THE SECOND ANNUAL
CSCN & Penn Chronobiology Program Joint Collaboration Research Retreat

06.17.2015 Penn Law School-Levy Conference Center
8:00am - 5:30pm

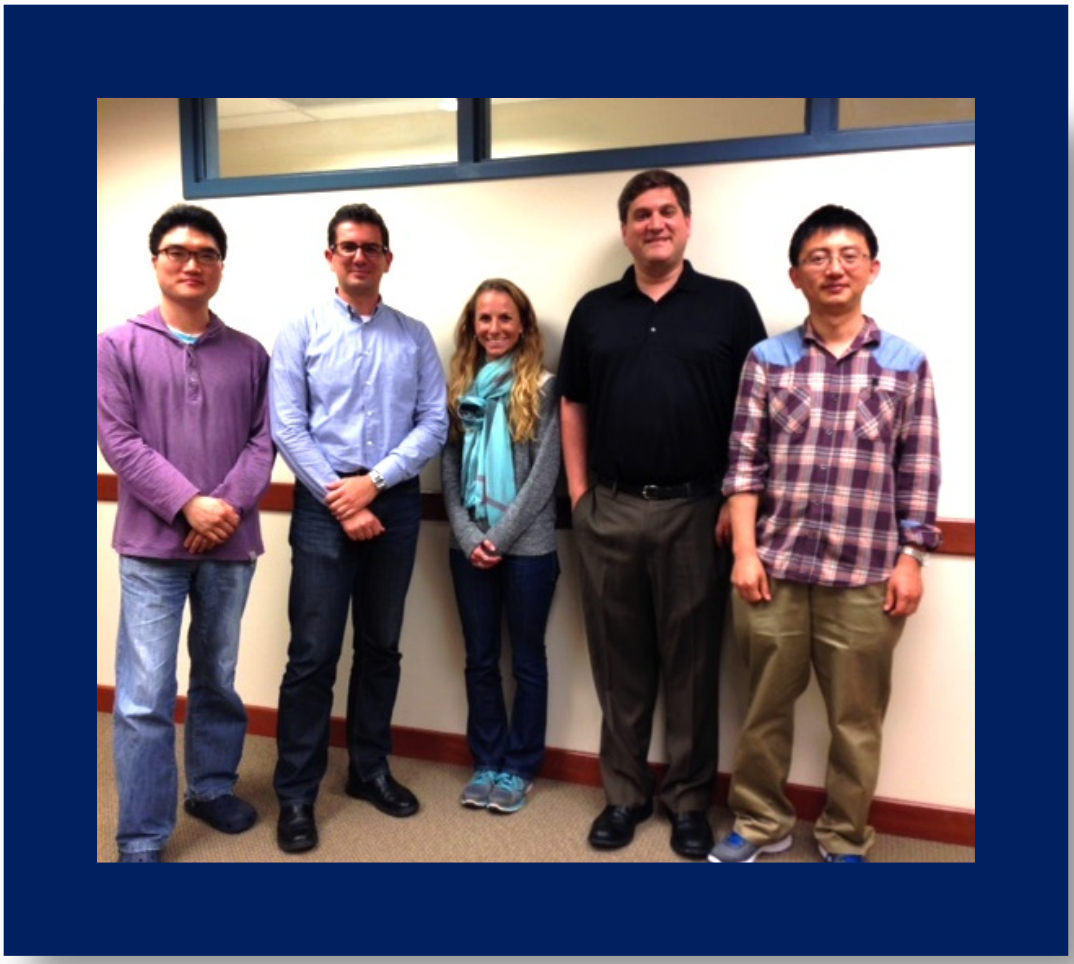
Perelman School of Medicine
University of Pennsylvania

PARTNERSHIP VISION TEAMWORK

CENTER FOR SLEEP AND CIRCADIAN NEUROBIOLOGY

2015 CSCN & Chronobiology Collaborative Retreat
Schedule of Events - Wednesday, June 17, 2015
Levy Conference Center, Penn Law School

8:00 AM – 8:45 AM	Poster Mounting & Catered Breakfast
8:45 AM – 9:05 AM	Opening Remarks from the Center Director (Allan I. Pack, MBChB PhD)
9:05 AM – 9:15 AM	Welcome from the Retreat Planning Committee Chair (Michael A. Grandner, PhD)
9:15 AM – 10:30 AM	Session 1: SLEEP DISORDERS AND SLEEP LOSS
	Wailuddin S. Khadeer "Use of Mobile Electronic Devices in Bed Associated with Sleep Duration, Insomnia, and Daytime Sleepiness"
	Olga Tkachenko "The Impact of Recovery Sleep Opportunity on Neurobehavioral Measures Following Chronic Sleep Restriction"
	Margaret C. Souders "Pilot Study of a Tailored Behavioral Intervention for Insomnia in Children with Autism Spectrum Disorder: Preliminary Results"
	Christopher Cielo "Restless Legs Syndrome in Children with a History of Prematurity"
	Enda M. Byrne "Shared Genetic Risk Factors between Schizophrenia and Subjective Sleep Quality and Duration in a Population-based Cohort of Australian Twins"
10:30 AM – 11:00 AM	Break and Posters
11:00 AM – 12:00 PM	Session 2: SLEEP, ENERGY AND METABOLISM
	Stephen Wang "Effect of Weight-loss on Tongue Fat and Upper Airway Structures"
	Arjun Sengupta "Estimation of Brain Response During Sleep from Serum Metabolome by NMR Spectroscopy"
	Isaac J. Perron "Diet/Energy Balance Affect Sleep and Wakefulness Independent of Body Weight"
	Sarah C. Mc Loughlin "Exercise Training Affects Metabolic and Locomotion Deficits of BMAL1 Prenatal Knockout Mice"
12:00 PM – 1:00 PM	Lunch
1:00 PM – 2:00 PM	Posters
2:00 PM – 2:45 PM	Session 3: BASIC SLEEP AND CIRCADIAN SCIENCE
	Nicholas F. Trojanowski "Distinct Mechanisms Underlie Two Types of Caenorhabditis Elegans Sleep"
	David S. Garbe "Sex Differences in Drosophila Sleep Patterns"
	Jennifer C. Tudor "Increasing Protein Synthesis in the Hippocampus Prevents Cognitive Impairments Caused by Sleep Deprivation"
2:45 PM – 3:15 PM	Break (Award Selection Panel meeting at this time)
3:15 PM – 4:30 PM	Adrian R. Morrison Keynote Address (3:15pm introduction by Amita Sehgal, PhD)
	"Origins: A Very Short History of Circadian Biology" William J. Schwartz, MD, Professor of Medicine University of Massachusetts Medical School, Department of Neurology
4:30 PM – 5:30 PM	Awards and Reception



Dear Friends and Colleagues,

We would like to welcome you to the annual Center for Sleep and Circadian Neurobiology Retreat – Penn Chronobiology Program Joint Retreat. This is our 12th year, and second annual collaboration with the Chronobiology Program.

