation (r = -0.58, p < .05) was observed between the SHS and the SHST, an instrument that reflects adaptive sleep hygiene status by a lower score. A significant negative correlation (r = -0.26, p < .05) was found between the SHS and the ESS (see figure 1). A significant negative correlation (r = -0.42, p < .05) was found for the SHS and the PSQI (see figure 2).

Figure 1

![Figure 1](image)

Figure 2

![Figure 2](image)

Conclusions: Adaptive sleep hygiene levels, as measured by the SHS, were found to be associated with lower levels of general daytime sleepiness and higher levels of sleep quality. The five major components of the SHS, as well as the 33 individual items, were demonstrated to have internal consistency. These results are encouraging in that such a complex multi-factorial construct as sleep hygiene may be measured with a reasonable degree of reliability and validity. Future research will be directed toward improving the psychometric qualities of the instrument as well as developing clinically useful subscales.

References:

Validation of Bispectral Analysis for the Detection of Sleep

Morgan JD, Greenwald S, Schmedlen L, Sack RL
(1) Oregon Health Sciences University, Portland OR, (2) Aspect Medical Systems, Inc., Newton, MA

Introduction: There is a need for less complicated methods of recording human sleep. The BIS Monitor® (Aspect Medical Systems, Inc., Newton, MA) is a small, portable EEG/EMG recording apparatus, with easily applied electrodes, developed for use in monitoring the depth of general anesthesia. It processes electrical signals using a Fourier transformation-based bispectral index (BIS) that generates a value between 1 and 100 to estimate a patient’s level of consciousness. Pilot studies suggest it has potential to be a sleep-detecting device (1,2); however, a detailed comparison to polysomography (PSG) has not previously been done. Our goal in this study was to test the accuracy of the BIS by comparing it to standard PSG.

Methods: We concurrently monitored overnight sleep using BIS and PSG in seven healthy volunteers (ages 22 to 35) who were not taking medications. PSG recordings were hand-scored using conventional criteria. The recordings were carefully synchronized so that the data could be compared epoch-by-epoch for the determination of sensitivity and specificity. The BIS recording was scored as “sleep” if the BIS score < 80. Next, the mean and standard deviations of the BIS score were calculated for each sleep stage (see Figure). In addition, sleep efficiency (the number of epochs of detected sleep divided by time in bed) was calculated for each subject using BIS and PSG.

Results: The epoch-by-epoch analysis of BIS recording yielded a 94% sensitivity and 64% specificity (See Table). The BIS score was significantly different from wake in all stages of sleep except for Stage 1 (see Figure). The average sleep efficiency was 86.5% from PSG data and 88.7% from the BIS; the Pearson correlation for these measurements was 0.96.

Figure 1

![Figure 1](image)

Conclusions: The BIS score is a highly processed signal that is influenced by both EEG and EMG signals. It is a very convenient and relatively inexpensive device that could be used in an ambulatory setting. Because of the signal processing method employed, BIS monitoring is not able to utilize specific waveforms (e.g., K-complexes, sleep spindles, delta waves, etc.); on the other hand, it provides an evaluation of sleep that is free of inter-scorer variability. It is highly sensitive for the detection of sleep, and provides a numerical estimate of sleep stage. The over-
all estimate of sleep efficiency corresponded closely to PSG. Future studies with the BIS include its potential use in MSLT examinations and as a primary care screening tool for sleep abnormalities.

References:

Supported by the Short-Term Medical Student Research Program, Oregon Health Sciences University (NIH grant PHS type 5, Activity T35, HLO 7890-03)

730.R

Comparison of the New Masimo SET V3 Technology with a Conventional Pulse Oximeter During Polysomnography

Whitman RA, Garrison ME
University of Kansas Medical Center

Introduction: The aim of this study was to compare the saturation profile of patients undergoing polysomnography using the new Masimo SET V3 technology with the Nellcor N-200, a conventional pulse oximeter commonly used in the sleep laboratory for assessing arterial oxygen saturation. Masimo SET technology has been shown to provide greater accuracy in situations involving low perfusion and motion artifact (1,2).

Methods: In thirteen patients referred to the sleep disorders laboratory for evaluation of possible sleep-disordered breathing, a Quartz Medical Q-400 with Masimo SET V3 technology (Q) and two Nellcor N-200’s were applied to the patient concurrently. One N-200 was placed in the Mode 1 operating configuration (N1), which has a stated data averaging time of 5 to 7 seconds. The other N-200 was placed in the Mode 2 configuration (N2), which has a stated data averaging time of 2 to 3 seconds and is the recommended operating mode for polysomnography (operator’s manual). The Q-400 was configured in the 2-second data averaging mode. The N1 oximeter was placed on the index finger of one hand and the N2 and Q were placed randomly on the ring and index finger of the opposite hand. All three oximeters were turned on simultaneously at the beginning of the study and turned off simultaneously at termination of the study. The data from all three oximeters were downloaded into PROFOX oximetry analysis software (version PFWS 08/99). Three saturation indices (mean, low and number of desaturations > 4%) were extracted from the report and analyzed.

Results: There were no differences in mean saturation between Q, N2 and N1 (95.8 ± 1.5, 96.2 ± 1.4, 96.4 ± 1.6 respectively) with no difference greater than one percent among the three oximeters for individual patients. The lowest saturations recorded were 68%, 13%, and 44% for Q, N2, and N1 respectively. Individual patient differences in the lowest recorded saturation for Q versus N2 ranged from +9% (when Q was lowest) to -56% (when N2 was lowest). Q was lower than N2 in 8 of a total of 13 patients with a mean difference of 5%. When N2 was lower, the mean difference was 30%. When comparing Q to N1, the differences ranged from +6% to -24%. Q being lower in 9 patients with a mean difference of 8% and a mean difference of 10% when N1 was lower. There was a large difference in the number of desaturations greater than 4% between Q and both N2 and N1. The mean number of desaturations were 78 ± 102, 51 ± 93, and 51 ± 92 for Q, N2, and N1 respectively.

Conclusions: In this population of patients referred for polysomnogra-ph, data from the Quartz Medical Q-400 using a 2-second data averaging mode was associated with a greater number of significant desaturations than the Nellcor N-200 in either mode 1 or mode 2 operation while overall mean saturations were the same. This finding suggests that Masimo SET V3 technology has higher signal fidelity relative to actual physiologic changes in saturation than conventional oximetry technology, which should lead to improved diagnostic capabilities.

References:

731.R

Attenuation of the First Night Effect

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Introduction: The disruptions in sleep patterns which characterize the first night effect have led many researchers to disregard the first night of data during a sleep study; a practice which is costly in both time and resources for the researcher and the subject. A few studies have explored the effects of ambulatory monitoring in the home or creating a hotel-like environment in the sleep laboratory on the first night of sleep. None have studied the effects of creating, in the sleep laboratory, a home-like environment which also reflects subject’s preferences and routines on adaptation to the laboratory setting. The purpose of this study was to determine the effects of introducing familiar objects and routines into a home-like setting in the sleep laboratory on the first night of sleep in a group of elderly subjects.

Methods: Twelve female subjects, mean age 70.5 years, slept for two consecutive nights in a sleep laboratory specifically designed with a living area, sleeping area, kitchen, and full bath. Subjects brought personal items into the laboratory environment which was modified to meet their needs and they maintained normal evening and bedtime routines which they usually followed in their home environments. All night polysomnographic recordings were obtained on both nights and two measures of subjective sleep quality were obtained on both mornings following final awakening. Summary statistics and Student’s t-tests were used to analyze the data.

Results: In evaluating measures of sleep continuity, the mean number of awakenings and duration of wake were significantly greater on Night 1 when compared to Night 2. Although total sleep time and sleep efficiency increased on Night 2, the difference was not statistically significant. Latency to Stage 1 showed no significant difference between the two nights. Latency to Stage REM was significantly longer on Night 1. In analyzing measures of sleep architecture, there were no statistically significant differences in the duration of Stage 1 and Stage 2 sleep between the two nights. There was a significant increase in slow wave sleep and REM sleep on Night 2. There were no significant differences in self-reported sleep quality.

Conclusions: The data suggest that subject-specific modifications of the sleep laboratory environment in this study decreased, but did not completely eliminate, the sleep continuity and sleep architecture disruptions that are characteristic of the first night effect.

Research partially supported by the American Association of University Women
Assessment of a Simulated Driving Task for Sleep Research

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Introduction: Sleep scientists commonly use neurobehavioral tasks to examine performance deficits induced by sleep loss. Simulated driving tasks are “face valid” performance tasks that require some of the constituent skills necessary for actual driving. As with any neurobehavioral task, however, the importance of establishing the psychometric properties of such instruments before incorporating them into experimental protocols cannot be overestimated. Therefore, as our group begins studies of simulated driving in adolescents, we first sought to determine the number of practice trials necessary to learn a driving task (York Computer Technologies, Kingston, Ontario, Canada).

Methods: Volunteers were screened for evidence of major medical disorders, sleep disorders, psychoactive medication use, and extreme morningness or eveningness. Seven adolescents (mean age=13.8 years, sd=1.6, 2 girls) and two adults (ages 20.3 and 24.8 years, both females) maintained an 8-hour sleep schedule for two nights before participating, and refrained from caffeine, alcohol, and illicit drugs for at least 24 hours. Testing occurred in a 3-hour block between 0900 and 1800 hours on a driving simulator, consisting of a personal computer, 15” monitor, and peripheral steering wheel, accelerator and brake accessories. The task appears as a two-lane highway during the daytime, with lane markings, signs, and occasionally, other simulated vehicles. Participants drove nine 10-minute sessions with 5-minute breaks between sessions. One participant drove eight sessions. Participants were instructed to maintain the simulated car’s position in the middle of the right-hand lane, to obey speed signs, and to keep both hands on the steering wheel, while operating the pedals with the right foot only. During breaks, participants could stretch, go to the washroom, or have a snack or non-caffeinated beverage. Relevant measures of the driving task included mean and standard deviation of lane position (tracking and tracking variability), mean speed deviation from posted speed signs and speed variability, and number of off-road incidents.

Results: Repeated measures ANOVA with eight participants indicated that performance on four driving measures remained constant throughout nine trials, while tracking variability increased significantly [ F(8,56)=3.59, p<.05]. This small decline in performance was notable only after trial five. Slopes for each driving measure were calculated for all nine participants separately to examine individual differences in practice that might be obscured by group data. Table 1 shows that mean slopes for four measures—mean tracking, tracking variability, speed deviation, and speed variability—were very close to zero. The higher mean slope for off-road incidents was due primarily to four participants whose driving was more erratic during trials five to nine.

Table 1

<table>
<thead>
<tr>
<th>Driving Measure</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean tracking</td>
<td>-.006</td>
<td>.036</td>
<td>-.05</td>
</tr>
<tr>
<td>Tracking variability</td>
<td>.037</td>
<td>.050</td>
<td>-.02</td>
</tr>
<tr>
<td>Speed deviation</td>
<td>.009</td>
<td>.157</td>
<td>-.25</td>
</tr>
<tr>
<td>Speed variability</td>
<td>.029</td>
<td>.059</td>
<td>-.03</td>
</tr>
<tr>
<td>Off-road incidents</td>
<td>.184</td>
<td>.238</td>
<td>.00</td>
</tr>
</tbody>
</table>

Conclusions: Even for nondrivers, practice effects on the driving simulator in healthy, well-rested individuals are negligible, and the task appears to be rapidly “overlearned.” Visual inspection of individual data, corroborated by participants’ self-reports, indicates both rapid acquisition of the task and appearance of performance-affecting fatigue and boredom with repeated testing. Taken together, these findings indicate that little pre-study practice is necessary on this neurobehavioral task and that investigators may consider limiting session length to 60 minutes or less to avoid fatigue and boredom with the task.

This study was supported in part by MH101358.

Wrist Actigraphy as a Method of Sleep Detection Parkinson’s Disease

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Introduction: Last year we reported on preliminary actigraphic and polysomnographic (PSG) results for six patients from a multicenter trial evaluating the efficacy of melatonin to treat sleep disorders in persons with Parkinson’s disease (PD). 1 This abstract updates our findings. Since the severity of motor symptoms in PD (i.e. bradykinesia, rigidity and tremor) are often more prominent on one side of the body versus the other, in addition to simply comparing actigraphy to PSG, we investigated whether differences between the more affected side and the less affected side could influence the agreement between actigraphy and PSG for total sleep time (TST).

Methods: A clinician familiar with the assessment and treatment of PD evaluated patients with sleep complaints. Less and more affected sides were determined using the motor portion of the United Parkinson Disease Rating Scale (UPDRS). Data were collected overnight using the MiniMitter Actiwatch® (AW6 series) employing a digital integration method and Sandman software for PSG. An experienced certified sleep technician, utilizing a 12-channel montage, performed and scored PSG using the standard R&K criteria. The sleep technician was blind to actigraphy scored sleep. Both Actiwitches and PSG equipment were synchronized prior to data collection to maximize epoch-by-epoch analyses. PSG and actigraphically determined TST were compared using a preset “high sensitivity” setting available in the Actiware-Sleep® program.

Results: Data analysis of actigraphy and PSG in 16 subjects (mean age = 63 years, range = 56-72) revealed an agreement rate of .92 and Spearman’s correlation coefficient of .78 (p<.003) for TST for the less affected side. For the more affected wrist, the actigraphy and PSG agreement rate was .87 with a Spearman’s correlation coefficient of .78 (p<.003) for TST (Figure 1).

Figure 1
Conclusions: Our data continue to indicate that actigraphy is a reasonable method of sleep detection in the PD population, especially when a “high sensitivity” algorithm is applied. These findings also suggest that the severity of motor symptoms may not significantly affect the agreement between PSG and actigraphy. As we collect data on a larger number of PD patients, we will continue to investigate the possible role of movement disorders in actigraphic analyses.

References:

Research supported by NIH NR04774

734.R

Evaluation of the French Version of the Epworth Sleepiness Scale in a Group of 274 Subjects With Hypersomnia

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Introduction: The Epworth sleepiness scale proposed by Johns 1991 to assess sleepiness in ordinary life of subjects has been extensively used in clinical and epidemiological surveys. In the first studies, the ESS was found correlated to the multiple sleep latency tests (MSLT) in patients with hypersomnia. More recently, some studies (Chervin and Aldrich 1991) did not find any correlation between ESS and MSLT in a group of apneics. The ESS is an English written scale which has not be validated in French. We proposed to evaluate the French version of the ESS proposed by M. Billiard to the MSLT in a group of patients addressed for hypersomnia to our laboratory.