The talks and posters presented here today represent the far-reaching breadth and multidisciplinary focus of the sleep community at the University of Pennsylvania. We would like to thank all of the trainees and faculty who submitted abstracts this year. The work demonstrates the productivity , innovation and diversity of sleep/wake and circadian research being conducted within the School of Medicine and beyond, including the Children's Hospital of the University of Pennsylvania, the School of Nursing, the Philadelphia VA Medical Center (newly name the Michael J. Crescenz VA Medical Center), and the School of Veterinary Medicine. We are also honored to welcome our keynote speaker, William J. Schwartz, MD.

We hope the wide range of research topics, from basic science to clinical and epidemiologic studies, will stimulate increasing collaboration, introduce researchers to innovative techniques and new areas of inquiry, and inspire novel approaches toward the study of sleep and consequences of sleep loss.

-The 2014 Retreat Planning Committee

Michael A. Grandner, PhD, MTR (Committee Chair), Andrea Spaeth, PhD. Georgios Paschos, PhD, Mi Shi, PhD, Yool Lee, PhD, and Karen McLaughlin, Administrative Coordinator

Welcome Message from Allan I. Pack, M.B.Ch.B., Ph.D., FRCP

We are pleased to present the 2015 Research Retreat by the Center for Sleep and Circadian Neurobiology. This year, we continue the collaboration of the Chronobiology Program headed up by Amita Sehgal, PhD from the Department of Neuroscience.

Again this year, faculty and trainees come together to present an impressive array of state-of-the-art basic science, clinical and translational studies in sleep and circadian research. We are in the Levy Conference Center in the Penn Law School for this one-day event.

Our thanks once again to this year's Research Retreat Committee, chaired by Michael Grandner and joined by Andrea Spaeth, Georgios Paschos, Mi Shi, and Yool Lee in choosing an interesting program to be presented to you today.

For the third year, the keynote address will be named for emeritus professor of veterinary medicine, Adrian Morrison, DVM, PhD. It is our way of honoring Dr. Morrison's contributions. We are honored to welcome William J. Schwartz, MD from the University of Massachusetts Medical School to present the keynote address.

Words of Welcome from Amita Sehgal, PhD

We are delighted to host the 2nd retreat of the Penn Chronobiology Program together with the Center for Sleep and Circadian Neurobiology.

The Chronobiology Program brings together researchers working in the very diverse areas impacted by circadian clocks. These include metabolism, cardiovascular biology, immunology, cancer, sleep and other behaviors. Research in these areas at Penn is at the forefront of the circadian field, and the collaboration with the CSCN further expands the scope and interdisciplinary nature of the work. The strength of this collaboration is borne out by the presentations at the retreat today. Thanks to the members of the planning committee who worked tirelessly to put together this outstanding program.

Today, we welcome keynote speaker, **William J. Schwartz, MD**

William J. Schwartz received his M.D. (1974) and neurology residency training (1978-1981) at the University of California, San Francisco, completed a research fellowship at the National Institute of Mental Health (1975-1978), and was on the faculties of Harvard Medical School and the Massachusetts General Hospital (1981-1986) before moving to the University of Massachusetts. Visiting Professorships have included the Boerhaave Professor at Leiden University Medical Centre (2005) and the Baerends Visiting Chair at Rijksuniversiteit Groningen (2008), both in the Netherlands; and the Hood Fellow at the University of Auckland (2012), in New Zealand.

In 2005, Dr. Schwartz was honored with the Neurology Residents' Teacher of the Year Award, and in 2014 was selected for the Dean's Award for Outstanding Faculty Contribution to Graduate Education in the Graduate School of Biomedical Sciences at the University of Massachusetts Medical School. Dr. Schwartz is the Editor-in-Chief of the Journal of Biological Rhythms.

William J. Schwartz, MD will deliver his keynote address titled, "Origins: A Very Short Story of Circadian Biology" that will add greatly to our program of exciting and innovative research today.

Abstracts - Oral Presentations

Listed in Alphabetical Order by First Author

Shared Genetic Risk Factors between Schizophrenia and Subjective Sleep Quality and Duration in a Population-based Cohort of Australian Twins

Enda M Byrne[1,2]

[1]The University of Queensland, Queensland Brain Institute, Brisbane, Australia, [2] Visiting Research Fellow, Center for Sleep and Circadian Neurobiology, University of Pennsylvania

Trainee Award Eligible

Disruption of circadian rhythms and perceived changes in sleep quality are common features of psychiatric disorders. Insomnia or hypersomnia are commonly reported in major depressive disorder (MDD) and bipolar disorder.

The observation of circadian disruption in psychiatric disorder patients, and the high heritability of schizophrenia and bipolar disorder ($h^2 \sim 0.8$) has led to the hypothesis that polymorphisms in genes encoding components of the circadian clock may influence susceptibility to psychiatric disorders. A large number of candidate gene studies have been conducted to test this hypothesis, with no consistently replicated findings.

Hypothesis-free genome-wide association studies from the Psychiatric Genomics Consortium (PGC) have begun to identify genetic variants that confer risk to psychiatric disorders. Specifically, 108 individual loci have been identified for schizophrenia, the largest of any psychiatric study to date. None of the identified associations were found in genes encoding core components of the molecular clock. However, genes associated with schizophrenia may still be associated with sleep and circadian phenotypes.

In this study, the results from the PGC schizophrenia study were used to build a predictor to test whether those who carry more schizophrenia risk alleles have poorer self-reported sleep quality. 2,887 twins from the Australian Twin Registry who had also been genotyped using a GWAS chip were asked to report on the quality of their sleep on a 5-point scale. After correcting for age, sex and BMI, those carrying more schizophrenia alleles had significantly poorer sleep quality ($p = 0.001$). These results indicate that there are shared genetic risk factors for schizophrenia and subjective sleep quality in the population. Furthermore, investigation of correlation between results from the PGC schizophrenia analysis and those from a large consortium-based GWAS of sleep duration, also found significant evidence of genetic overlap.

Restless legs syndrome in children with a history of prematurity

[1]Cielo CM, [1]DelRosso LM, [2]Nixon GM, [3]Meltzer LJ, [2]Biggs SN, [1]Traylor J, [1]Marcus CL.

[1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Monash University, Melbourne, Australia

[3]National Jewish Health, Denver, CO

Introduction: Little is known about which children are at increased risk for restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). Polysomnographic data from the Caffeine for Apnea of Prematurity-Sleep study showed that 14% of a cohort of ex-preterm children aged 5-12 years had an elevated periodic limb movement in sleep (PLMS) index (>5/hour) but the clinical importance of this finding is unknown. We hypothesized that ex-preterm children would have a high prevalence of RLS and PLMD.

Methods: Subjects underwent polysomnography and caregivers completed questionnaires. A diagnosis of RLS or PLMD was established by meeting the ICSD3 criteria with positive symptoms derived from the Owens RLS questionnaire and the Pediatric Sleep Questionnaire (PSQ). Clinically available serum ferritin levels were assessed.

Results 5 (19.2%) of the 26 subjects with a PLMS index > 5who completed the RLS questionnaire had RLS; 10 (7.0%) of the 143 subjects with a PLMS index < 5had RLS (p=0.04). 11 of the 26 subjects with an elevated PLMS index (42.3%) had PLMD. 9 subjects were referred for serum ferritin evaluation, and levels ranged from 11 to 48.9 mcg/L.

Conclusion: children with a history of prematurity have an increased risk of RLS and PLMD. Iron deficiency likely contributes to RLS and PLMD symptoms in this population. Clinicians evaluating ex-preterm children with sleep disturbances should evaluate for RLS and PLMD. Prospective studies including serum ferritin evaluation are needed to confirm these findings.

Support: NIH RO1 HL098045; NIH KL2 TR000139.

Use of Mobile Electronic Devices in Bed Associated with Sleep Duration, Insomnia, and Daytime Sleepiness

Rebecca A. Gallagher MSEd, Michael L. Perlis PhD, Subhajit Chakravorty MD, Lauren Hale PhD, Marna Barrett PhD, Jesse Schuschu, Wailuddin S. Khadeer, and Michael A. Grandner PhD

INTRODUCTION: In recent years, mobile devices have become ubiquitous in bedrooms. The extent to which use of these devices is related to habitual sleep factors among adults is not well studied.

METHODS: Data from the Sleep and Healthy Activity, Diet, Environment, and Socialization (SHADES) study were used. Data were collected from surveys of adults age 22-60 in southeastern Pennsylvania (N=1007). Sleep duration was assessed using the NHANES item and was categorized as short (≤6h), normal (7-8h, reference), and long (≥9h). Insomnia was assessed using the Insomnia Severity Index (ISI) and was categorized as none (reference), mild, moderate, or severe. Sleepiness was assessed as scores of ≥10 on the Epworth Sleepiness Scale (ESS). Subjects were asked to rate the frequency of mobile electronic device use at night on a scale of 0 ("Never") to 4 ("Every night"). Variables included presence of device, any use, texting, emailing, browsing internet, calling, or social networking in bed, being woken by a call/text/email, being woken by device alarm, and checking device during the night. Since most use was among younger participants, age was restricted to 22-29 (N=473) and analyses were adjusted for age, sex, education, and race/ethnicity.

RESULTS: Simply having access to a device near the bed was not associated with short sleep, insomnia, or sleepiness, nor were most specific behaviors (e.g., calling or texting). Short sleep duration was associated with e-mailing "every night" (OR=2.95;p=0.003), browsing the internet (OR=5.73;p=0.003) and checking the device at night (OR=2.78;p=0.015). Being woken by a call "every night" was associated with moderate insomnia (OR=5.03;p=0.029), and checking the device was associated with mild (OR=4.25;p=0.001) and moderate (OR=17.69;p<0.0001) insomnia, as well as excessive sleepiness (OR=2.31;p=0.037).

CONCLUSIONS: Using the internet in bed was associated with shorter sleep duration and frequently checking the device at night was associated with less sleep, more insomnia, and excessive sleepiness.

SUPPORT: The SHADES study was funded by R21ES022931. Dr. Grandner is also supported by K23HL110216.

Sex differences in *Drosophila* sleep patterns

David S. Garbe[1], Abby Vigderman[1], & Amita Sehgal[1,2]

[1] Neuroscience Department, [2] Howard Hughes Medical Institute, University of Pennsylvania, Philadelphia, PA USA

Trainee Award Eligible

Female *Drosophila melanogaster*, like many other organisms, exhibit different behavioral repertoires after mating with a male. In female flies, these Post-Mating Responses (PMRs) include increases in egg production and oviposition (egg laying), decreases in receptivity (readiness to mate), and decreases in daytime sleep. Sex Peptide (SP), a protein transferred from the male during copulation, is largely responsible for these changes in behavior. Previous studies uncovered the receptor and neuronal circuits involved in receiving and relaying the mating signals that induce changes in egg laying and rejection behavior; however, less is known about the mechanisms that influence changes in sleep. In this study, we demonstrate that the canonical sex peptide receptor (SPR) is responsible for transmitting SP to induced post-mating decreases in sleep. Additionally, we show that the sensory neurons responsible for decreasing post-mating sleep are the same ones required to induce changes in egg laying and rejection behaviors. Thus, our data suggests that all three behaviors are governed through the same ligand/receptor pair acting through similar sets of neurons.

Exercise training affects metabolic and locomotion deficits of *BMAL1* prenatal knockout mice

Sarah C. McLoughlin, Elizabeth Hennessy, Sven-Christian Pawelzik, Garret A. FitzGerald

Institute for Translational Medicine and Therapeutics, University of Pennsylvania, USA

Trainee Award Eligible

Circadian rhythms orchestrate the expression of numerous physiological processes, behaviors and more than 40% of protein coding genes. Disruption of circadian rhythms by shift work or jet lag can have detrimental effects on human health. Prenatal loss of the circadian gene *BMAL1* leads to disruption of circadian rhythms in gene expression and activity concomitant with a range of defects including premature aging, hyperglycemia, inflammation and locomotion defects. While the mechanism of how *BMAL1* interacts with the aging process is unknown, *BMAL1* has been shown to be important in the aging-related pathway, autophagy. Inducible, but not basal, autophagy is necessary for the beneficial effects of exercise. The aim of this study was to determine if endurance exercise can ameliorate defects of *BMAL1* prenatal knockout mice. We show that a relatively mild, 8-week, controlled exercise program can increase exercise tolerance, RER, and activity levels of *BMAL1* prenatal knockout mice compared to sedentary controls. Conversely, exercise appears to exacerbate hyperglycemia in this model. We conclude that, despite deficits in basal autophagy, *BMAL1* prenatal knockout mice have the capacity to respond to exercise leading to improvements in a subset of defects. Future work will investigate the mechanisms by which exercise ameliorates phenotypes arising from prenatal loss of *BMAL1*.