Methods: We made a retrospective study on 274 subjects referred during a 3 years period to our laboratory with a diagnosis of hypersomnia. These patients had a full night polysomnography and a MSLT, then they completed an ESS the day of the MSLT. In the group, 122 subjects had sleep apnea, 11 Upper Airway Resistance Syndrome (UARS), 12 periodic leg Movement Disorder (PLMD), 38 narcolepsy, 31 idiopathic hypersomnia, 34 hypersomnia associated with a psychiatric disease and 26 were sleep deprived with poor sleep hygiene. The statistics correlation was made by Pearson correlation in the total group and by Spearman in the different subgroups.

Results: ESS was significantly correlated to the MSLT in the total group (p < 0.0001), in the UARS and idiopathic hypersomnia patients. However, there was no correlation found for narcoleptics, PLMD and other hypersomniacs. In the group of patients with sleep apnea, we found a correlation between the RDI and the ESS (Pearson, p < 0.0057). The most significant questions correlated with the MSLT was item 7.

Conclusions: ESS is very useful to screen sleepiness in the general population. The French version of the ESS appears to be a good method to assess sleepiness in a large group of hypersomniacs. However, the correlation between ESS and MSLT is only significant in 3 groups: apnea, UARS and idiopathic hypersomnia. The sensibility and the specificity of the French version of the ESS to discriminate hypersomniacs with an average sleep latency ≤7 minutes are low: respectively 59% and 70%. Thus ESS may help the clinician to understand better the daily impact of the sleepiness, but may not be an accurate method to diagnose hypersomniacs.

Conclusions: The ESS is commonly presented by medical, corporate, and information service groups as a tool with which web surfers can assess their own sleepiness. Interpretations are provided that are consist—

References:

735.S

ESS.com

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Introduction: The Epworth Sleepiness Scale (ESS) is described by its originator as a subjective measure of sleep propensity [1], but whether the ESS provides useful clinical information about underlying objective sleepiness has been debated [2,3]. Virtually no data to link health outcomes with ESS scores have been published. However, the simplicity and low cost of the ESS appear to have endeared it to both medical and corporate groups that seek to provide sleep-related information on the internet. We used multiple web-based search engines to identify internet sites that offer the ESS to the public. The goal was to assess the frequency, sponsorship, and nature of ESS use on the web.

Methods: In November, 2000, we used the http://www.metacrawler.com/ website to find English language websites identified by any of several popular search engines— including AltaVista, Excite, Infoseek, WebCrawler, About, DirectHit, Google, and Internet Keyword — to contain the phrase “Epworth Sleepiness Scale.” Sites found to contain the eight ESS questions were reviewed to determine the type of sponsor and to assess information given on interpretation of ESS scores.

Results: A total of 91 sites were identified and reviewed. The table summarizes the numbers of sites (and percent within each sponsorship category) that provided the information listed in the first column. Acad = Academic Medical; Priv = Private Medical; Corp = Corporate; Info = Web Information Service.

Table 1

<table>
<thead>
<tr>
<th>Information Listed:</th>
<th>Sponsor:</th>
<th>Acad</th>
<th>Priv</th>
<th>Corp</th>
<th>Info</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS question-items</td>
<td>11</td>
<td>134</td>
<td>21</td>
<td>25</td>
<td>25</td>
<td>91</td>
</tr>
<tr>
<td>Interpretation given</td>
<td>10 (91)</td>
<td>19 (56)</td>
<td>19 (90)</td>
<td>19 (76)</td>
<td>67 (74)</td>
<td></td>
</tr>
<tr>
<td>ESS &gt; 9 - 11 ments clinician consult</td>
<td>5 (45)</td>
<td>10 (29)</td>
<td>11 (52)</td>
<td>11 (44)</td>
<td>37 (41)</td>
<td></td>
</tr>
<tr>
<td>Further subdivision of results</td>
<td>5 (45)</td>
<td>9 (26)</td>
<td>7 (33)</td>
<td>3 (12)</td>
<td>24 (26)</td>
<td></td>
</tr>
<tr>
<td>Severe vs. excessive sleepiness</td>
<td>0 (0)</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Results for apneics or narcoleptics</td>
<td>1 (9)</td>
<td>2 (5.9)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>4 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Insufficient sleep is a common cause of sleepiness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Depression is most common cause of chronic sleepiness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The ESS is commonly presented by medical, corporate, and information service groups as a tool with which web surfers can assess their own sleepiness. Interpretations are provided that are consistent—
tent with some, but not all, medical research. The ESS is sometimes used to distinguish multiple sleepiness categories for which no medical validation has been published. Comparisons of personal ESS results to those of sleep apneics and narcoleptics, without much more explanation, may be deceptive because other more prevalent reasons for excessive daytime sleepiness are not mentioned. Frequently proffered advice to consult physicians about highly common ESS results is likely to help some readers, but outcomes of population screening with the ESS have not been studied. All sites seem to ignore the fact that ESS scores address subjective sleep propensity and show either small or negligible associations with objective measures of sleepiness [1-3]. We conclude that current use of the ESS on the web often may be misleading.

References:

Supported by a Sleep Academic Award from the NIHHLBI (K07-HL03645)

736.S

Sleep Education in High-school Students: An Italian Experience

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University of Rome "La Sapienza"

Introduction: Several studies have pointed out the high prevalence of sleep problems and irregular sleep habits in adolescence with negative impact on daytime functioning and increased vulnerability to injuries. The best approach to prevent these problems is to improve teenagers’ sleep patterns, through informing them about the risk of unhealthy sleep habits. Recent studies pointed out the importance of educational programs in increasing knowledge of healthy behaviors in teenagers. The aim of this pilot study was to evaluate the impact on Italian teenagers’ knowledge of a sleep educational program, known as “Crash in bed instead…” already tested in the US teen population. The aims of this educational program were to increase knowledge of sleep, sleepiness and the risk of drowsy driving in adolescent population.

Methods: A sample of 225 students (124 females and 101 males), aged 17-18.7, attending one high school of Rome was enrolled in this study. In order to assess their sleep patterns all students completed the Sleep Habit Survey (Carskadon, 1992). Furthermore, at the beginning of the course, students were given a pre-test consisting of 10 multiple-choice questions about sleep and sleepiness to evaluate the baseline knowledge, then they participated in a two-hours interactive course administered by a sleep professional. At the conclusion of the course, a post-test measured the gain in knowledge. Three months later we estimated retention of information by another post-test. Improvement was measured by the difference between pretest and post-test. To assess improvement in knowledge after the course, group test scores were analyzed using a repeated measures one way ANOVA.

Results: Consistent with previous studies, we found difficulties in falling asleep and night-wakings in 10.6% of subjects, a sleep schedule irregularity in 34% of students and occurrence of one or more injuries in the last six months in 18.6% of subjects. No marked sex differences were identified. We found significant differences among mean scores, based on the number of correct answers to questions, of baseline value (4.2), post-test value (8.6) and test value 3 months later (6.6). (F (2,18=297.82; p<.001). Post-hoc comparisons of means showed significant differences among all the three tests. Post-test scores were significantly higher than pre-test scores by group, demonstrating retention of the most important information about sleep presented in the course. Students showed an average 50% gain in the percentage of correct answers following the course and good long-term retention of information.

Conclusions: Our results showed students’ positive attitude toward school sleep education courses, low baseline knowledge and good ability to learn. A two hours course describing sleep, sleepiness and the risk of poor sleep on daytime functioning can improve the knowledge level. The results of our pilot study pointed out that sleep programs for secondary students are recommended. However, further studies are needed to better verify the long-term impact of a better sleep knowledge on adolescent life-style.

References:
(1) Carskadon MC et al: Reliability of six-scales in a sleep questionnaire for adolescents, Sleep Res. 1992, 421
(2) James SL et al Community based education of youth and the dangers of driving drowsy. Sleep (21) 1998, 383

737.S

A NASA Education and Training Module on Alertness Management: A Survey of Implementation and Application

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Introduction: In 1993, the NASA Ames Fatigue Countermeasures Program developed an Education and Training Module to transfer scientific knowledge to the operational community. The Program has held 2-day “train the trainer” workshops at NASA Ames as a mechanism to distribute the Module [1]. From 1993 through 2000, 31 workshops have been held with 660 participants representing 234 organizations. A questionnaire was developed to assess the implementation of the educational materials at these organizations.

Methods: A 16-item questionnaire was developed that inquired about the number of classes held based on the Module, number of participants, the forums for these presentations, ratings of the materials, and outcomes from the educational efforts. A total of 512 surveys were mailed to former workshop participants, representing more than 200 organizations.

Results: A total of 242 surveys were returned from workshop participants (47% response rate). The respondents reported having presented the Module in a total of 6,339 classes with almost 117,000 participants. At one organization, 220 presentations had been made to over 21,000 attendees. In regards to how the training materials were used, safety (21%), recurrent (11%), new hire training (11%), and mandatory classes (11%) were the most commonly cited reasons. Flight crewmembers (27%) were the group most likely to receive the training with management (17%) personnel also mentioned. These training courses were generally given on an annual basis (28%), weekly by some (15%), while about 39% responded with “other.” About 62% responded that activities were current, 15% indicated no, and 23% did not respond to the question. For those that were no longer active, classes were offered over an average of about 1 year, ranging from 1 day to 4.4 years, with an average of 31.7 classes given during those timeframes. Most commonly, respondents reported using a modified version of the Module (41%) and
30% reported using a company-developed module based on the NASA materials. About 16% of the respondents report using the Module “as is” and 13% respond with “other.” About three-fourths of the respondents (76%) report having trained others to present the Module, with an average of 5.7 others trained (max=40). Rated on a scale from 1 to 5 where 5 = “extremely,” the materials received an average rating of 4.4 for “useful,” 4.2 for “clear,” and 4.1 for “complete.” Class participants rated the materials an average of 4.0 for “useful,” 3.9 for “clear,” and 3.9 for “complete,” though only 42% of the respondents indicated that class evaluations were done. More than half of the respondents (58%) reported that the Module and materials have provided a basis for change at their organization.

Conclusions: The survey results indicated that a large population of the aviation community received educational materials based on the NASA Module provided primarily through about 6,300 classes. The materials were used in a variety of forums over several years. Generally, ratings by the presenters and participants were quite favorable for usefulness. About 140 respondents reported that the educational materials were the basis for positive changes related to fatigue at their organizations. Scientifically accurate and practical educational information can establish a critical, objective foundation upon which to address a broad range of fatigue-related issues.

References:

738.S

On the Association of Sleep Scheduling and Sleep Quality: An Actometric Pilot Study


Introduction: Although standard rules for good sleep hygiene often include certain sleep schedules, only little data exists on the relationship between sleep schedules and measures of sleep quality. Experimental sleep deprivation and extension as well as phase shifts forward and backward have been shown to affect sleep structure, day-time performance and sleep quality. Sleep scheduling varies substantially within the general population, e.g. between long and short sleepers or between morning and evening types. Evening types forced to live against the rhythm of their internal clock have lower sleep efficiency than morning or evening types with self-chosen sleep schedules. Thus the question arises: Is general advice for an ideal sleep scheduling adequate?

Methods: 40 healthy subjects (22 female, 18 male; mean age=60±20 yrs.; range=22-86 yrs.) remained in their natural environment and exercised their regular daily activities, but were asked to exercise good sleep hygiene. Levels of sleep scheduling, such as bedtime, sleep duration and wake up-time were estimated by means of computer analysis of actometry-data of 14 consecutive days. Subjective sleep quality was measured every morning (SSA - Saletu et al., 1987). A sleep quality index (SQI) consisting of three 4-folded items (“Did you sleep well?”; “Was your sleep deep?”; “Was your sleep relaxing and refreshing?”) with a high internal consistency (cronbach’s alpha=.87) was derived from the questionnaire. Intra-subject correlations (Pearson) between sleep scheduling measures and the SQI were computed for every subject and then explored for potential patterns and determinants of inter-subject differences.

Results: Intra-subject correlations between sleep scheduling measures and sleep quality varied substantially between subjects (bedtime-SD=0.32, sleep-duration-SD=0.35, wake up-time-SD=0.30). They all correlated significantly with the intra-subject means of bedtime and wake up-time and in tendency with the intra-subject mean of sleep duration. They built a pattern of subjects with an earlier and shorter sleep period experiencing their sleep better the earlier and shorter they sleep and conversely subjects with a later and longer sleep period judging their sleep quality the better the later and longer they sleep (Figure 1). Linear regression models including the intra-subject means of bedtime, sleep duration, and wake up-time as predictors turned out to explain a significant part of variance of the intra-subject correlations (SQI*bedtime R²=.23/p<.05, SQI*sleep duration R²=.37/p<.001, SQI*wake up-time R²=.28/p<.05).

Figure 1

Conclusions: Results suggest that individuals with extreme sleep scheduling see them sleep better, when they even surpass their individual mean sleep times. In individuals whose mean sleep times correspond to the group means, sleep scheduling and sleep quality are unrelated. These findings show the necessity to take notice of individual differences by giving advice for a good sleep hygiene. This pattern might furtherly indicate that individuals forced to live in disagreement with their individual chronotype may benefit in terms of improved live quality and physical health by flexible work hours or chronobiotic therapy (e.g. light, melatonin). It seems promising to develop a Sleep Scheduling Index (SSI) which predicts sleep quality by combining actual sleep scheduling with individual markers like phase position and habitual sleep duration in further research. So optimal sleep hygiene could be determined in the individual.

Research supported by European Commision BMH4-CT97-2040 (DG12-SSMI)

739.S

Psychiatric Resident Exposure to Sleep Medicine: A Survey of Psychiatric Program Directors

Krahn LE, Hansen MR, Tinsley JA
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Introduction: The landmark contributions to sleep medicine by psychiatrists include the recognition of REM sleep, sleep-onset REM episodes in narcolepsy, the role of sleep symptoms in psychiatric disorders and the effects of psychiatric medications upon sleep. Psychiatric textbooks contain more pages devoted to sleep content than others including neurology or internal medicine (1). Psychiatric candidates obtaining American Board of Sleep Medicine certification have declined from 10 in 1991 to 3 in 1998. This study was designed to determine the exposure of psychiatric residents to sleep medicine through didactic lectures, required or elective rotations, and access to psychiatrists involved in sleep medicine, either clinically or in research. The questionnaire also asked program directors their opinion about the future career prospects of psychiatry residents in the sleep field.
Methods: Methods/Results: A short survey was designed to assess several relevant issues. Responses were received from 117 (66%) of the 177 general psychiatry residency programs in the United States listed in the Fellowship and Residency Electronic Interactive Database (FREIDA). Five responded but declined to provide information. The sleep disorders centers affiliated with the psychiatry residencies were operated by a variety of departments: 39 pulmonary (36%); 33 neurology (28%); 23 psychiatry (20%); 10 interdepartmental (9%); 1 psychology (<1%) and 1 internal medicine (<1%). A sleep medicine rotation was available as an elective at 51 programs (44%) and a requirement at only one. Thirteen programs (11%) used to offer a sleep rotation but no longer do so. One program plans to add a sleep elective soon. The majority of programs had didactics with topics pertinent to sleep (82%) with a mean of 5 hours and a range of 0-18 hours. Table 1 shows the breakdown of content areas. Fifty-nine programs (50%) did not have a single psychiatric faculty member who was board certified by the ABSM, ABPN with added qualifications in clinical neurophysiology, active in clinical sleep medicine or engaged in sleep research. Nevertheless, 86 (73%) program directors either definitely or somewhat agreed that sleep medicine was a “viable career option for graduating psychiatric residents”. Although program directors did not always know how many graduates in the past 5 years became involved with the sleep field, the known information is in table 2.

Results: Results included in the Methods section.

Table 1

<table>
<thead>
<tr>
<th>Didactic Topics (PGY I-IV) Potentially Relevant to Sleep Medicine</th>
<th>Offered</th>
<th>Not Offered or Not Answered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep physiology</td>
<td>86 (74%)</td>
<td>31 (26%)</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>96 (82%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Relationship of sleep &amp; psychiatric disorders</td>
<td>87 (74%)</td>
<td>30 (26%)</td>
</tr>
<tr>
<td>Hypnotic pharmacology</td>
<td>85 (73%)</td>
<td>32 (27%)</td>
</tr>
<tr>
<td>Stimulant pharmacology</td>
<td>80 (68%)</td>
<td>37 (32%)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>45 (38%)</td>
<td>72 (62%)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Number of Programs with</th>
<th>Faculty involved in sleep</th>
<th>Graduates involved in sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSM certified</td>
<td>12 (10%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>ABPN certified – CNP added qualification</td>
<td>9 (8%)</td>
<td>--</td>
</tr>
<tr>
<td>Clinical (includes PSG interpretation)</td>
<td>16 (14%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Research</td>
<td>16 (14%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Completed sleep fellowship</td>
<td>--</td>
<td>7 (6%)</td>
</tr>
</tbody>
</table>

Conclusions: Activity in sleep medicine is decreasing among psychiatrists likely for multiple reasons, including few mentors, fewer sleep electives for psychiatry residents, and within the sleep community more emphasis on sleep-related breathing disorders rather than neuropsychiatric conditions. Despite the program directors’ enthusiasm for psychiatric careers in sleep, graduating residents are unlikely to pursue this path without exposure during training. Psychiatry will increasingly lose its critical mass in the sleep field unless more residents are encouraged to pursue sleep electives and eventual fellowship training.

References:
(2) 2. American Board of Sleep Medicine (personal communication)

The costs of this study were supported by the discretionary funds of the Department of Psychiatry and Psychology, Mayo Clinic and Foundation, Rochester MN

740.S

Confirmation of a High Prevalence of Restless Legs Syndrome in a Primary Care Population

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(1) Stanford University Center of Excellence for Sleep Disorders, Stanford, California, (2) Johns Hopkins University, Baltimore, Maryland, (3) Moscow Clinic, Moscow, Idaho

Introduction: The Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness of sleep disorders and to determine their prevalence within a primary care practice in Moscow, Idaho. Data gathered by our group documented that 29.3% (368 out of 1,254) of the patients within the Moscow Clinic population had symptoms of Restless Legs Syndrome (RLS) (1,2). These “preliminary RLS diagnoses” were based on only a few RLS-specific questions. To substantiate the diagnoses for this group of identified patients, we implemented our RLS Project in 1999.

Methods: To further substantiate this high prevalence of RLS (29.3%) observed in our prior studies (1,2), we decided to focus our questions primarily on RLS and study the Moscow Clinic patients for another year. The three participating physicians were trained by an expert to diagnose and treat RLS. Each patient seen at the clinic was asked to complete the ten question RLSQ, a validated diagnostic questionnaire for RLS. After scoring the questionnaire as either positive or negative, all positive patients and a randomly selected number of patients negative for RLS were asked to further participate by completing three RLS questionnaires, five general sleep questionnaires, and a sleep log for one week. Additionally, these patients were subjected to a structured diagnostic interview for RLS performed by their primary care physician, who was blinded to the questionnaire data. Finally, an RLS expert, independently and blinded to the RLSQ data, reviewed the enrolled patients’ medical charts to make a diagnosis of RLS based on the charted information.

Results: After ten months of data collection, 1690/1866 (90.6%) of the patients agreed to complete the RLSQ. Of this population, 417/1690 (24.7%) were positive for RLS. Two hundred and eighteen RLS positive patients and one hundred twenty-three RLS negative patients have agreed to participate further. Currently, 148 patients have complete information (88 positive and 60 negative). An RLS expert has reviewed 93 of the completed charts. A comparison of the RLSQ, the primary care physicians (PCP), and the RLS expert are displayed in the table below.

Table 1

<table>
<thead>
<tr>
<th>RLSQ RLS +</th>
<th>RLSQ RLS –</th>
<th>PCP: RLS +</th>
<th>PCP: RLS –</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS Expert: RLS +</td>
<td>51</td>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>RLS Expert: RLS –</td>
<td>9</td>
<td>29</td>
<td>6</td>
</tr>
</tbody>
</table>
Conclusions: Our results indicate excellent sensitivity and specificity for the RLSQ. For the expert vs. the RLSQ, the sensitivity was 92.7% and the specificity was 76.3%. The majority of the disagreement between the RLSQ and the RLS expert occurred when the questionnaire found the patient to be positive for RLS and the expert felt the patient should be negative for RLS. These patients may either have mild leg symptoms that look like RLS except for unusual features or may have a different diagnosis, such as leg cramps. The sensitivity for the expert vs. the primary care physician was 92.7% and the specificity was 84.2%. The project succeeded in developing the necessary tools for primary care physicians to diagnose the Restless Legs Syndrome. Our results also confirmed that in this somewhat isolated, primarily northern European descent population there is a high prevalence of RLS, about twice that observed in most other populations studied. This may represent a higher prevalence in a primary care population, a founder effect for the genetic component of RLS, or some environmental factor in this area. Determining the basis for this prevalence may provide some indication of the genetic and environmental factors contributing to RLS.

References:

Research supported by The Restless Legs Syndrome Foundation through a grant from Pharmacia Corporation

741.S

The Effect of Pre-Study CPAP Education on Split-Night Sleep Study Outcome

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Introduction: Polysomnograms are commonly conducted in a “split-night” format, in which respiratory pattern is assessed during a 2-3 hour baseline segment followed by CPAP titration (1). To optimize the success of such studies, many laboratories invite patients to a pre-study educational session for teaching about sleep apnea, familiarization with the study environment, and a brief trial with nasal CPAP (2). Such sessions consume time and add cost to the study, but may improve study success rates. To better assess this, we are conducting a retrospective analysis of split-night polysomnograms performed with and without a pre-study educational session.

Methods: Retrospective studySleep laboratory at Sleep HealthCenters, National Jewish Medical and Research CenterFifty-two patients received split-night polysomnograms; twenty-seven patients received pre-study education and twenty-five had no pre-study education. Educational sessions were thirty to sixty minutes in length, with a Sleep Counselor/Polysomnographic Technologist, who provided educational brochures, sleep apnea education, CPAP education, mask fitting with CPAP acclimatization and post session questionnaire.

Results: Sleep latency in the pre-study education group was 16.6 ± 2.7 minutes vs 20.6 ± 4.8 minutes in the no education group (p=0.018). REM at optimal CPAP in the pre-study group was 17.7 ± 3.7 minutes vs 11.7 ± 2.4 minutes in the no education group (p=0.02). There were also trends toward a reduction in %Stage I and increase in %Stage II sleep in the pre-study education group vs the no education group

Conclusions: These preliminary results suggest that patients who received a pre-study educational session had improved sleep quality during subsequent split-night polysomnogram. If we confirm this with a larger retrospective analysis, a prospective, randomized trial may be in order.

References:
(2) Sanders MH, Costantino JP, Atwood CW. The Impact of Split-Night Polysomnography for Diagnosis and Positive Pressure Therapy Titration on Treatment Acceptance and Adherence in Sleep Apnea/Hypopnea. Sleep 2000;23:17-24
Conclusions: This research development model has fostered the involvement of students and residents in sleep medicine, helped faculty increase their research productivity, and further educated faculty in several specialties about sleep medicine. Due to its success, this model is now being considered for fostering research throughout the Department of Medicine at EVMS.

Supported by Sleep Academic Award H103652-01A1

743.S

Sleep Disorders in a Community Sleep Clinic: A Cooperative Study

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(1) Elmhurst College, (2) Suburban Pulmonary & Sleep Associates

Introduction: The scope of sleep disorders awareness has been broadened by heightened media attention. In a recent study Punjabi, Welch & Strohl (2000) reported a six fold increase in the prevalence rates of individuals presenting to a sleep center. While primary care physicians make a substantive amount of the referrals, it was stated that internal medicine physicians constitute the major source of referrals to sleep clinics.1 Despite these best efforts of medical practices, it is assumed that the rates of individuals seeking care are an underestimation of the actual number needing care.2 To address these issues and provide quality care for patients we designed a comprehensive team approach to Sleep Medicine care. Components of psychology, nutrition, respiratory therapy, nursing care, insurance advocacy unique to the sleep laboratory, and medical care were set up in an orchestrated fashion to provide a pathway of care. An educative component provided the first contact with the patient from the clinic. Full explanations and written materials were provided as the next step. Explicit delineation of treatment was an ongoing process. Standard sleep logs, self-report measures and surveys were used along with medical decisions about symptomology emergence and recitation to determine outcome. We proposed that our approach provided a standard of care that contributed to the clinical and measurement needs in the field to substantiate the nature and scope of sleep difficulties.

Methods: Our methods involved the simultaneous and sequential measurement of the patients’ care through the tracked system. The integration of chart notes and the authors’ reviewed case conference staffings with the health care providers on the team contributing at relevant times. The psychology component has provided initial educative care of psychological issues affecting sleep followed by various therapeutic pathways. The respiratory care component addressed the rehabilitative pulmonary needs of the patients. The insurance advocacy specialist meets with the patient immediately to apprise them of their coverage and costs for the estimated care. The nutritionist completed an initial intake with the patients and provided them with educative materials and a plan to pursue for weight management. The nursing worked with all medical contacts with the patients. Medical care provided began with initial intakes PSG. The physician and psychologist meet in monthly case conferences and weekly staffing for coordination issues pertaining to medical and allied health services management.

Results: The chart reviews and tallying of presenting diagnoses indicated that the population being served was in similar to National cooperative studies. In a two month summary, we determined our presenting diagnoses to be in a similar formation as two national 7 chart provides a graphical representation of the diagnosed condition.

Table 1

<table>
<thead>
<tr>
<th>Sleep Disorder</th>
<th>(Current study) n = 285</th>
<th>(Punjabi et al., 2000) n = 3970</th>
<th>(Coleman et al., 1982) n = 3900</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Sleep Apnea</td>
<td>73</td>
<td>67.8</td>
<td>23.9</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>2.1</td>
<td>3.4</td>
<td>15.1</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>8.3</td>
<td>2.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>5.9</td>
<td>4.9</td>
<td>12.6</td>
</tr>
<tr>
<td>RLS-PLM</td>
<td>5.2</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Schedule Disorders</td>
<td>2.1</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Other-Insomnia</td>
<td>11.2</td>
<td>8.3</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Conclusions: We conclude that the frequency of sleep symptomology presented is in parity to what other sleep clinics have reported. We feel that we may be reaching more individuals with Sleep Apnea and Insomnia given our educative outreach to patients. We strongly feel that our comprehensive package of care to the patient is effective. We look to future developments of a sleep hygiene marketing approach to address the issue of the low prevalence rates of sleep disorders.

References:

Searle Pharmaceutical contributes $1,000.00 annually to an Undergraduate Sleep Research Fellowship at Elmhurst College. Two to three students are selected by Dr. Sexton-Radek and Dr. Freebeck to provide behavioral observations and educative materials to patients after their training period.

744.T

Increased Expression of Preprohypocretin mRNA in Rat Hypothalamus after Sleep Deprivation and Sleep Rebound

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Introduction: Hypocretins (orexins), hypothalamic neuropeptides originally associated with feeding behavior, have been causally linked to canine narcolepsy, and have been recently found to be substantially depleted in post-mortem hypothalami of human narcoleptic patients. Other evidence suggests a wider role for these peptides in the regulation of the sleep-wake cycle. These findings prompted us to examine the effects of sleep deprivation on the expression of preprohypocretin, the precursor of both hypocretin A and B, at the mRNA level.

Methods: Rats were deprived of sleep using the classical platform method. After 96 hr of sleep deprivation one group was sacrificed; a sec-

was present at least two of the projects at national meetings in 2001.

gy. Residents will present at least two of the projects at national meetings in 2001.

was present at least two of the projects at national meetings in 2001.
ond group was returned to the home cage and allowed to sleep for 24 hr before being sacrificed (the sleep rebound group); controls remained in the home cages throughout. All brains were rapidly removed, frozen over dry ice and stored at -80 °C. Twenty micron coronal sections were prepared at 0.3 mm intervals covering the entire extent of the hypothalamus. In situ hybridization for preprohypocretin was performed using a 48 base oligonucleotide complementary to bases 177-215, tagged at the 3' end with 35S-dATP. Autoradiographic analyses were performed with the MCID AIS/C system and took into account not only the optic density of signals along the anterior-posterior axis, but also the proportion of area taken by the signals within a fixed size sampling window, as illustrated in Figure 1.

**Results:** Preprohypocretin ISH signals were entirely confined to the hypothalamus but formed a continuum across different nuclei. As shown in Table 1, the mean density of ISH signals averaged over the entire hypothalamus was increased by 12% in the Sleep Deprived group and by 18% in the Rebound group (p <0.05), compared to Controls. A second series of measures were taken at the level where the highest number of grains was found in each brain. Mean optical density at that level was 12% and 18% higher in the Rebound group than in the Control and Sleep Deprived groups, respectively. The proportion of the sampling area taken up by the signals was 21% higher in the Rebound group than in the other two groups. A measure combining optical density and area revealed a 30% increase in the sleep deprived group and an 88% increase in the Rebound group relative to controls (p< 0.001).

![Figure 1](image)

| Table 1: Preprohypocretin mRNA levels after sleep deprivation |
|---|---|---|
|       | Control | Sleep Deprived | Rebound |
| Mean density over the entire hypothalamus (µCi/g) | 5.89 ± 0.29 | 6.58 ± 0.43 | 6.97 ± 0.44* |
| Section with the highest grain count | 635.50 ± 69.85 | 650.25 ± 78.78 | 727.86 ± 69.68 |
| Density (µCi/g) | 10.51 ± 0.63 | 10.05 ± 0.68 | 11.82 ± 0.40* |
| Proportion of sampling area | 0.14 ± 0.02 | 0.14 ± 0.02 | 0.17 ± 0.01 |
| Density x Area | 1.39 ± 0.21 | 1.81 ± 0.39 | 2.61 ± 0.34*** |

*Test comparisons: * p < 0.05; ** p < 0.001 vs. control group; # p < 0.05 vs. sleep deprived group.