Diet/Energy Balance Affect Sleep and Wakefulness Independent of Body Weight

Isaac J. Perron[1,2], Allan I. Pack[1], Sigrid Veasey[1]

[1]The Center for Sleep and Circadian Neurobiology and [2]The Neuroscience Graduate Group, Perelman School of Medicine, University of Pennsylvania, PA

Trainee Award Eligible

Obesity is highly prevalent in the United States and is strongly associated with excessive daytime sleepiness (EDS), even in individuals without obstructive sleep apnea or narcolepsy. Remarkably, obese patients who undergo bariatric surgery for weight loss report dramatic improvements in EDS before significant weight loss occurs, suggesting that other factors besides adiposity may contribute to daytime wake impairments. We hypothesize that energy balance (i.e., weight gain/loss) has independent effects on EDS and sleep/wake architecture. Rodent models of adiposity exhibit an EDS phenotype, evidenced by increased sleep time and fragmented sleep/wake states, which can be reversed by normalizing body weight. However, no study to date has tried to disentangle the relative contributions of diet/energy balance from body weight on sleep/wake architecture. To test this, we implemented a novel feeding paradigm that generates mice of equal body weight, but divergent energy balance. Adult mice were randomized to receive either regular chow (RC; 13.5% kcal from fat) or high fat diet (HFD; 45% kcal from fat) for eight weeks. After this chronic feeding, subsets of mice from each group were fed the opposite diet (a.k.a. diet switch), causing newly-fed HFD mice to gain weight and RC-fed mice to lose weight. Sleep/wake behavior was assessed at baseline (Week 0), pre-diet switch (Week 8), and post-diet switch (Week 9). At Week 9, absolute body weight was similar between diet switch conditions ($p>0.05$), but weight-loss mice exhibited significantly increased wake time ($p<0.05$) and consolidated sleep/wake bouts ($p<0.05$) compared to mice gaining weight. Multivariate analysis revealed that both body weight and energy balance contribute to total wake time ($p<0.01$ for both), while only energy balance related to bout fragmentation ($p<0.05$). Further, we compared how sleep/wake behavior changed from Week 8 to Week 9. We found that one week of diet switch caused significant, bi-directional changes to body weight, total sleep/wake time, and sleep/wake fragmentation, with acute HFD worsening and RC rescuing these respective metrics. Collectively, our study shows that acute changes to diet/energy balance is sufficient to drive sleep/wake abnormalities and may be stronger regulators of sleep/wake than body weight.

Estimation of brain response during sleep from serum metabolome by NMR spectroscopy

Arjun Sengupta[1], Elizabeth Harders[2], Phillip W. Gehrman[2], Aalim M. Weljie[1]

[1]Department of Systems Pharmacology and Translational Therapeutics and [2]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, United States of America.

Trainee Award Eligible

Brain activity during sleep and wakefulness is key to the understanding of sleep related disorders such as insomnia, parasomnias, sleep apnea, and narcolepsy. Increasing evidence also points to the bidirectional interaction of sleep and metabolism. However, there is no simple and quantitative test to estimate brain function as it relates to sleep and metabolic function. We profiled the blood serum metabolome of healthy individuals every 2 hours over a period of 48 hours that included regular sleep and wakefulness periods using NMR spectroscopy. Brain activity of the participants was monitored via overnight polysomnography. Multivariate regression modelling was used to correlate these two different data sets. We observed encouraging results that suggests the possibility of estimation of brain activity during sleep. These results have the potential to uncover the connection of altered brain function and metabolic biochemistry in dysregulated sleep.

Pilot Study of a Tailored Behavioral Intervention for Insomnia in Children with Autism Spectrum Disorder: Preliminary Results

Margaret C. Souders PhD CRNP, Whitney Eriksen, BSN, PhD c, Stefanie Zavodny, BSN, Jordana Popovich, MSN, CRNP, James Connell, PhD, Roseanne Schaaf, PhD, Lisa Guy, PhD, Connor Kerns, PhD, Rebecca Sinko, OT, Alexandra Ellison, MSN,CRNP, Beth Malow, MD

Note: 2 pages

Background: Children with Autism Spectrum Disorder (ASD) have demonstrated elevated rates of chronic insomnia, possibly stemming from an arousal dysregulation that produces a constellation of behavioral symptoms that include anxiety, sensory differences, and difficulties sleeping. Based on the theory that a subset of children with ASD are in a hyper-aroused state, we developed a **Tailored Behavioral Intervention (TAB)** for insomnia to supplement the **Standard Care (SC)** established by the ATN: Sleep Tool Kit. The **TAB** developed for this study includes: (1) positive routines, (2) the **Calming Module (CM)**, a novel component designed to decrease arousal levels with 12 soothing, relaxing activities, (3) faded bedtime protocol, and (4) **Performance feedback procedures (PFP)**, a highly effective feedback consultative strategy used to support parents and foster study fidelity. Based on the child's arousal profile, selected activities from the CM are incorporated into an evening routine to relax the child and promote sleep.

Objectives: (1) Determine the feasibility of implementing randomized control trial of a **TAB and SC** (n = 20) or **SC only** (n = 20) protocol for children with ASD and insomnia, evaluating recruitment, randomization, retention, and implementation of interventions by a multi-disciplinary team with parents of a child with ASD. (2) Complete a comparative cost analysis of the interventions, in terms of training and parent resources needed to teach the interventions, measure fidelity, and collect data on the primary outcome, sleep, as measured by actigraphy. (3) Compare the effects of the interventions on sleep parameters.

Methods: Children ages 6-10 years with ASD and insomnia, stable medical conditions and daytime behaviors and their families are eligible to participate. Measures for all participants include sleep history, 10 days of Actigraphy, sleep diary, and Sensory Profile, Children's Sleep Habits Questionnaire, and Pediatric Anxiety Rating Scale taken at baseline and 8 weeks post-intervention, and a Parent Acceptability Survey following completion. Arousal profiles for each child are developed by the interdisciplinary team. **SC** is led by the nurse or OT. Families are randomized to either **TAB and SC** or **SC** only. The **TAB** and SC group receives 8 (1hr) home-based sessions with **PFP**.

Results: To date, 37 families have been enrolled, with completed data sets for N = 13 **TAB and SC** and N = 11 **SC only**. Protocol was very acceptable to families (M = 6.5, Scale: 0-7) and all subjects have tolerated wearing the actigraph. The intervention significantly decreased wake minutes (M = 55.91 minutes), and activity mean ($p < .05$) based on actigraphy for children in the TAB and SC, compared to those receiving SC only. The intervention significantly increased sleep minutes (M = 32.88 minutes; $p < .05$). Both groups showed decreases in sleep latency (time to fall asleep), but those receiving the TAB and SC showed significantly greater improvement. Following intervention, the TAB and SC group fell asleep 15 minutes faster than baseline, and 11 minutes faster than the control group post-intervention. The mean sleep latency at week 8 in the TAB and SC group was (M = 18.91 minutes) and on average the participants in the TAB and SC group no longer met criteria for early insomnia. Total CSHQ score decreased significantly in the TAB and SC group, with no significant changes noted in the SC only group. Parents in the TAB group reported significantly fewer night wakings than the control group. Significant decreases are also noted in

the TAB group in the total CSHQ score and the bedtime resistance and parasomnia subscales, but these changes were not significantly different from the SC only group. Many children in the sample were taking more than one behavioral medication during the study, with nearly half of the children taking melatonin (48%) and meeting criteria for insomnia at baseline. Medication doses remained the same throughout the study. One child in the SC only group had no change in sleep parameters and had some mild-moderate snoring at night. He was referred to the Sleep Center and diagnosed with moderate OSA and had a T&A with subsequent improved sleep.