**Conclusions:** These observations suggest that sleep deprivation increases preprohypocretin mRNA levels and that this effect becomes significantly more pronounced following sleep rebound. It will be of interest to determine which of the two forms of hypocretin is primarily affected and whether these changes are reflected in levels of expression of receptors, particularly the hypocretin 2 receptor that has been found to be affected in canine narcolepsy. Changes in the hypothalamic hypocretin system may relate to metabolic and energy regulatory changes that are characteristic of sleep deprivation.

**Supported in part by funds from AFIP (Brazil) and CAMH (Canada)**

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745.T

**Norepinephrine Deficient Mice do not Exhibit Increased REM Sleep: A Preliminary Study**

Hunsley MS, Thoman EB, Palmiter RD
Howard Hughes Medical Institute, Department of Biochemistry, University of Washington

**Introduction:** Neurons in the pontine locus coeruleus (LC), one of the major sources of the neurotransmitter norepinephrine (NE) in the CNS, exhibit high firing rates during Wake, intermediate firing rates during NREM sleep, and are quiescent during REM sleep. The role of NE in sleep is unclear, although it appears to play a role in the regulation of REM sleep. A model of REM sleep gating has been proposed, which causally links the “turning on” of REM sleep-generating cholinergic neurons in the brainstem with the “turning off” of NE neurons in the same area (Jones, 1991). In this preliminary study, we investigated the sleep/wake states of mice that are deficient in NE. The model predicts that these mice may have increased REM sleep.

**Methods:** Production of the NE deficient mice (they are unable to synthesize NE) is described elsewhere (Thomas, Matsumoto and Palmiter, 1995). Mice were housed in a 12:12 light/dark cycle. Eleven adult male NE deficient mice and 11 controls were observed for 1 hour each, between 8-11am. Behavioral state was recorded every 5 seconds; REM, NREM and Wake were scored. Behavioral criteria for each state were modeled after Caroll et al. (1999). For each mouse, total percent of recording time for NREM, REM and Wake was determined, as well as the average bout length of the state, and the number of bouts that occurred.

**Results:** Total percent of NREM, REM and Wake did not differ between the genotypes. However, the NE deficient mice had fewer NREM bouts (F=8.7; df=1,20; p<0.01), longer average NREM bouts (F=5.6, p<.05), shorter REM bouts (F=4.9, p<.05), and fewer Wake bouts (F=7.7, p<.05).

**Conclusions:** Because the NE deficient mice do not exhibit large REM sleep changes, this suggests that the activation of cholinergic neurons to produce REM sleep does not depend on NE. Therefore, in normal animals the reciprocal relationship of acetylcholine and NE may be coincident, rather than dependent. Although the total amounts of the sleep/wake states did not differ in the present study, the differences between the two groups in the length and number of the sleep and wake state bouts suggest that the lack of NE does have an effect on the regulation of these states. Future studies include using EEG to record for longer durations, and during different times of the day.

**References:**

(1) Jones BE. The role of noradrenergic locus coeruleus neurons and neighboring cholinergic neurons of the pontomesencephalic tegumentum in sleep-wake states. Prog Brain Res 1991;88:533-543.


Activity of Adenosine Metabolizing Enzymes in Sleep-Related Brain Regions

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Introduction: Adenosine is a molecule that plays a number of roles in the central nervous system. One of its functions, as was described previously, is participation in sleep promotion. The metabolism of adenosine is complex. It involves two major enzymes-adenosine deaminase (ADA) which converts adenosine to inosine, hence for degradation while the other enzyme (adenosine kinase (AK)) recycles adenosine back to AMP from which adenosine can again be formed. While regional distribution of ADA has been previously described, including by us (Molec. Brain Res. 80:252-255, 2000), we do not know the relative regional differences in these two key enzymes in sleep/wake regulatory regions. To determine this is the major goal of our study. Subsidiary goals were to investigate the diurnal variations, and changes related to age of the animal, on activity of both of these enzymes. Studies were conducted in rats. 5 brain regions were obtained by the micropunching according to anatomical landmarks. The regions sampled were: cortex (CTX), tubero-mammillary nucleus (TM), ventrolateral preoptic nucleus (VLPO), horizontal diagonal band (HDB), locus coeruleus nucleus (LC).

Methods: Biochemical assays were applied using HPLC (Millenium32 software) for ADA, and radioassay for AK.

Results: For ADA: (1) all regions were significantly different from each other except HDB, VLPO and LC, with the highest and lowest levels being in TM and CTX, respectively (63.41±28.0 vs. 15.01±4.8 nmoles/mg/15 min; p=0.0001); (2) neither diurnal variation or age of rat had effect on the activity of ADA within a given brain region. For AK: (1) there were significant regional differences by ANOVA (p<0.0001) with the highest level of activity in CTX; (2) there were only minor diurnal differences in activity; (3) old rats had elevations in activity with significant differences in CTX and LC.

Figure 1

Conclusions: There are substantial regional differences in the relative amounts of the two key metabolic enzymes ADA and AK (see ratio of activities in figure). The region with the highest ADA, i.e., TM, has the lowest AK while the region with the lowest ADA, i.e., cortex, has the highest AK. Thus, there are substantial differences in the way adenosine is handled metabolically in these key sleep-related brain regions.

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Linkage Analysis of a Familial Case of Advanced Sleep Phase Syndrome

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(1) Department of Neurobiology and Physiology, Northwestern University, (2) Department of Neurology, Northwestern University, (3) Howard Hughes Medical Institute, Northwestern University

Introduction: The timing of sleep/wake across the 24-hour day is thought to be regulated by circadian and homeostatic mechanisms. The circadian pacemaker determines the phase of the rhythm of sleep propensity, whereas the sleep homeostatic process regulates sleep propensity in response to the amount of time spent awake. The molecular mechanisms underlying the circadian system have been characterized in several model systems with the discovery and cloning of a number of circadian genes. Mutations in a number of these genes have revealed phenotypes of altered circadian timing, including the phase of the sleep/wake rhythm. Advanced sleep phase syndrome (ASPS) is a human circadian phenotype characterized by a relatively early phase of the sleep period. Unlike situations such as jet lag, this phenotype is not a transient response to changes in entrainment cues or perturbations of normal sleep and wake times, but a chronic advanced phase of the sleep time. Since the sleep duration and architecture of ASPS subjects appear normal, ASPS may represent an alteration of the circadian regulation of sleep timing. The identification of familial cases of ASPS suggests a genetic basis (1,2). The goal of the present study is to assess, by linkage analysis, the genetic basis of the ASPS phenotype.

Methods: Diagnosis of ASPS was determined based on the American Sleep Disorders Association (ASDA) criteria (3). The diagnoses were confirmed by subjective and objective measures of sleep and circadian parameters (2). 9 affected subjects and 5 unaffected controls were selected for linkage analysis. Genomic DNA was extracted from these collected blood samples and immortalized cell lines established. A genome-wide scan of 293 fluorescent markers was completed for haplotype and linkage analyses.

Figure 1

Results: From the pedigree shown in the figure, the ASPS phenotype appears to segregate as a single, autosomal, dominant gene. Results of the haplotype analysis have excluded 20 of the 22 autosomes and have identified a locus segregating with the phenotype. To date, no significant LOD scores have emerged from this ongoing study.

Conclusions: Careful phenotypic characterization of a familial case of
ASPS coupled with molecular genetic approaches may lead to the identification of a circadian gene(s) responsible for this phenotype. The elucidation of the genetic mechanisms of ASPS may lead to a better understanding of the basic circadian control of sleep and wake states, as well as possible treatments for those with ASPS.

References:

Research supported by Army Research Office grant DAAG55-98-1.

749.T

Sleep in Randomly Selected Control Subjects with the Prion 129 Val/Met Polymorphism


Introduction: A mutation in codon 178 of the prion protein (PrP) gene is associated with two transmissible spongiform encephalopathies, Fatal Familial Insomnia (FFI) and Creutzfeldt-Jakob Syndrome (CJS). A cislocated Methionine (met) / Valine (val) polymorphism in codon 129 determines the phenotype. 129met segregates with FFI and 129val with FFI and CJS. A cis-phase variant (FFI) and Creutzfeldt-Jakob Syndrome (CJS). A cis-located Methionine (met) / Valine (val) polymorphism in codon 129 determines the phenotype. 129met segregates with FFI and 129val with CJS 1. The 129met/val polymorphism without the 129 codon mutation is very common in the general population. Experiments in mice also suggest a role for the PrP in normal sleep regulation 2. In the present study, we explored if the 129val/met polymorphism influences sleep in a population of normal volunteers, with special emphasis on items related to insomnia complaints.

Methods: A population based random sample of 884 adults was used in this analysis 3. All subjects had undergone a blood draw as a part of an overnight sleep protocol and were asked to complete a 4-item insomnia questionnaire. The 129met/val polymorphism was typed using a previously described Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique 1. Logistic and/or linear regression that controlled for confounding factors were used for statistical analysis. p < 0.05 was considered statistically significant.

Results: 129 met and val allele frequencies were 0.66 and 0.34 respectively. The genotype distribution did not deviate from expected Hardy Weinberg frequencies. Effects on sleep were as follows: A borderline significant association was obtained with 129 val and one of 4 insomnia questions. 129val carriers reported less frequent occurrence of waking up repeatedly during the night and having difficulty getting back to sleep (Odds ratio= 0.72, 95% CI=0.64,1.01; p=0.05). Using the polysonomographic data (adjusted for confounding factors of age, sex, BMI and AHII), we found that the 129val carriers spent more time awake after sleep onset (p=0.04). None of these effects were linearly related to Val allelic dosage and effects were not significant when using subjects with the more frequent occurrence of insomnia symptoms (almost always versus never, rarely).Conclusion: Our results do not support the hypothesis that PrP polymorphism modulates insomnia in the general population. Discrepant results were obtained using the subjective (questionnaire) and objective (Polysonomography) data. In one case (the questionnaire), the 129val polymorphism decreased insomnia symptoms while in the other (sleep recording), it increased sleep disruption. Discrepancies between objective and subjective measures of insomnia are not uncommon, indicating great difficulties in measuring insomnia. The results were only marginally significant, associations were weak and unrelated to severity or allelic dosage. Further studies will be needed to extend and confirm this preliminary finding.

Conclusions: Our results do not support the hypothesis that PrP polymorphism modulates insomnia in the general population. Discrepant results were obtained using the subjective (questionnaire) and objective (Polysonomography) data. In one case (the questionnaire), the 129val polymorphism decreased insomnia symptoms while in the other (sleep recording), it increased sleep disruption. Discrepancies between objective and subjective measures of insomnia are not uncommon, indicating great difficulties in measuring insomnia. The results were only marginally significant, associations were weak and unrelated to severity or allelic dosage. Further studies will be needed to extend and confirm this preliminary finding.

References:

Research supported by Army Research Office grant DAAG55-98-1.

749.T

Increased NREM sleep in Mutant Mice Lacking CREB


Research supported by FAPESP and NIH

750.T

Increased NREM sleep in Mutant Mice Lacking CREB


References:

Introduction: We are interested in the role of the cyclic adenosine monophosphate (cAMP)/ protein kinase A (PKA)/cAMP-responsive element binding protein (CREB) pathway, an intracellular signaling pathway involved in many biological processes, in the regulation of sleep. Pharmacological and biochemical studies have suggested that the CREB signaling pathway may be involved in regulating the sleep/wake cycle (1,2,3). In particular, data suggest that this pathway may be involved in the maintenance of wakefulness.

Methods: We carried out circadian wheel-running monitoring and EEG and EMG recordings to examine sleep architecture and circadian activity in knockout mice lacking the alpha and delta isoforms of the CREB protein and their wildtype littermates.

Results: CREB mutant mice have more NREM sleep during subjective day and night at the expense of wake. CREB mutant mice also show an increased average length of a bout of REM sleep (defined as a period of REM sleep that lasts longer than 30 seconds). Preliminary analysis suggests that the time course of sleep rebound after a six-hour period of total sleep deprivation is altered in CREB mutant mice. CREB mutant and wildtype mice do not differ in their circadian period. However, CREB mutant mice show less wheel-running activity during a L/D cycle.

Conclusions: Because levels of CREB cannot be directly altered pharmacologically, the availability of genetically modified mice with a reduction in levels of CREB allows an examination of this protein in...
behavior. In addition to previous studies that show an increase in P-
CREB after waking(2) as well as an increase in waking after a pharma-
cological increase in cAMP levels(3), our study points to CREB as hav-
ing a role in the maintenance of wakefulness. However, our study shows
that this role in the maintenance of wakefulness is biologically separate
from any role of CREB in an alteration of free-running circadian period.
Future studies will determine potential sites of action of the CREB pro-
tein by the generation of a mouse in which the CREB mutation is
restricted to specific neural systems.

References:
(1) Perez E, Zamboni G, Amici R., Jones CA, Parmeggiani PL. cAMP
accumulation in the hypothalamus, cerebral cortex, pineal gland and
brown fat across the wake-sleep cycle of the rat exposed to different
(2) Cirelli C, Pompeiano M, Tononi G. Neuronal gene expression in the
(3) Lelkes Z, Alföldi P, Erdoes A, Benedek G Rolipram, an antidepress-
ant that increases the availability of cAMP, transiently enhances wake-

Research supported by NIH, Merck Fund and Whitehall Foundation

751.U

Alertness and Neurobehavioral Performance On Simulated Night
Shifts Following Evening Naps

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ment of Psychiatry, St. Louis University

Introduction: Alertness and performance of most skills in humans
decline to their lowest daily levels during usual night sleep hours. Even
after weeks or months on the night shift, physiologic adaptation to night
work is incomplete at best, and often is minimal. Practical countermea-
sures to enhance alertness and performance on the night shift are need-
ed, particularly for those occupations key to public safety. The present
study systematically examines the effects of napping before five con-
secutive simulated night shifts (SNAP), or before the first two of five
consecutive simulated night shifts (2NAP), as compared to a no-nap
group (ONAP). The impact of these conditions upon alertness and vari-
ous performance measures during night shift hours is the focus of this
preliminary report.

Methods: Subject selection criteria and the schedules for daytime sleep
and naps can be found in a companion abstract in this volume.1 Thirty-
three subjects (14 m, 19 f; mean age 47 ± 12.3) randomly assigned to one
of the three nap conditions (N=11 for each) are included in this report.
Sex representation was similar and mean age did not differ among
groups. Each subject participated during five consecutive nights and the
intervening four days. The simulated night shift, began at 2300 and
ended at 0735, during which time the Maintenance of Wakefulness Test
(MWT; 2345, 0210, 0420 and 0645), a Neurobehavioral Assessment
Battery 2 (NAB; 2300, 0125, 0335, 0600), and various cognitive tests
(0040 and 0515) were administered. Only the MWT and some variables
from the NAB are reported below.

Results: Mean minutes of sleep during each of the nap opportunities
were: 92 and 103 minutes for the 2NAP group and 84, 79, 77, 67, and 63
minutes for the SNAP group. Daytime sleep data are presented else-
where.1 Data analysis consisted of mixed-model ANOVA: 3 groups x 5
nights x 4 time points per night. MWT analysis indicated a main effect
for time-of-night on the MWT (p<.01), with latencies becoming much
shorter as the night shift progressed. There was a night x group interac-
tion (p<.01), a time-of-night x group interaction (p<0.01) and a trend for
a night x time-of-night interaction (p=.054). Compared to ONAP, the
2NAP group was significantly more alert on night 1 (mean latencies 14.8
min for 0NAP and 27.4 min for 2NAP, p<.01) and tended to be more
alert on night 2 (0NAP = 18.2 min, 2NAP = 26.7 min, p=.055); there was
a trend for 5NAP to be more alert on night 1 than 0NAP (0NAP=14.8
min, 5NAP=22.0 min, p=.07). 2NAP was more alert than 5NAP on night
2 (2NAP=26.7 min, 5NAP=17.3 min, p<.05). No group differences were
seen for the MWT on nights 3, 4, or 5. Lapses on the psychomotor vig-
lance test (PVT, part of the NAB) increased during the night as well as
across nights (p<.01 for both). However, there was no main effect of
group, nor were there significant interactions. Data were similar for the
slowest 10% of responses on the PVT. The Digit Symbol Substitution
Test (DSST) showed significant main effects for group (p<.05), night
(p<.01), and time-of-night (p<.01); 5NAP performed better than 2NAP
on every night but 0NAP did not differ from either group. DSST per-
formance decreased slightly across the night but improved from night 1
to 5. The fatigue scale of the Profile of Moods Scale (POMS) and a visu-
al analog scale of sleepiness showed significant time-of-night effects
(p<0.01 for both). Neither had a significant group effect or interaction.

Conclusions: These preliminary analyses suggest a modest positive
effect of evening naps on alertness and neurobehavioral performance,
limited to the first of five consecutive simulated night shifts. The robust
time-of-night effects on all measures reported indicate that the depend-
ent variables employed are quite sensitive to fluctuations in alertness/performance. Examination of the total time slept within the 24-
hours prior to each night shift showed no differences among groups,
suggesting that evening naps reduced sleep time during the main day-
time sleep period the following day. Based on these preliminary analy-
ses, the failure of evening naps to represent additional sleep in this sim-
ulated night work design probably accounts for the minimal effect of
naps on night shift alertness and performance.

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752.U

Using A Web-based Survey to Assess College Students’ Sleep

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Introduction: Advances in computer technology and Internet communi-
cation afford a new means of survey research and information dissemi-
nation. Use of web-based surveys and information pages may be a par-
 ticularly effective way to reach large numbers of adolescents and young
adults, many of whom are suspected to have poor sleep hygiene and
undiagnosed sleep problems (1).

Methods: During National Sleep Awareness Week in March of 2000, all
students at the University of Kentucky who had registered email
accounts (approximately 13,000) were sent an email message with the
subject heading: “Are You Sleepy?” They were invited to fill out a brief,
interactive questionnaire with links to information on sleep and sleep

A423

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problems. The questionnaire asked about sleep habits and contained questions designed to elicit symptoms of excessive daytime sleepiness (EDS), sleep-disordered breathing (SDB), Restless Legs Syndrome (RLS), narcolepsy, insomnia, and depression.

Results: A total of 1635 students completed the survey within one week. They ranged in age from 14 to 58 with a mean of 24.5. There were 654 males and 981 females. There were no gender differences on any of the sleep measures. Students from Freshman year through Graduate School reported nearly identical sleep habits, with an overall average of 7.3 hours on weeknights and 8.7 hours on weekends. Mean bedtime on weeknights was 12:45 AM and on weekends was 1:35 AM. Only 22.9 % reported getting 8 or more hours of sleep on weeknights.Other findings related to sleepiness and sleep disorders were:1.EDS: 41.8% scored 10 or higher on the Epworth Sleepiness Scale, the suggested cutoff point between normal and excessive daytime sleepiness. Using a more stringent cutoff of 12, 25.8% appeared to be excessively sleepy.2.SDB: 4% said they both snored loudly enough to bother others and made gasping and snorting sounds while sleeping “a lot of the time” or “most of the time”.3.RLS: 13.7% said they experience creepy-crawly feelings in their legs that make them feel that they just have to move them “a lot of the time” or “most of the time”.4.Narcolepsy: 3.4% said that “a lot of the time” or “most of the time” they had experienced 3 out of 4 of the classic signs of narcolepsy, namely, sleep paralysis, hypnagogic imagery, excessive daytime sleepiness, and cataplexy.5.Insomnia: 19.5% reported that it takes > 30 minutes to fall asleep and 13.1% claimed that they frequently woke up in the night and could not go back to sleep.6.Depression: 27.7% scored 7 or higher on a 7-item depression scale (scored 0 = never to 3 = most of the time) with items such as “felt life was not worth living” and “felt depressed”.

Conclusions: Responses from this sample were remarkably similar to findings previously reported in population-based studies of sleep-disordered breathing (2) and RLS (3). Web-based surveys may be an effective way to collect data on sleep habits as well as to disseminate information about sleep to college students, a group that appears to have a fairly high incidence of poor sleep hygiene and signs of potentially serious sleep disorders.

References:

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753.U

Quality of Life and Subjective Perception of Sleep Disorders Patients
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Introduction: Quality of life has been examined in many specific sleep disordered populations. For example, Zammit et al. (1999) found that insomniacs have poorer quality of life than normal controls as indicated by lower scores on all scales of the SF-36 as well as higher depression and anxiety scores. The present study sought to explore quality of life in a general sleep disordered population and further examined patients’ subjective perception of the impact of their illness. It was felt that such data could help identify the needs of sleep disordered patients and provide information to guide the services offered in diagnostic and treatment centers.

Methods: After appropriate consents were signed, patients who were attending their initial visit were asked to complete a survey inquiring about various aspects of their sleep disorders experience. They were then asked to complete the SF-36, the Hospital Anxiety and Depression Scale (HADS) as well as the Functional Outcomes of Sleep Questionnaire (FOSQ). All participants were assured that the data would be kept confidential and that their treating physicians would not access the information.

Results: 87 participants (60% response rate) were included in the analysis. Overall, patients scored quite low on all the individual subscales of the SF-36 with their mean physical component score M = 38.85 (SD = 12.31), and mental component score M = 42.57 (SD = 11.39) being approximately one standard deviation away from the normative mean. On the HADS, 44.7% of patients scored in the clinically significant range for anxiety and/or depression. On the FOSQ measure, participants scored on average in the high range of the total score (M = 15.89, SD = 3.76) indicating that their sleep disorder was in fact impacting on their activities of daily living. Subjectively, 54% of the sample sought help for their sleep disturbance because they noticed that it was affecting their health or life and another 24% did so because of the concern of a loved one. 46% described their symptoms as having been severe to extremely severe at the time they first decided to seek help which was often more than a year prior to being seen. 53% reported having concerns regarding their own physical or emotional health at time of first visit. In terms of suggested improvement of services offered, 48% felt that they could benefit from more information on sleep disorders whereas 21% felt that they could benefit from stress management, counseling or support group type services (7% respectively for each service).

Conclusions: It is concluded that sleep disordered patients do suffer from reduced quality of life, both physically and emotionally, prior to receiving treatment for their disturbances. This is evidenced both by objective measures as well as by the subjective perception of the patients themselves and loved ones who notice the impact of the disease on daily life. Patients are aware of these limitations and express concern regarding this. They also appear to feel that a better understanding of their illness would be beneficial and many would be open to receiving some form of counseling to help them cope. Evidently, future research needs to focus on whether treatment of the sleep disorder would lead to an improvement in quality of life variables. Nevertheless, the presence of emotional difficulties such as depression and anxiety may require psychological intervention, particularly in cases where the illness has been longstanding and may therefore not resolve along with appropriate treatment for sleep disorders.

754.U

Working Schedule and Economic Costs of Sleep Disorders

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Introduction: Disruption of the normal sleep/wake rhythm as seen in individuals working on shift may lead to important sleep difficulties, daytime sleepiness and various health problems (1,2). These problems have an economic impact in terms of direct and indirect costs that have never been assessed.

Methods: The staff members of a psychiatric hospital (N=2000) were invited to participate in a study assessing sleep quality, sleep disorders
and socioeconomic impacts of work conditions. Overall, 817 employees have been volunteers. Two physicians performed the interviews during the working hours. All the participants answered a standardized questionnaire assessing work conditions, work schedule and their consequences on health, social and professional life (Shift Work EVAL Questionnaire (SWEQ))(3). Assessed costs included 1) direct costs for the past 12 month period: hospitalizations, consultations and medications; 2) indirect costs: road accidents and days of activity lost (sick leaves, inability to work, hospitalizations, medical consultations) Diagnostic exploration was done with the Sleep-EVAL knowledge system (©Sleep-EVAL, MM Ohayon, 1994) that used the DSM-IV and the ICSD classifications. Three groups were constituted according to their work schedule: 1) a group with a fixed daytime schedule (n=442); 2) a group on rotating daytime shifts (n=323); and 3) a group with shift or nighttime schedule (n=52).

Results: Subjects working on rotating daytime shifts were younger (37.6±8.4 y.o.) than the two other groups (fixed daytime schedule: 42.0±8.3 y.o.; shift or nighttime workers: 41.4±6.5 y.o.; p<.05) and had a higher proportion of women (78.6% vs. 68.1% in the group with a fixed daytime schedule and 59.6% in the group of shift or nighttime workers (p<.001). The highest rate of daytime sleepiness was found in the rotating daytime shift group: 29.1% reported a moderate or severe daytime sleepiness as compared with 19.2% in the group of shift or nighttime workers and 12.2% in the group with a fixed daytime schedule (p<.001).

Higher rates of sleep disorder diagnoses were found in the group with rotating daytime shifts (27.3%) and in the group of shift or nighttime workers (40.4%) as compared with the group with a fixed daytime schedule (19%; p<.001). Direct costs were comparable between groups. However, indirect costs were higher in the rotating daytime shifts group ($1805 / year) as compared with the fixed daytime schedule group ($1265 / year) (p=.02). They were also higher in subjects with a sleep disorder diagnosis ($2145 vs. $1301; p<.0001). The indirect costs are comparable between the three groups when the subjects have no sleep disorder diagnosis. However, indirect costs are significantly higher among subjects with a sleep disorder working on rotating daytime shifts ($2712/year) as compared with subjects with a sleep disorder working on a fixed daytime schedule ($1703/year) or shift or nighttime work ($1531/year).

Conclusions: Irregularity of working schedule can be as disturbing as shift working on sleep quality. Moreover, it has the highest impact and indirect costs.

References:

Predicting Off-Duty Napping in Medical Residents
Baltsis SM, Wolfson A
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Introduction: The shocking transition to medical residency is cause for alarm. The sudden demands of working extended hours, mastering diagnoses, performing procedures, prescribing treatments, and relating to patients while changing roles from student to physician subject residents to many stressors, one being sleep loss (Schwartz et al., 1987). The present study aimed to characterize the role of sleep over the transition from student to medical resident.

Methods: 91 graduates of College of the Holy Cross, currently in their residency, were mailed 5 questionnaires that solicited background/demographic, sleep/wake habit, sleepiness, mood, health, performance, and sleep education information. In addition, a 7-day retrospective diary intended to describe sleep/wake/work schedules was included. Residents were asked to complete a questionnaire and diary and to encourage 4 colleagues to do the same. 64 of the 455 questionnaires were returned (14%), and 53 are used in the present analyses.

Table 1
Component loadings on three factors.

<table>
<thead>
<tr>
<th></th>
<th>Perceived Wellness/Sleepiness</th>
<th>Morningness/Eveningness</th>
<th>Coping Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>0.82</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>Dozing in Different</td>
<td>-0.63</td>
<td>0.22</td>
<td>0.05</td>
</tr>
<tr>
<td>Situations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance</td>
<td>0.62</td>
<td>0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>General Health Scale</td>
<td>0.50</td>
<td>0.35</td>
<td>-0.29</td>
</tr>
<tr>
<td>Choice of Wake-up</td>
<td>0.41</td>
<td>-0.71</td>
<td>-0.21</td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morningness/Eveningness</td>
<td>0.44</td>
<td>-0.68</td>
<td>0.23</td>
</tr>
<tr>
<td>Choice of Bed Time</td>
<td>0.36</td>
<td>-0.63</td>
<td>-0.44</td>
</tr>
<tr>
<td>Year of Residence</td>
<td>-0.23</td>
<td>-0.37</td>
<td>0.70</td>
</tr>
<tr>
<td>Caffeine/Alcohol/Drug Intake</td>
<td>0.41</td>
<td>0.03</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Results: A factor analysis of 9 variables from the mail survey revealed three factors with eigenvalues > 1.0: perceived wellness/sleepiness, morningness/eveningness, and coping experience. (See Table 1 for component loadings on the three selected factors). These factors accounted for 27.0%, 20.2%, and 14.3% of the variance in the data respectively (61.5% of the total variance). A multiple regression, implementing the three factors as predictor variables of off-duty napping tested significant, accounting for 18.7% of the variance [F (2, 49) = 3.46, p < .05]. In three subsequent linear regressions, each using a different factor loading as the predictor variable, only coping experience was significantly predicted off-duty napping [t (51) = -2.73, p < .01]. (The three variables that loaded highest on the coping experience factor were choice of bedtime, year of residency, and caffeine/alcohol/drug intake).

Conclusions: These results suggest that as a medical resident masters his/her coping experience, he/she will experience less off-duty napping. As off-duty napping may be indicative of increased sleepiness and fructured sleep, sleep education concerning the importance of consolidated sleep for both medical residents and the medical community is a necessary step toward ensuring the safety of medical residents and their patients.

References:
Sleep Inertia: Subjective, Behavioural and Electrophysiological Measurements

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CANADA

Introduction: Recent studies report that sleep inertia dissipates in a saturating exponential manner, the exact time course being task dependent, but generally persisting between one to two hours (1,2). A number of factors, including sleep architecture, sleep depth and circadian variables are thought to affect the duration and intensity of sleep inertia. The present study sought to replicate findings for subjective alertness and reaction time and also to examine electrophysiological changes through the use of event-related potentials (ERPs). Secondly, FFT analyses were used to examine the effect of sleep depth on the initial intensity of sleep inertia.