Conclusions: Preliminary results suggest that the sleep protocol was acceptable to families and was feasible to implement by the multi-disciplinary team. TAB and SC group decreased sleep latency and wake minutes and significantly increased sleep minutes.

Actigraph Measure	TAB (N=13)		Control (N=11)		TAB-SC P-values
	Baseline-Week 8	Difference (P-value)	Baseline-Week 8	Difference (P-value)	
Start time (Child is put to bed)	9:13PM-9:29PM	+16 min (NS)	8:00PM-8:54PM	+54 min (NS)	NS
End time (Parent reports child wakes up)	7:09AM-6:55AM	-14 min (NS)	6:58AM-6:46AM	-12 min (NS)	NS
Duration (min) (Time in bed)	596.41-569.30	-27.11 (0.005)	597.13-594.37	-2.75 (NS)	0.023
Activity mean (Nighttime movements)	32.32-21.91	-10.41 (0.003)	28.09-24.97	-2.75 (NS)	0.042
Wake minutes (Time awake during night)	162.36-106.45	-55.91 (0.005)	125.95-116.10	-9.85 (NS)	0.036
Sleep minutes (Time asleep)	434.04-466.93	+32.88 (0.048)	470.36-478.27	+7.91 (NS)	NS
Sleep latency (min) (Time to fall asleep)	34.23-18.91	-15.32 (0.002)	36.11-31.61	-4.50 (0.084)	0.076

Funded by the Department of Defense GRANT AR120166

The Impact of Recovery Sleep Opportunity on Neurobehavioral Measures Following Chronic Sleep Restriction

Olga Tkachenko[1], Christopher W. Jones[2], Jeremy Allen[2], Siobhan Banks[34], Mathias Basner[2], David F. Dinges[2]

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Introduction: Using a large cohort of experimentally sleep-restricted healthy adults, we examined whether recovery from chronic partial sleep restriction (SR) differed among neurobehavioral measures given varying doses of recovery sleep opportunity.

Methods: N=306 adults (21-50y, 46% female) had 2 baseline laboratory sleeps (BL1-2; 10h TIB), then randomization to either a control condition (10h TIB on all nights; n=28) or to 5 SR nights (SR1-5; 4h TIB) followed by randomization to 1 of 7 single-night recovery sleep opportunity conditions (R1; 0, 2, 4, 6, 8, 10, or 12h TIB; n=278). Performance outcomes included the Psychomotor Vigilance Test (PVT), the Digit Symbol Substitution Task (DSST), and subjective outcomes included the Karolinska Sleepiness Scale (KSS) and the fatigue subscale of the Profile of Mood States (POMS-F). Sleep physiology was recorded. Mixed model repeated measures analyses were used to compare changes in outcomes from baseline to post-recovery sleep dose (R1-BL2) between the sleep-restricted and control cohorts.

Results: After recovery sleep of less than 6h, SR subjects differed statistically from controls on all outcomes as measured by change from baseline to post-recovery sleep. With 6h TIB, SR subjects no longer differed from controls on the DSST and KSS. After 8h TIB, SR subjects did not differ from controls on the POMS-F. On the PVT, only subjects given 10 or 12h TIB on the recovery night were able to match performance with the control group.

Conclusion: There appears to be a premature perception of full recovery from sleep restriction evident in subjective ratings and cognitive throughput measures, despite continued deficits of attention.

Support (If Any): NIH R01 NR004281; NIH Clinical and Translational Research Center (CTRC) grant UL1TR000003; National Space Biomedical Research Institute, NASA award NCC 9-58.

Distinct mechanisms underlie two types of *Caenorhabditis elegans* sleep

Nicholas F Trojanowski[1,2,3], Matthew D. Nelson[1,4], Steven W. Flavell[5], Christopher Fang-Yen[2, 3], David M. Raizen[1]

[1]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Department of Bioengineering, School of Engineering and Applied Science, University of Pennsylvania, Philadelphia, Pennsylvania; [3]Department of Neuroscience, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [4]Current address: Department of Biology, Saint Joseph's University, Philadelphia, Pennsylvania; [5]Howard Hughes Medical Institute, Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior, The Rockefeller University, New York, NY

Electrophysiological recordings have enabled identification of physiologically distinct yet behaviorally similar states of mammalian sleep. In contrast, sleep states in non-mammalian animals are typically described behaviorally, and therefore non-mammalian sleep is often regarded as a homogenous state characterized by quiescence of feeding and locomotion, reduced responsiveness, and rapid reversibility. In the nematode *C .elegans*, behavioral sleep has been described under two conditions: developmentally timed sleep (DTS or lethargus) occurs during transitions between larval stages, just before the molt (Raizen *et al,* Nature 2008), while stress-induced sleep (SIS) occurs following exposure to cellular stress during any stage of life (Hill *et al*, Curr. Biol. 2014). Behaviorally, DTS and SIS appear identical, as during both states feeding and locomotion cease and arousal threshold is increased. Based on genetic analysis, DTS is similar to circadian-timed sleep in *Drosophila* (Singh *et al*, Sleep 2014) whereas SIS is similar to sleep induced by cellular stress in *Drosophila* (Lenz *et al*, Brain Behav. Immun. 2015). We used optogenetic manipulations of neuronal and muscular activity, pharmacology, and genetic perturbations to uncover circuit and molecular mechanisms of DTS and SIS. We find that locomotion quiescence induced by DTS- and SIS-associated neuropeptides (NLP-22 and FLP-13, respectively) occurs via their action on the nervous system. However, in mutants with activated signaling through the Gs/cAMP pathway, overexpression of NLP-22 causes locomotion phenotypes distinct from those seen after overexpression of FLP-13, suggesting that their neuronal target(s) and/or molecular mechanisms differ. We also find that while feeding quiescence feeding quiescence during SIS results from a loss of excitability in the nervous system, during DTS feeding is inhibited due to loss of pharyngeal muscle excitability. Together these results indicate that, as in mammals, distinct types of sleep in *C. elegans* are subserved by different mechanisms. Thus, our data uncover a previously unappreciated heterogeneity in non-mammalian sleep.

Increasing protein synthesis in the hippocampus prevents cognitive impairments caused by sleep deprivation

Jennifer C. Tudor[1], Emily J. Davis[1], Caroline Chung[1], Robbert Havekes[1], Philippe Pierre[2] and Ted Abel[1].

[1]University of Pennsylvania, Department of Biology, Philadelphia, PA, USA, [2]Centre d'Immunologie de Marseille-Luminy, French National Institute of Health and Medical Research (INSERM), Marseille, France

Sleep loss produces deficits in hippocampus-dependent memory storage, but the molecular and cellular mechanisms that underlie these effects of sleep deprivation remain unclear. Several studies have suggested that signaling pathways associated with translation are altered during sleep and after periods of sleep deprivation. Here, we demonstrate that five hours of total sleep deprivation increases phosphorylated AMP-activated protein kinase (AMPK) alpha, reduces mTOR complex 1 (mTORC1) and reduces phosphorylated eukaryotic translation initiation factor 4E binding protein 2 (4EBP2), which subsequently leads to impaired protein synthesis in the hippocampus. However it is yet to be determined whether restoring protein synthesis in the hippocampus is sufficient to prevent the cognitive deficits associated with sleep deprivation. Viral expression of 4EBP2 selectively in hippocampal excitatory neurons in mice that were sleep deprived for five hours increased phosphorylated 4EBP2 levels, which was sufficient to restore hippocampal protein synthesis to non-sleep deprivation levels. Furthermore, viral expression of 4EBP2 prevents the memory deficits associated with sleep deprivation in the object place recognition task. These findings indicate that AMPK-mTORC1-4EBP2 signaling and subsequent impaired protein synthesis is the critical component underlying the memory deficits associated with sleep deprivation in hippocampus-dependent learning tasks. Furthermore, this study defines the molecular mechanism by which loss of sleep impairs cognitive processes and highlights a vital role for protein synthesis and mTOR signaling on long-term memory formation.

Effect of Weight-Loss on Tongue Fat And Upper Airway Structures

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Trainee Award Eligible

Note: 2 pages

RATIONALE

Enlargement of the soft palate, tongue, and lateral pharyngeal walls are risk factors for obstructive sleep apnea (OSA). Tongue fat has been shown to be important in the pathophysiology of OSA and can be objectively measured using Dixon MRI. Significant improvements in OSA have been reported in obese patients following weight-loss; however the underlying changes in upper airway soft tissues are still unclear. This study investigated soft tissue changes in the upper airway following weight-loss.

METHODS

43 obese subjects underwent a sleep study and upper airway MRI. After 6 months, subjects returned for follow-up measurements. Subjects were categorized as weight-loss if ≥5% of their initial weight was lost (n = 20, mean age 44.4 ± 13.8 years, mean weight change -13.28 ± 6.87%; baseline vs. follow-up means: weight 113 ± 28 vs. 97 ± 21 kg, BMI 38.8 ± 7.8 vs. 33.4 ± 5.5 kg/m^2, AHI 39.0 ± 29.7 vs. 19.8 ± 21.2 events/hour) or weight stable if they differed <5% of their initial weight (n = 23, mean age 48.2 ± 11.3 years, mean weight change -0.76 ± 2.94%; baseline vs. follow-up means: weight 113 ± 27 vs. 112 ± 28 kg, BMI 39.4 ± 8.5 vs. 38.7 ± 8.9 kg/m^2, AHI 31.7 ± 31.8 vs. 27.4 ± 23.6 events/hour). Volumetric analysis was performed on axial T1 spin echo and Dixon MR images using Amira 5.4.3. Comparisons were made using paired t-tests.

RESULTS

Weight-loss subjects showed significantly greater decreases in total soft tissue (-7.70 ± 7.5%, p = 0.0043), tongue fat (-23.2 ± 15.82%, p=<0.0001), parapharyngeal fat pad volume (-31.29 ± 14.4%, p<0.0001), and lateral pharyngeal wall volume (-9.08 ± 12.1%, p = 0.0108) than weight stable subjects (Table 1). Tongue volume (p = 0.40) reduction was greater in weight-loss subjects but not significant. Soft palate (p = 0.88) changes did not differ between groups. Changes in weight (p < 0.0001), BMI (p < 0.0001), and AHI (p = 0.02) were significantly greater in weight-loss subjects.

DISCUSSION

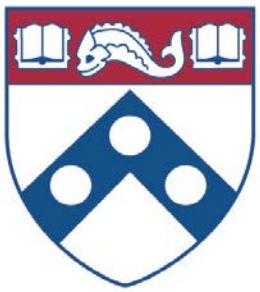
Subjects with greater than 5% initial weight-loss showed significant decreases in tongue fat and lateral pharyngeal wall volume. These losses, when combined with other soft tissue changes, contributed to improvements in AHI; however, reductions in parapharyngeal fat pads did not appear to independently play a role in those improvements. These data suggest that reductions in tongue fat and lateral pharyngeal wall volume may explain the mechanism behind AHI improvement following weight-loss.

Abstract was funded by: NIH 5 P01 HL094307-05

Differences in 6 Month Changes Between Weight Stable and Weight-Loss Groups

Measure	Absolute Change*			Percent Change*		
	Weight Stable (n=23)	Weight-Loss (n=20)	p†	Weight Stable (n=23)	Weight-Loss (n=20)	p†
Weight (kg)	-1.65 ± 7.26	-35.28 ± 23.95	<0.0001	-0.76 ± 2.94	-13.28 ± 6.87	<0.0001
BMI (kg/m^2)	-0.38 ± 1.07	-5.45 ± 3.73	<0.0001	-1.02 ± 2.81	-13.27 ± 6.87	<0.0001
AHI (events/hour)	-4.34 ± 18.70	-19.15 ± 20.52	0.0185	34.1 ± 138.2	-44.2 ± 50.7	0.0173
Total Soft Tissue (mm^3)	-4043 ± 12704	-15796 ± 16392	0.0034	-2.17 ± 7.01	-7.70 ± 7.51	0.0043
Soft Palate (mm^3)	-360 ± 1529	-369 ± 1414	0.9802	-2.5 ± 16.95	-3.12 ± 16.18	0.8838
Genioglossus (mm^3)	-2520 ± 6728	-5061 ± 9742	0.2610	-2.28 ± 6.89	-4.79 ± 9.65	0.2667
Tongue Fat (mm^3)	-208 ± 2653	-6387 ± 4485	<0.0001	-0.47 ± 9.14	-23.2 ± 15.82	<0.0001
Total Tongue Volume (mm^3)	-2883 ± 10417	-7694 ± 12547	0.1155	-2.06 ± 7.91	-5.42 ± 8.86	0.1263
Fat Pads (mm^3)	-284 ± 1096	-2102 ± 1557	<0.0001	-5.04 ± 17.64	-31.29 ± 14.35	<0.0001
Total Lateral Walls (mm^3)	-369 ± 2463	-2493 ± 3248	0.0070	-1.49 ± 12.58	-9.08 ± 12.09	0.0180

*Estimates presented as mean ± standard deviation change from baseline; †p-value from T-test



Abstracts - Poster Session

Listed in Alphabetical Order by First Author

Poster Location Number Listed

01: Circadian Regulation of Gene Expression in the SCN
Ballance H, Daly DT, Lahens NF Hayer KE, Growe J, Wu G, Hogenesch JB

02: Physical Activity and Habitual Sleep Duration: Does the Specific Type of Activity Matter?
Jilesh C, Barilla H, Gallagher RA, Grandner MA