Methods: Ten participants spent two consecutive nights and subsequent mornings in the sleep lab. Sleep architecture was recorded for a full nocturnal episode of sleep based on participants’ habitual sleep patterns. Subjective alertness (SSS, VAS), reaction time (RT) and event-related potentials (ERPs) were measured five-minutes after awakening, and at 15-minutes thereafter for 90 minutes. A five-minute auditory oddball task was used to obtain average RT to the target stimulus and amplitude and latency for N100 and P300. Power spectral analyses (FFT) were used to calculate slow wave activity (SWA) at Cz for the total sleep time, 90-minutes before awakening and five minutes before awakening. Mean SWA (delta power) was then correlated with SSS, VAS and RT measures five-minutes after awakening.

Results: As predicted, subjective alertness measured by the SSS showed a significant linear (F(1,8)=37.67, p<.001, h2 =.88) and quadratic (F(1,8)=2.94, p=.001, h2 =.83) increase as time awake increased. VAS scores also indicated increasing subjective alertness as time awake increased in both a significant linear component (F(1,8)=79.88, p<.001, h2 =.91) and quadratic component (F(1,8)=7.29, p=.027, h2 =.48). Unexpectedly, reaction time decreased (i.e., got faster) in a significant linear manner only (F(1,8)=5.89, p=.041, h2 =.42); no quadratic component was detected. The ERP data were not conclusive. P300 showed a transitory decrease in latency from five minutes after awakening to 20 minutes after awakening but this difference was not sustained. There was a significant relationship between SWA at Cz five minutes before wake and initial VAS score at time one (r=-.71, p=.031) as well as VAS score at time one (r=-.68, p=.043). The negative relationship indicated that higher amounts of SWA (greater sleep depth) was correlated with lower initial alertness.

Conclusions: The results support previous findings that sleep inertia as measured by subjective alertness dissipates in an exponential manner, lasting approximately 60-90 minutes. Although a similar linear decrease in RT has recently been reported(3), other studies report an exponential decrease(1). The finding that electrophysiological measures were largely inconclusive may indicate that they were not sensitive enough to capture changes in brain activity using the present paradigm. The transitory nature of the P300 latency decline from time one to time two, followed by increase in latency at subsequent later times possibly indicates an attention/arousal conflict. The significant relationship between SWA and subjective alertness supports the notion that increased sleep depth, as operationalized by SWA, results in more intense sleep inertia.

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The Effect of Daytime Naps on Next-Day Mood And Nocturnal Sleep Quality

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Introduction: The present investigation examined the effects of daytime napping upon nocturnal sleep and next-day mood. An afternoon nap is known to decrease the subsequent night’s restorative delta wave sleep (Feinberg et al., 1985); this loss of restorative sleep was hypothesized to result in disturbed mood the following day.

Methods: Thirty undergraduates either napped (Nap group) or did not nap (No-nap group) for 90 minutes, between 1-4 pm. The six sub-scales (Depression, Tension, Anger, Vigor, Fatigue, and Confusion) and the Total Mood Disturbance scores from the Profile of Mood States were compared from baseline to post-nap for both groups of subjects, to assess for changes in mood. Post-experimental nocturnal sleep was investigated with Sleep Diaries (TST, SOL, Awakenings, Sleep Quality, and Sleep Restfulness) and Actigraphy (TST, SOL, and Sleep Efficiency).

Results: On a between-group ANCOVA, which co-varied the baseline POMS Depression scale, there was a significant decrease in POMS Depression scores from baseline to post-experimental day in the No-nap group, F(1,14)=32.94, p<.000, but no statistically significant difference in POMS Depression scores from baseline to post-experimental day in the Nap group F(1,14)=0.121, p<.733. There also was a significant between-groups difference on post-experimental POMS Depression scores, even with baseline POMS Depression scores co-varied F(1,26)=11.38, p<.002; the Nap group had higher Depression scores than the No-nap group. The same pattern occurred with POMS Tension; there was a significant decrease in POMS Tension scores from baseline to post-experimental day in the No-nap group, F(1,14)=9.55, p<.008, but no statistically significant difference in POMS Depression scores from baseline to post-experimental day in the Nap group F(1,14)=4.63, p<.051, and there was a significant between-groups difference on post-experimental POMS Depression scores, even with baseline POMS Depression scores co-varied F(1,26)=6.012, p=.021; the Nap group had higher Depression scores than the No-nap group. There were no between-group sleep differences on Actigraph or Sleep Diary measures.

Conclusions: Although the Nap group had significantly higher post-test POMS Depression and Tension scales, relative to the No-nap group on the morning after the nap, the only baseline to post-test differences were decreases in POMS Depression and Tension scores in the No-nap subjects. Presumably this is because the No-nap group was given the opportunity for normal, restorative post-experimental sleep that permitted improved mood, while the Nap group’s afternoon sleep interfered with restorative sleep, and thus prevented the mood-restoring properties of sleep. There were no between-group sleep differences on Actigraph or Sleep Diary measures, but the most crucial sleep variable, slow wave sleep (expected to decrease in the Nap group) was not assessed since nocturnal polysomnography could not be done. This finding has possible clinical implications. Specifically, poor sleep habits, like regular,
long, afternoon naps, could cause and/or maintain negative mood in those with depression or anxiety disorders. As a result, assessment and treatment of sleep hygiene in patients with negative mood states may be clinically important.

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758.U

Evaluation of the Sleep Related Complaints in a Sample of Flight Attendants of Intercontinental Flights: Preliminary Results

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Introduction: Shift work and jet lag have been extensively studied due to its growing importance (1). Shift workers and those under constant jet lag suffer from important disturbances related to a desynchronization between the internal rhythm and the external environment, leading to sleep related complaints, poor alertness and performance (2). Studies involving aircrew are important because they are exposed to both conditions at the same time, as the flights are, in its majority, night flights, with the crossing of five different time zones with a short stay in the destination. It has already been determined that the crew fatigue can lead to an impaired performance and contribute to the occurrence of accidents (3). The purpose of this study was to evaluate sleep-related complaints and other habits of an aircrew group (flight attendants) through the application of a sleep questionnaire to evaluate their major complaints and suggest countermeasures.

Methods: Ninety six intercontinental flight attendants (crossing at least 5 time zones in each flight) were interviewed. They were randomly chosen and the excluding criteria were heart condition, depression, asthma and flight related diseases. Nurturing mothers were also excluded. A sleep questionnaire was used to evaluate the sleep complaints.

Results: The figure shows the major sleep complaints found in this group, for men and women separately (men, n=53; women, n=43). The age average for the women’s group (WG) was 40.4 years (ranging from 33 to 54 yrs) and for the men’s group (MG) was 42.9 yrs (ranging from 34 to 50 yrs). They had been flying international flights was (average) 15.1 yrs in the WG and 11.9 yrs in the MG.

Figure 1

The graphic shows the major sleep complaints of a group of flight attendants

Conclusions: The sleep complaints in the studied population are 53.5% in the WG and 39.6% in the MG. The most frequent complaints were: insomnia (WG - 73.9%, MG - 38.1%), day time sleepiness (WG - 60.8%, MG - 52.8%), snoring for the WG (30.4%) and unsatisfactory sleep for the MG (38.1%). The results show that the sleep complaints are usually more frequent in women than in men. Further studies are being carried out to evaluate the sleep related complaints of the studied population in order to understand the underlying mechanisms of the obtained results.

References:

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759.U

Factors Associated with Daytime Sleepiness and Performance in a Sample of Commercial Drivers

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Introduction: We have evaluated daytime performance in a sample of commercial drivers. This was done as part of an investigation of the prevalence of sleep apnea. The sample we studied was based on a random sample of holders of commercial drivers licenses (CDL) provided by the state of Pennsylvania.

Methods: All individuals studied lived within 50 miles of our sleep center. From the random sample, 249 individuals with a higher risk for sleep apnea as judged by the multivariable apnea prediction (MAP; Maislin et al, Sleep 18:158, 1998) and 159 individuals with a lower risk had in-depth testing. This involved the following: 7 days of actigraphy monitoring of sleep/wake at home prior to in-laboratory testing; overnight in-laboratory polysomnography; multiple tests of daytime performance on the day following their sleep study. The tests, which were each administered four times during the day, included the following: multiple sleep latency test (MSLT); psychomotor vigilance test (PVT); divided attention task. From the PVT we extracted multiple variables: median response time; frequency of lapses; duration of lapse domain; optimum response times and the vigilance decrement slope over the period of testing. From the divided attention task we extracted the average deviation from the center, and the decrement in lane tracking over the duration of the task.

Results: Significant associations between the degree of sleepiness and decrements in performance were found with the respiratory disturbance index (RDI). Subjects with an RDI above 30 episodes/hour showed the highest sleepiness and greatest impairments in performance. For MSLT, the least squares estimated value for those with severe apnea (RDI ≥30 episodes/hour) was 5.0 minutes while it was 8.4 minutes in those with RDI <5 episodes/hour (p=0.0003). The degree of impairment in all tests was also associated in a highly significant way with sleep duration, as measured at home by wrist actigraphy, with the greatest changes being seen in those who slept on average less than 5 hours/night the week prior to the laboratory study. Multiple linear regression was used to further evaluate these relationships. Both sleep apnea severity and average sleep
duration at home produced independent effects on daytime performance. The magnitude of the effects on daytime performance of severe sleep apnea, which occurred in 4.7% of the sample, and of sleeping less than 5 hours/night, which was found in 13.5% were similar.

Conclusions: Thus, in this population-derived sample of CDL holders, both chronic partial sleep deprivation and the presence of sleep apnea contribute to decrements in daytime performance, although chronic partial sleep deprivation is more common than apnea.

Research supported by Trucking Research Institute contract DTFH61-93-R-00088 and NIH grants HL-60287 and RR-00040.

760.U

Epworth Sleepiness Scale Outcome in a Brazilian Population

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Introduction: Introduction: The Epworth sleepiness scale (ESS) measures the subjective daytime sleepiness degree. This investigation determines the profile of ESS-measured subjective sleepiness across a population sample of healthy adults by means of: 1. ESS means and the average reported sleep time (RST). 2. Prevalence rate of subjects with ESS scores > 10 points. 3. The correlation of ESS scores and RST.

Methods: ESS was applied to 755 subjects. Three groups were created: Group A (18-39 years); group B (40 to 59 years), and C (60 years old and up). The t test (p=1%) detected statistically significant nonmean values for all three groups and between genders. A significantly gender group C mean ESS was found for a p value = 10% t test. The values are portrayed for all three groups and between genders. A significantly gender group C shows higher ESS-measured degree of sleepiness in this age group (1,2). Young females display higher ESS-measured subjective sleepiness compared with females. This confirms increased ESS-measured degree of sleepiness in this age group (1,2). Young females display higher ESS-measured subjective sleepiness compared with females. This confirms increased ESS-measured degree of sleepiness in this age group (1,2).

Conclusions: Group A presents a higher ESS>10 prevalence when compared with groups B and C males and females and other populations. This confirms increased ESS-measured degree of sleepiness in this age group (1,2). Young females display higher ESS>10 points. This is in keeping with a longer sleep need is young females. Group C elderly males display a trend for elevated indexes of sleepiness (ESS>10 and ESS average) compared with females. Higher prevalence of sleep-related breathing disorders males and insomnia in females may account for these findings.

References:


761.U

Can Sleep Attacks Occur Without Feeling Sleepy?

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Introduction: Litigation stemming from drowsy driving crashes in the U.S., U.K. and Australia has resulted in claims that involuntary sleep attacks can occur without the driver having felt drowsy or sleepy prior to the crash. This issue was addressed experimentally in two controlled laboratory sleep deprivation studies.

Methods: Sleep attacks were studied in a total of n=32 subjects. In experiment 1, n=13 healthy male subjects (M=27yr) underwent 42hr total sleep deprivation during which they completed a 1hr computerized performance battery every 2hr. A 20min psychomotor vigilance task (PVT) occurred midway through each test bout and served to identify sleep attacks (i.e., 30sec performance lapses that ended when a computer alarm sounded). These 30sec lapses were confirmed to be sleep attacks by power spectral analyses of EEG and EOG (1). In experiment 2, n=19 healthy male subjects (M=29yr) underwent 88hr total sleep deprivation (n=14) or 88hr partial deprivation in which 2hr naps were provided every 12hr (n=5). Subjects completed 30min test bouts every 2hr throughout deprivation. These bouts contained 10min PVT tests. For both experiments 1 and 2, statistical analyses focused on ratings of the Stanford Sleepiness Scale (SSS) and 10-point visual analogue sleepiness scale (VAS) made at the beginning of each PVT performance trial. Ratings from 6hr, 4hr and 2hr prior to the test bout containing the first sleep attack, and within five minutes of the PVT trial in which the sleep attack occurred, were considered. ANOVAs (Huynh-Feldt corrected) and paired t-tests were used to compare changes in subjective sleepiness leading up to the first sleep attack within each experiment.

Results: The modal time for a sleep attack was equally split between 08:00 and 16:00 in experiment 1, and was 06:00 in experiment 2. As the table below illustrates, mean subjective sleepiness ratings on both the SSS and VAS increased systematically as time approached the test bout containing the sleep attack (allanova main effects for time, p<0.05).
References:

Research supported by: NIH RR04281 and RR00040; DTNH22-93-D-07007; AFOSR F49620-1-0388

762.U

A Man’s Claim to Have Been Raped Unaware While Asleep: Report from a Sleep Specialist to the Criminal Court.

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Introduction: To our knowledge there is no study of victims asleep and not waking up while being raped. In front of the Court could sleep as such be a culprit? A District Attorney requests a sleep specialist’s opinion about victim’s sleep. The mission was not to determine if the victim was telling the truth but to ascertain whether his statement could conceivably be true. On June 9, 1997, Mr X, a 24-year-old trainee leaves his office and meets his 42-year-old manager who invites him to go to a swimming pool, then to share drinks. The trainee consumes seven 25cl beer bottles (pure alcohol consumption totaling 11.375 cl) between 9pm and 1am. The manager having no more means of getting back home the trainee proposes that he sleep downstairs on a sofa of his studio while he would sleep in his bed on a mezzanine. The next morning the trainee wakes up alone, and raped. He goes to the Hospital Medicolegal Department and filed a complaint. The manager was arrested, admitting to a sexual act, but claiming that the complainant had been awake and consenting.

Methods: In the file it appears that the rape occurred during the first part of sleep. Serious anal lesions were observed. Sperm was found inside rectum. DNA analysis identified the accused. The methodology includes: psychiatric and psychological testing followed by three overnight polysomnography. The aim was to compare the third night PSG data after alcohol ingestion before bedtime (same dose as June 9) with the second night, to serve as reference.