03: Ultraviolet Light Induces Behavioral Quiescence
DeBardeleben H, Raizen, D

04: An Evaluation of Personal Characteristics as Predictors of Vulnerability to Sustained Partial Sleep Loss
Dennis L , Trentalange M, Allen JS, Jones C, Frager N, Dinges DF

05: Stability of Trait-Like Vulnerability to Total Sleep Deprivation and Chronic Sleep Restriction in the Same Protocol
Frager N, Dinges DF, Goel N

06: Use of Mobile Electronic Devices in Bed Associated with Sleep Duration, Insomnia, and Daytime Sleepiness
Gallagher RA, Perlis ML, Chakravorty S, Hale L, Barrett M, Schuschu J, Khadeer WS, Grandner, MA

07: Short Sleep Duration, Insomnia, and Snoring Associated with Drowsy Driving
Gallagher RA, Perlis ML, Gurubhagavatula I, Chakravorty S, Hale L, Barrett M, Findley J, Schuschu J, Khader WS, Grandner MA

08: Reduction in Unrealistic Sleep Expectations Mediates the Effect of Cognitive Behavior Therapy for Insomnia in Patients with Cancer
Sheila N, Garland SN, Brownlow J, Daraio J, Gehrman P, Carlson LE, Campbell T

09: Comparing Different Methods of Assessing Habitual Sleep Duration for Epidemiologic Research
Grandner MA, Gallagher RA, Chakravorty S, Hale L, Barrett M, Schuschu J, Khadeer WS, Perlis ML

10: Relationships among Habitual Sleep Duration, Race/Ethnicity, and Cardiometabolic Disease Outcomes: Data from >450,000 US Adults from the 2013 Behavioral Risk Factor Surveillance System
Grandner ML, Perlis M, PhD, Petrov M, Girardin, JL

11: Understanding Recurrent Posttraumatic Nightmares: Variables Contributing to Nightmare Symptomatology
Harb, GC, Brownlow J, Ross RJ

12: Poor Sleep Quality Associated with Lower Work Performance and Greater Healthcare Costs: Longitudinal Data from Kansas State Employee Wellness Programs
Hui, SKA, Grandner MA

13: The Role of Poor Sleep Quality in Motivating and Maintaining Healthy Behavior: Data from the Kansas State Employee Wellness Program
Hui, SKA Grandner MA

14: The G-protein Coupled Receptor DMSR-1 Mediates the Somnogenic Effects of RFamide Neuropeptides following Cellular Stress in C. elegans
Iannacone M, Zhou J, Artiushin G, Nelson M, Yuan J, Bau H, Raizen DM

15: Serum Micronutrient - Status Associated with Sleep Duration in Adolescents
Ji X, Liu J

16: Daytime Cognitive Function Associated with Habitual Sleep Duration
Khadeer WS, Grandner MA

17: CBT-I for Veterans with Psychosis: Study Design
Klingaman EA

18: Wake-related Lingual Muscle Activity Is Suppressed in Rats with Circadian Rhythm Disrupted by Constant Lights-on Condition
Kubin L, Benincasa-Herr K, Mann GL

19: Regulation of Sleep by Metabotropic Glutamate Signaling in Drosophila Melanogaster
Ly S, Pack AI, Naidoo N

20: Time-of-Day Variations in Brain Function: An ASL Perfusion Imaging Study
Ma N, Spaeth A, Fang Z, Goel N, Basner M, Dinges D, Rao H

21: Population Assessment of Sleep Duration, Chronotype and Body Mass Index
Malone SK, Patterson F, Lu R, Hanlon AL

22: Associations among Sleep Duration, Chronotype, and BMI in High School Students using Actigraphy Measured Sleep Parameters
Malone SK, Zemel B, Compher C, Souders M, Pack AI, Chittams J, Thompson AL, Lipman TH

23: Predictions of Sleep Disturbance for Different Nighttime Airport Operation Strategies Using a New Markov State Transition Sleep Model
McGuire S, Basner M

24: Binge Drinking and Habitual Sleep Duration, and the Roles of Depression and Smoking: Data from the 2013 BRFSS
Rana SA, Chakravorty S, Grandner MA

25: Where Are the Sleep Duration Disparities? The Relationship between Sleep Duration and Race/Ethnicity Depends on State of Residence: Data from 50 States and the District of Columbia, BRFSS 2013
Schuschu J, Pigeon W, Girardin JL, Grandner MA

26: The Relationship between Sleep Duration and Obesity Depends on State of Residence: Data from 50 States and the District of Columbia, BRFSS 2013
Schuschu J, Pigeon W, Girardin JL, Grandner MA

27: Abdominal Fat Differences Between Sexes in Lean and Obese Apneics
Shenberger E, Kuna ST, Wang S, Leinwand S, Schwab RJ

28: Chronobiology of Acute Aortic Dissection in Marfan Syndrome Patients: Insights from the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) and the International Registry of Acute Aortic Dissection (IRAD)
Siddiqi HK, Luminais SN, Montgomery D, Bossone E, Dietz H, Evangelista A, Isselbacher E, LeMaire S, Milewicz D, Nienaber CA, Roman M, Sechtem U, Silberbach M, Eagle KA, Pyeritz RE

29: Resting Metabolic Rate Varies by Race and by Sleep Duration
Spaeth AM, Dinges DF, Goel N

30: Effect of Short-Term Fasting on Late-Night Neurobehavioral Performance during Sleep Restriction
Spaeth AM, Goel N, Dinges DF

31: Vitamin E Intake Associates With Spatial Memory Performance During Sleep Restriction In Healthy Women
Taylor AL, Basner M, Dinges DF, Gur RC, Goel N, Spaeth AM

32: Brain Response During Sleep Estimated from NMR Metabolomics
Ubeydullah ER, Sengupta A, Harders E, Gehrman PW, Weljie AM

33: Anxiety Symptoms Predict Short Sleep Duration, but Only in Individuals Who are Not "Natural" Short Sleepers
Wang J, Perlis ML, Chakravorty S, Gallagher RA, Hale L, Barrett M, Schuschu J, Khader WS, Grandner MA

34: Modeling Circadian Rhythmicity of Cardiac Arrhythmias
Zaleski J, Diekman C

35: Degeneration in Arousal Neurons in Chronic Sleep Disruption Modeling Sleep Apnea
Zhu Y, Fenik P, Zhan G, Xin R, Veasey S

Circadian regulation of gene expression in the SCN

Ballance H.I.[1], Daly D.T.[2], Lahens N.F.[1], Hayer K.E.[1], Growe J.[1], Wu G.[1], Hogenesch J.B.[1*]

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Trainee Award Eligible

We performed a circadian RNA expression profile of the mammalian master pacemaker, the suprachiasmatic nucleus (SCN) in mice, at 2-hour resolution using microarrays, and at 6-hour resolution using RNA-seq. We found hundreds transcripts that cycle in the SCN, two dozen of which cycle across all other studied brain regions. We identified a rush hour of cycling transcripts regulating axonal synaptic connectivity and neurotransmission, extending to intracellular signaling through a panoply of cycling kinases and phosphatases. Further, we found cycling regulators of ER calcium stores, protein folding, and RNA metabolism. *Tdp-43*, *Prnp*, and transcripts for other aggregation prone proteins, cycle in phase with heat shock chaperones, underscoring the function of the circadian clock in maintaining cellular homeostasis. Our profile of SCN RNA expression highlights the rapidly expanding panorama of circadian regulation of physiology in health and disease.