Results: The victim was a deep sleeper with no history of sleepwalking or sleep terrors. Psychological assessment shows no evidence of any psychopathology. Compared to night 2, night 3 was characterized by (minutes): faster sleep latency (2.39/3), decrease of SWS latency (5.7/10), SWS amount increase (129.7/106.4, + 22 %; SWS first hour: 54/31), REMS latency increase (149.3/52), REMS amount decrease (35.3/49.7) and increase TST (321/296). As regards the crucial relationship between sleep and pain, if the notion of “depth of sleep” has been linked to the level of sleepers’ response to external stimuli, there are few studies about the effects of painful stimuli. Lavigne et al (2000) conclude that the processing of nociceptive inputs is attenuated across sleep stages. Sleepwalking can be accompanied by a sharp rise in pain threshold. But in fact the scientific question concerning sleep resistance to external stimulations is largely unanswered.

Conclusions: May 23, 2000. The third night PSG data after alcohol intake shows an increased intensity of deep SWS. This manifestation of stronger activity of SWS reinforces the probabilities of incomplete awakening with its attendant confusion, dulling of painful stimuli, and amnesia. The recorded third night sleep is compatible with the victim’s statement and with the medical observations. The accused was found guilty and sentenced to 5 years in jail, 4 years and 7 months suspended (he had spent 5 months in preventive detention).

References:

763.U

Work-related Predictors of On-duty Alertness in Irregular Work Schedules

Pilcher HH, Anderson J, Edwards G, Coplen MK
(1) Department of Psychology, Bradley University, (2) Office of Research and Development, Federal Railroad Administration

Introduction: Irregular work schedules are experienced by a wide range of workers in modern society. Locomotive engineers are one group of workers that frequently are required to work irregular hours. Most engineers are on-call 24 hours a day with no scheduled days off and frequently must report to work with as little as a 90-minute notice. An earlier study (Baker, et.al., 1997) found that sleep duration in Australian railroad engineers varied according to the duration of the off-duty period and to the time of onset of the off-duty period. In a preliminary study, we examined how the irregular work/rest cycles in engineers predict on-duty alertness (Pilcher & Coplen, 1999). However, we used data where each day was defined from midnight to midnight. Defining each day in this manner artificially split the midnight activity (e.g., sleep, work) between two separate days. To address this issue, we redefined the days in the data set as circadian days (from wake-up time to wake-up time following major sleep episodes). This allowed us to create a more logical definition of each day in the irregular work/rest cycles experienced by most engineers. The purpose of the current study was to examine how well work-related variables predict on-duty alertness using circadian days to organize the data set.

Methods: The current data were gathered as part of the Federal Railroad Administration’s fatigue program by the Volpe National Transportation Systems Center (Pollard, 1996). A sample of 179 locomotive engineers (mean age: 43.5±6.4) completed a 14-day activity log providing information on their daily work/rest activity. The current data set used circadian days defined from wake-up time to the next wake-up time following major sleep episodes. Major sleep episodes were typically classified as a sleep period of at least 4 hours in duration. In some cases, decisions had to be made when there were either two or more similar length sleep episodes occurring or when no sleep episode of at least 4 hours in length occurred for 36 hours or more. In those cases, major sleep episodes were usually defined as a sleep episode that occurred at night. As part of the activity log, participants provided estimates of alertness (scale of 1: fully alert to 4: fighting sleep) every 2 hours while at work. After removing days when no duty time occurred and days where incomplete information did not allow for the reliable calculation of the circadian day, the modified data set contained 1381 days. A series of regression analyses were completed using work-related variables to predict average on-duty alertness. To reflect irregular work schedules, we utilized variables indicating the time that the participants were called by their work with information about when to report to work (time called), time that the participants went on duty (on-duty time), time that the participants went off duty (off-duty time), the duration of the work period (work duration), the duration of the off-duty period (off-duty duration), and the length of the circadian day (day length). In addition, because these work-related variables frequently changed from day to day, we calculated the amount of variance for each of the work-related variables. We also completed a supplementary regression analysis examining the degree to which the variables in our final regression model overlapped to control for artificially inflating the R2 value.

Results: The regression model presented in Table 1 provided the best
predictive model of average on-duty alertness in the current data set. All variables in the model accounted for a significant amount of variance in on-duty alertness. Together the work-related variables accounted for 19.7% of the variance in on-duty alertness in the irregular work schedules used in the current data set. The variance around on-duty time, the variance around off-duty time, day length, and variance around day length did not significantly predict on-duty alertness. Finally, the variables in the final regression model all had variable inflation factors of less than 2.5, indicating that they were largely independent of each other.

Table 1
Forward Regression of On-Duty Alertness

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>ΔR²</th>
<th>Model R²</th>
<th>Step F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-duty time</td>
<td>.074</td>
<td>.074</td>
<td>82.12***</td>
</tr>
<tr>
<td>Work duration</td>
<td>.056</td>
<td>.129</td>
<td>65.69***</td>
</tr>
<tr>
<td>Off-duty duration</td>
<td>.018</td>
<td>.147</td>
<td>21.24***</td>
</tr>
<tr>
<td>Time called variance</td>
<td>.015</td>
<td>.162</td>
<td>18.36***</td>
</tr>
<tr>
<td>Work duration var</td>
<td>.012</td>
<td>.174</td>
<td>14.59***</td>
</tr>
<tr>
<td>Off-duty duration var</td>
<td>.006</td>
<td>.179</td>
<td>7.24**</td>
</tr>
<tr>
<td>Time called</td>
<td>.004</td>
<td>.183</td>
<td>4.64*</td>
</tr>
<tr>
<td>On-duty time</td>
<td>.014</td>
<td>.197</td>
<td>18.27***</td>
</tr>
</tbody>
</table>

Conclusions: The current data indicate that a variety of components related to irregular work schedules impact on-duty alertness. Furthermore, the two biggest predictors were the time that the participants got off of work and the duration of the work period.

References:
(1) Baker A, Reid K, Roach G, Dawson D. Sleep duration as a function of clock time and duration of break period in train drivers working irregular shifts. Sleep Res, 1997; 26, 700
(2) Pilcher JJ, Coplen MK. Predictive models of on-duty alertness in irregular work/rest cycles. Sleep Research Online, 2(Suppl. 1), 1999, 264.

Note: The views of the authors do not purport to reflect the position of the Federal Railroad Administration or the Department of Transportation.

764.U

Self-reported Sleep Duration of College Students: Consideration of Ethnic Differences

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(1) Sleep Center, Department of Psychiatry, Kingsbrook Jewish Medical Center, NY, (2) SUNY Downstate Medical Center, NY

Introduction: While it is recommended to sleep 8 hours at night, recent results of the ‘Sleep in America Poll’ indicated that American adults reportedly sleep only an average of 6.57 hours. However, that report did not address whether there were possible ethnic disparities in reported sleep durations. As reported in 1997, data from the National Health and Nutrition Examination Survey, which used a nationally representative probability sample of non-institutionalized adults, showed that a greater proportion of African Americans (11%) compared to European Americans (8%) slept more than 8 hours. About a decade earlier, estimates of sleep duration greater than 8 hours were 11% for African Americans and 18% for European Americans, according to the Alameda National Health Interview Survey. These prevalence data are important since sleeping greater than 8 hours is associated with mortality and significant morbidities. The present study sought to determine habitual sleep duration of college students from an urban university campus.

Methods: A sample of 294 students between the ages of 18 and 51 years, (male = 114, female = 180) from undergraduate courses offered by the department of Psychology at the College of Staten Island volunteered in this study. Participating students were asked to complete an anonymous questionnaire assessing sleep-wake habits. Description of the items comprising the questionnaire has been published previously. In this report, data on habitual sleep duration obtained on weekday and on weekend are analyzed. Although a number of volunteers omitted certain items on the questionnaire, all of them completed the survey. Students were selected from day as well as night classes. Hence, some older students also participated in the study, thus increasing the age range.

Results: Minority and White college students did not differ regarding age, gender, credit load, and grade point average (GPA) (see Table 1). Compared to Whites, minority students reported lower sleep duration both on weekdays and on weekend (marginal means and SE are presented in Table 2).

Table 1

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Age</th>
<th>GPA</th>
<th>Credit</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>23.8 (7.8)</td>
<td>2.9 (.8)</td>
<td>12.2 (4.1)</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>Minority</td>
<td>23.9 (7.0)</td>
<td>2.8 (.9)</td>
<td>12.8 (3.9)</td>
<td>34%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Table 2

Univariate ANOVA

<table>
<thead>
<tr>
<th>Sleep Duration</th>
<th>Minority</th>
<th>White</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekday (hrs)</td>
<td>6.7 (.17)</td>
<td>7.1 (.11)</td>
<td>3.49</td>
<td>0.063</td>
</tr>
<tr>
<td>Weekend (hrs)</td>
<td>6.9 (.30)</td>
<td>7.6 (.18)</td>
<td>4.53</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Conclusions: Results of our survey are consistent with previous survey data showing better sleep patterns for White college students compared to minority students. Interestingly, although both minority and White students slept more on weekend, nonetheless differences persisted favoring longer sleep for Whites. The finding of less sleep duration among minority students does not seem to suggest an inherent inability to acquire equivalent amount of sleep as reported by White students. Rather, socioeconomic disparities might explain observed ethnic differences in sleep duration. Indeed, when healthy sleepers of different ethnicities were studied in laboratory setting, where sleep-wake schedules were regularized, virtually no polygraphic differences in sleep patterns were observed.

References:
(2) Carskadon MA. Patterns of sleep and sleepiness in adolescents. Pediatrician 1990;171:5-12.
Sleep Efficiency during Chronic Nocturnal Sleep Restriction with and without Diurnal Naps

McConnell KJ, Maislin G, Rogers NL, Price NJ, Mullington JM, Zuzka MP, Brodhuan CG, Cerceo L, Van Dongen H, Dinges DF

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Introduction: A single daytime nap used to supplement chronically restricted nighttime sleep has the potential to reduce the impact of chronic partial sleep deprivation. However, there have been no studies on the extent to which chronic restriction of nocturnal sleep in combination with a diurnal nap is achievable day after day. To address this issue, sleep efficiencies were evaluated during an experiment in which 18 different combinations of nocturnal sleep and diurnal nap durations were each studied for 10 consecutive days.

Methods: A total of n=91 healthy adult subjects (53m; 38f; mean age 29.3y) participated in a 14-day laboratory study. The study involved two nights of baseline sleep (8.2h TIB between 21:54 and 06:06) and one night of recovery sleep (14h TIB between 21:54 and 11:54) separated by 10 nights of sleep restriction. The sleep-restriction conditions involved random assignment to one of 18 different sleep combinations, varying from 8.2h to 4.2h TIB per 24h. Nocturnal anchor sleep involved 4.2h, 5.2h, 6.2h, or 8.2h TIB, and was combined with a diurnal nap duration of 0.0h, 0.4h, 0.8h, 1.2h, 1.6h, 2.0h, or 2.4h (see Table which shows 13 of the 18 conditions). There were 4 anchor nocturnal sleep only conditions, and 14 anchor plus nap conditions. PSG (for nocturnal anchor sleep as well as diurnal naps) was recorded during both baseline days, 8 of the 10 restriction days, and recovery. The PSG records were scored visually using standard criteria. Sleep efficiency (SE = [TST/TIB] x 100%) was extracted for each nocturnal anchor sleep, diurnal nap sleep, and total sleep per 24h. Linear regression versus anchor sleep condition

Results: To date, 13 of the 18 conditions (i.e., 808 sleep recordings for n=61 subjects) have been analyzed, with the remaining 5 conditions to be completed in coming months. The Table shows average sleep efficiencies across the 10-day restriction period for each of the 13 conditions. Mean sleep efficiencies are displayed for nocturnal anchor sleep, diurnal nap sleep, and total sleep per 24h. Linear regression versus anchor sleep condition

Table 1

<table>
<thead>
<tr>
<th>Time in bed (TIB in h)</th>
<th>Sleep efficiency (SE in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nocturnal anchor</td>
<td>nocturnal anchor</td>
</tr>
<tr>
<td>diurnal nap</td>
<td>diurnal nap</td>
</tr>
<tr>
<td>4.2</td>
<td>94</td>
</tr>
<tr>
<td>0.0</td>
<td>91</td>
</tr>
<tr>
<td>0.4</td>
<td>79</td>
</tr>
<tr>
<td>0.8</td>
<td>94</td>
</tr>
<tr>
<td>1.2</td>
<td>87</td>
</tr>
<tr>
<td>2.0</td>
<td>88</td>
</tr>
<tr>
<td>2.4</td>
<td>83</td>
</tr>
<tr>
<td>5.2</td>
<td>86</td>
</tr>
<tr>
<td>0.0</td>
<td>95</td>
</tr>
<tr>
<td>0.4</td>
<td>92</td>
</tr>
<tr>
<td>0.8</td>
<td>89</td>
</tr>
<tr>
<td>1.2</td>
<td>94</td>
</tr>
<tr>
<td>2.0</td>
<td>92</td>
</tr>
<tr>
<td>2.4</td>
<td>93</td>
</tr>
<tr>
<td>6.2</td>
<td>88</td>
</tr>
<tr>
<td>0.0</td>
<td>84</td>
</tr>
<tr>
<td>0.4</td>
<td>95</td>
</tr>
<tr>
<td>0.8</td>
<td>92</td>
</tr>
<tr>
<td>1.2</td>
<td>92</td>
</tr>
<tr>
<td>2.0</td>
<td>93</td>
</tr>
<tr>
<td>2.4</td>
<td>94</td>
</tr>
</tbody>
</table>

Conclusions: In general, sleep efficiencies were remarkably high in these chronic conditions. On average, subjects were able to sleep even during very short diurnal naps (24min) when sleep was chronically restricted at night. Sleep latency appears to be the underlying factor responsible for the variation in sleep efficiencies observed. Further analyses are underway on PSG sleep architecture in these different chronic sleep conditions.

Research supported by NASA cooperative agreement NCC 9-58 with NSBRI, and NIH grants NR04281, RR00040 and K23AG8672

Effects of Environment on Post-Weaning Developmental Changes in Sleep Patterns

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Introduction: Changes in sleep patterns occur in early development and aging. However, little is known about changes that occur between weaning and sexual maturity. Environmental enrichment (EE) between one and three months of age effects behavioral and physiological measures. Enriched animals perform better on memory tasks, have increased expression of growth factors (1), and are less susceptible to genetically induced deficits (2). In addition, enriched animals display increased amounts of paradoxical sleep (PS), an effect maintained until senescence (3). Here, we tested the effects of environment on maturational patterns of sleep.

Methods: Twelve male and female Long-Evans rats were housed under 12:12 L/D cycle. At weaning electroencephalographic and electromyographic electrodes were implanted. Following a 24-hour baseline recording, animals were assigned to either enriched or standard conditions. Animals were then repeatedly recorded for 24 hours every ten days. EE animals were housed 3 per cage (100x100x50 cm) that contained multiple novel objects that were changed every day. Every two days the animals were moved to a new cage. To avoid social stress, cage-mates remained constant. Animals in the standard environment (SE) were maintained in standard housing.

Results: We found an increases in power in the 6-8 Hz range in PS during as a function of age (*F=2.7, p=0.01) and environment (** F=3.0, p=0.007) (fig.1). In SWS, an overall reduction in the lower frequency bands (1-3 Hz) progressed with development (F=2.8, p=0.001), and EE animals had more power in the lower frequency bands creating a steeper distribution of power during SWS (**F=2.3, p=0.008) (fig. 2). EE animals also spent more time in PS during the dark phase at the expense of wake (i.e., no change in SWS time).

Figure 1
Conclusions: These results indicate that sleep patterns continue to change until puberty and these changes are modulated by experience.

References:
(3) van Gool, W., Mirmiran M. Effects of aging and housing in an enriched environment on sleep-wake patterns in rats. Sleep 1986, 9(2): 335-47.

Research supported by NIH grant #: 1RO1HD37351

Visual Discrimination Learning Across Multiple Session and Days

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Dept. of Psychiatry, Harvard Medical School

Introduction: Sleep appears to play a critical role in the consolidation of visual discrimination learning (Karni & Sagi, 1991). No improvement is seen when subjects are trained and then retested prior to a night’s sleep (Stickgold et al., 2000a), and no improvement is seen when subjects are deprived of sleep on the night following training and then retested after two nights of recovery sleep (Stickgold et al., 2000b). Both REM and SWS appear necessary for this sleep-dependent improvement to occur (Stickgold et al., 2000a; Karni & Sagi, 1991). While no improvement is seen if retesting occurs prior to a night’s sleep, it remains unclear whether additional training, before that night’s sleep, might lead to increased improvement on the following day. If this second training session produced no additional improvement after sleep, it would suggest that the initial training session had saturated some pre-sleep component of the learning process.

Methods: In this study, subjects were run through four session of the visual discrimination task, as described earlier (Stickgold et al., 2000a). Subjects were randomly assigned to four groups: 4000 - subjects were tested four times on day 1, at 9 AM, noon, 3 PM and 6 PM; 3100 - subjects were tested three times on day 1, at 9AM, noon, and 3 PM on day 1, and at 9 AM on day 2; 3001 - subjects were tested three times on day 1, at 9 AM, noon, and 3 PM on day 1, and at 9 AM on day 2; 1111 - subjects were tested at the same time on days 1, 2, 3, and 4. For each subject, threshold times for signal detection were obtained for each of the four sessions. Results from Stickgold et al (2000b) are presented for comparison: 11 - subjects were tested twice, with 24 hr between sessions; 1001 - subjects were tested twice, with 72 hr between sessions.

Results: The improvement seen between two test sessions which take place at least 24 hr apart depended only on the number of days between training and testing. Thus, if two sessions were one day apart, improvement averaged 11.0 ms, regardless of whether there were two or four sessions in total, while if the sessions were three days apart, improvement averaged 18.0 ms, regardless of whether there were two or four sessions, and, when there were four sessions, on what days the additional two sessions occurred (Table 1). In contrast, when multiple sessions were carried out on day 1, performance deteriorated with each additional session (Table 2). Thus, when sessions were carried out without intervening sleep, there was an actual decrease in performance levels. Since the first session appeared to saturate the learning process, we have begun to investigate an abbreviated training/test session, with 11 blocks of trials instead of the standard 25 trials. In this case, the 1001 group produced an average of 10.5 ms improvement, while the 1111 group produced 19.4 ms. Unfortunately, not all subjects have been run, and the difference is not statistically significant.

<table>
<thead>
<tr>
<th>Group</th>
<th>Test Interval</th>
<th>Improvement ± SEM (ms)</th>
<th>Relative Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1 d</td>
<td>12.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>11(11)</td>
<td>1 d</td>
<td>11.4 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>1 d</td>
<td>8.9 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>1001</td>
<td>3 d</td>
<td>19.8 ± 3.4</td>
<td>57%</td>
</tr>
<tr>
<td>1111</td>
<td>3 d</td>
<td>17.8 ± 3.5</td>
<td>56%</td>
</tr>
<tr>
<td>3001</td>
<td>3 d</td>
<td>16.3 ± 4.7</td>
<td>83%</td>
</tr>
</tbody>
</table>

Conclusion would appear to be that improvement across days follows a ballistic course after the initial training session, independent of further training sessions, but that repeated sessions on the first day lead temporarily to diminished performance. With abbreviated sessions, additional sessions might lead to increased overall improvement.

<table>
<thead>
<tr>
<th>Session</th>
<th>n</th>
<th>3-x-1 (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>58.4 ± 2.8</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>71.0 ± 4.4</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>80.7 ± 5.0</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>82.4 ± 7.8</td>
</tr>
</tbody>
</table>

Conclusions: These results suggest that the amount of improvement is totally determined by the number of days between the first and last test. There appears to be no difference between 1001, 3001, and 1111 protocols or between 1100 and 3100, while the improvement seen in the across 3 days was on average 65% greater than that seen after just 1 day. The conclusion would appear to be that improvement across days follows a ballistic course after the initial training session, independent of further training sessions, but that repeated sessions on the first day lead temporarily to diminished performance. With abbreviated sessions, additional sessions might lead to increased overall improvement.

References:
Coping Strategies for Sleep Disturbances in College Students

(1) Institute of Behavioral Medicine, National Cheng-Kung University, College of Medicine, Tainan, Taiwan, (2) Department of Family Medicine, National Cheng-Kung University, College of Medicine, Tainan, Taiwan

Introduction: Previous surveys have reported sleep disturbance to be a common problem in college students. The sleep complaints were also found to be associated with lower academic performance and daytime sleepiness. (1) However, previous studies seldom discussed about the coping strategies used by the students to resolve their sleep problems. Current study is aimed to explore not only the sleep habits and sleep disturbances in college students, but also the coping strategies they apply to overcome their sleep problems. In addition, subjective sleep quality and sleepiness were compared between students using different coping strategies.

Methods: Subjects were 1930 college freshmen (1390 males and 540 females) of National Cheng Kung University in Taiwan. Their average age was 18.51 (SD = 0.93). They filled out a survey questionnaire that includes the Pittsburgh Sleep Quality Index (PSQI)(2), Epworth Sleepiness Scale (ESS)(3), and questions concerning their sleep habits, sleep disturbances, and coping strategies.

Results: The result shows that 40.7% of the subjects reported having some types of sleep disturbances, including insufficient sleep (23.2%), sleep onset difficulty (14.5%), irregular sleep pattern (3.4%), morning and daytime fatigue (3.5%), poor sleep quality or light sleep (2.2%) and others (1.5%). The subjects having sleep disturbances were found to rate themselves sleepier (12.54 vs. 11.06; t=8.93, p<.001) on ESS and with lower sleep quality on PSQI (6.57 vs. 4.80; t=15.85, p<.001) than subjects with no sleep disturbances. In the subjects who reported sleep disturbances, about 27% of them could not find a coping strategy. Coping strategies applied included “cat naps” (27.1%), adjusting sleep schedule (12.9%), “try to ignore” the problems (12%), and various other strategies (19.8%; e.g., taking medication, “forcing oneself to fall asleep”). PSQI and ESS ratings among groups of subjects using different coping strategies were also compared with ANOVAs (see Table).

Table 1

<table>
<thead>
<tr>
<th>Coping Strategies*</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>7.13 (2.85)</td>
<td>5.98 (2.37)</td>
<td>5.40 (1.98)</td>
<td>6.60 (2.76)</td>
<td>6.95 (2.70)</td>
<td>11.90*</td>
</tr>
<tr>
<td>ESS</td>
<td>12.73 (5.58)</td>
<td>12.60 (3.49)</td>
<td>12.37 (3.70)</td>
<td>12.77 (3.31)</td>
<td>11.84 (3.73)</td>
<td>1.84</td>
</tr>
</tbody>
</table>

* Coping strategies: A – couldn’t find a strategy; B – “cat naps”; C – adjusting sleep schedule; D – “try to ignore” the problem; E – others.

p < .005; A > B, C, D, E; D=E>B=C (Tukey method)

Conclusions: Consistent with previous studies, the results of this study indicate a high percentage of sleep complaints among college students. Higher level of daytime sleepiness was also found to be associated with the sleep problems. The most common problems reported were insufficient sleep and sleep onset difficulty. Surprisingly, there were over one fourth of the students reported not being able to find a coping strategy for their sleep problems. These students were also the ones with poorest sleep quality. On the other hand, the most frequently used coping strategies, “cat naps” and adjusting sleep schedule, were found to be associated with better sleep quality. While these findings may indicate that the coping strategies applied were effective in improving their sleep quality, an alternative explanation is that the students with higher degree of sleep disturbances tend to be more helpless and not being able to find a method for coping. No difference in the ratings of daytime sleepiness among the groups with different coping strategies further suggests that the coping strategies applied may not be effective enough to overcome the daytime consequences of their sleep disturbances. The findings point to the importance to institute sleep education in college settings.

References:
Conclusions: Long-term vigilance performance was most impaired in narcoleptic patients, followed by insomniac patients. The latter result was unexpected since there are only very few reports in the literature, showing performance deficits of insomniac patients. Our results suggest that performance deficits in insomniac patients may appear only in extended test sessions and thus remained unrecognized in earlier studies. The present results also replicate our earlier finding that CPAP treatment improves CFF performance in OSAS patients.2

References:

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770.U

Meteorological Factors And Subjective Sleep Continuity: A Replication And Extension

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Introduction: Little is known about whether meteorological factors other than light1 influence sleep continuity. Last year, we reported that precipitation and barometric pressure were moderately correlated with sleep parameters2. In the present study, a replication was attempted using a new sample.

Methods: Sleep diary data, using scantron forms, were collected from 21 undergraduates from 1-17-2000 to 4-29-00 (105 days). Subjects (M:5, X=20.4; F:16, X=20.6) completed daily diaries that were collected once a week. Diaries contained two sections: one dedicated to day-time functioning (completed at bedtime) and one to sleep continuity (completed on awakening). Eight sleep variables were assessed: sleep latency (SL), number of awakenings (FNA), wake after sleep onset (WASO), total sleep time (TST), bedtime (TTB), wake time (TOB), total sleep opportunity (TSO) and sleep efficiency (SE). Meteorological data, obtained from the National Climatic Data Center, included daily means for barometric pressure (BP), precipitation (P), temperature (T), dew point (DP), snow depth (SD), and wind speed (WS). Hours of sunlight (HS) and moon luminosity (ML) were obtained from the U.S. Naval Observatory. Sleep diary data were averaged to yield mean sleep continuity profiles for each of the 105 days. These data were correlated with the meteorological variables for the 105 days. The resulting correlational analyses yielded a 8 x 8 correlation matrix. Mean sleep profiles were used to factor out night-to-night individual differences in sleep continuity.

Results: 39 of 64 correlations were significant (p <0.05). Correlational magnitudes ranged from 0.19 to 0.49. Sleep continuity measures that showed the greatest association with meteorological phenomena were, in order of magnitude, WASO, SE, SL, and TSO. Meteorologic variables that showed the greatest association with sleep continuity measures were, in order of magnitude, hours of sunlight, snow depth, dew point, temperature, barometric pressure, precipitation, and moon luminosity. The five largest correlations were as follows: HS*SL r = 0.49; HS*SE r = 0.43; HS*WASO r = 0.42; SD*WASO r = 0.36; DP*WASO r = 0.35. Barometric pressure was significantly correlated with SL (r = 0.22, p <.05) and tended to be correlated with FNA and SE (p<0.06). Precipitation was significantly correlated with WASO (r = 0.30, SE (r = - 0.23) and TSO (r = 0.23).

Conclusions: The data from the present study partially confirm our prior findings. While barometric pressure and precipitation continued to be relevant factors, hours of sunlight assumed a degree of importance not evident in our prior study. This, as with other differences between the two investigations, may be due to several factors including: the use of scanable forms and/or to differences in weather & group sleep continuity patterns across the two years. The latter two possibilities are the subject of on-going investigation.

References:

Profiles of Three Different Neurobehavioral Measures: Performance-Based, Physiological, and Subjective During 16 Days of Sleep Limited to 3 h per Day

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Introduction: Neurobehavioral tests are generally classified into three categories, performance-based, physiological, and subjective. Except for the alpha attenuation test, each of the neurobehavioral tests used in this research, has been used in many prior reports of the effects of reduced sleep, but never used with sleep so severely reduced, nor used for as long as reported here. The following research tested 3 subjects 18 times per day on average for 28 days under controlled laboratory conditions.

Methods: 3 male subjects mean age 39.3 y (33 y, 40 y, 45 y) had pri-
vate bedrooms in a simulated residential apartment scenario where they lived for three 30 day experiments. Their scheduled sleep time was reduced to 3 h per day. The subjects were paid $50 per day and were sleeping according to three different schedules (a comparison of those schedules is beyond the scope of this report). The study included 9 pre-treatment and transition days, 16 days of sleep reduced to 3 h per day and 5 recovery days. The data presented are for the 3 performance based tests: the descending subtraction test (DST, Dinges, 1990), the memory and search test (MAST, Folkard, 1976), and the grammatical transformation test (GTT, Baddeley, 1968). The physiological test is the EEG-based alpha attenuation test (Stampi, 1995), and the subjective sleepiness scale is the Stanford sleepiness scale (Hoddes, 1973).

Results: Data from all subjects and all sleep schedules have been combined to generate daily means as plotted in figure 1. The data are expressed as the raw number of correct responses for performance, a unitless ratio for the AAT (the lower the value, the greater the sleepiness), and the 1 to 7 point SSS scale; 7 being most sleepy. There is a robust practice effect in all three performance-based tests. This practice effect dissipates in 8 days, but performance on the GTT has been reported to increase continually over 7 weeks of testing (Blagrove, 1995). The MAST and GTT and to some extent the DST show a steady linear decline in performance but do not detect early deficits resulting from sleep reduction. The AAT and SSS are immediately sensitive to slight degrees of sleep reduction.

Conclusions: Different neurobehavioral tests should be used to measure different effects and amounts of sleep reduction. Performance-based tests are sensitive to severe sleep loss in the medium to long term. The practice effect prevents their use in the short term. Performance-based tests may also saturate and fail to respond to further sleep reduction. The Alpha Attenuation Test is sensitive in the short term and variable in the medium to long term. The SSS is sensitive in the short term but subjects habituate. The importance of neurobehavioral tests has been underscored by Dinges and Achermann 1999.