Physical Activity and Habitual Sleep Duration: Does the Specific Type of Activity Matter?

Jilesh Chheda, Holly Barilla, Rebecca Gallagher, and Michael A. Grandner PhD

Trainee Award Eligible

INTRODUCTION: Physical activity is associated with healthy sleep. It is unknown, though whether the source of physical activity is relevant.

METHODS: Data from the 2013 Behaviroal Risk Factor Surveillance System was used. N=429,110 adults provided information about sleep and physical activity. Sleep duration was assessed as total habitual sleep within 24hrs and was categorized as very short(≤4hrs), short(5-6hrs), normal(7-8hrs,reference), and long (≥9hrs). Participants were also asked whether they engaged in non-occupational physical activity in the past 30 days and, if so, what specific activity, resulting in N=75 separate activities coded. In addition to those who reported no activity (N=125,314), the most commonly-reported activity was walking (N=179,996). The 10 next most common activities were gardening/yard work (N=26,637), running (N=23,153), aerobics/calisthenics (N=19,008), biking (N=15,780), weight-lifting (N=10,222), golfing (N=6,511), swimming (5,001), yoga/pilates (N=3,370), jogging (3,270), and household/childcare (N=2,691). Population-weighted regressions, adjusted for age, sex, education, and BMI, assessed whether each activity (adjusted for all 74 others) was associated with sleep duration relative to both no activity and to walking.

RESULTS: Compared to no activity, walking was associated with decreased likelihood of very short (OR=0.59; p<0.0001), short (OR=0.83; p<0.0001), and long (OR=0.76; p<0.0001) sleep. Similarly, aerobics/calisthenics, biking, gardening, golfing, running, weight-lifting, and yoga/pilates were associated with decreased likelihood of very short, short, and long sleep. Swimming and jogging were negatively associated with very short sleep and jogging was negatively associated with long sleep. Compared to walking, aerobics/calisthenics, biking, and running were associated with a greater decreased likelihood of very short, short, and long sleep. Weight-lifting and yoga were also negatively associated with very short and short sleep, golf was negatively associated with very short sleep, gardening was negatively associated with long sleep, and household/childcare was positively associated with both very short and long sleep.

CONCLUSIONS: Most types of physical activity were associated with greater likelihood of 7-8hrs sleep. Some activities, especially running, biking, and aerobics/calisthenics, had effects over and above simply walking.

Ultraviolet light induces behavioral quiescence

Hilary DeBardeleben, PhD and David Raizen, MD, PhD

Trainee Award Eligible

The regulation and function of sleep are poorly understood. By studying this evolutionarily conserved behavior in a simple organism, *C. elegans*, we can determine basic mechanisms underlying sleep. *C. elegans* engages in two separately regulated sleep-like states: during lethargus (Raizen *et al* Nature 2008) and following exposure to stimuli that cause cellular stress such as heat shock or bacterial toxins (Hill *et al* Curr. Bio. 2014). Using machine vision for longitudinal tracking of quiescent behavior in individual worms, we have discovered a new stressor that induces quiescence, ultraviolet (UV) irradiation. Importantly, the quiescent response is delayed after UV exposure, suggesting that the quiescence is not a simple consequence of injury from the UV light. Additionally, UV-induced quiescence requires the ALA neuron and FLP-13 neuropeptides, similar to heat shock induced quiescence (Nelson *et al* Curr. Bio. 2014), indicating active neural control of the quiescent behavior. UV light induces DNA damage, which is repaired by the ATR complex; the ATR complex activates the p53 homologue CEP-1, a transcription factor that is required for UV-induced apoptosis in the germline (Lant *et al* Int. J. Biol. Sci. 2010). We studied both the role of the germline and of CEP-1 signaling in the regulation of UV-induced quiescence. Animals with the *cep-1* mutant allele *gk138* show a defect in UV-induced quiescence. Preliminary results show that this defect can be rescued by transgenic expression of *cep-1*, suggesting that the phenotype of the mutant is specific to the *cep-1* gene. Since *cep-1* is expressed in the germline and the pharynx (Derry *et al* Science 2001), we studied the role of the germline in UV-induced quiescence. We used a temperature sensitive mutant, *glp-4(bn2)*, which lacks a germline when grown at the restrictive temperature. Worms that did not have a germ line showed no defect in UV-induced quiescence, suggesting that CEP-1 is signaling outside of the germline, and possibly in the pharynx. Our findings establish a novel connection between UV-induced cellular stress and regulation of sleep in *C. elegans*. We speculate that this connection is relevant to the well-documented phenomenon of radiation therapy induced fatigue observed in cancer patients.

An Evaluation of Personal Characteristics as Predictors of Vulnerability to Sustained Partial Sleep Loss

Laura Dennis, Michael Trentalange, Jeremy S. Allen, Christopher Jones, Nicole Frager, David F. Dinges

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Introduction: Experiments have documented that there are stable phenotypic differences among individuals in vulnerability to the neurobehavioral effects of sustained partial sleep restriction (SR). This has prompted questions about the predictability of this inter-individual vulnerability, based on personal characteristics of people. We addressed these questions relative to a number of demographic, personality, and sleep-wake measures, to evaluate the hypotheses that certain demographics, other acquired and sleep-wake characteristics can help predict these neurobehavioral responses to sleep restriction.

Methods: In a controlled laboratory environment, N=51 healthy, ethnically-diverse subjects (n=23 females, age M=33y, education M=14y) received 2 nights of baseline sleep (B; 10h TIB) followed by 5 nights of SR (4h TIB). During wakefulness each day (08h, 10h, 12h, 16h, 18h, 20h), behavioral alertness was assessed using the Psychomotor Vigilance Test (PVT), a well-established measure of the cumulative neurobehavioral effects of SR. The average hourly increases from B days to SR days for PVT performance outcomes were evaluated relative to 4 pre-lab sleep measures: sleep quality (PSQI), morningness-eveningness (MEQ), sleep duration (actigraphy), and daytime sleepiness (ESS) as well as 6 pre-SR characteristics of subjects: age, gender, ethnicity, education, reading IQ, and personality (EPI).

Results: Subjects were ranked for the effects of SR on 8 PVT outcome variables. For each outcome, the median was used to separate those who had a larger PVT deficit to sleep restriction from those who had a smaller PVT deficit to sleep restriction. Independent t-tests were conducted between these two groups for all pre-lab sleep and all personality characteristics (N=104 t-tests). None of the 10 personal or sleep characteristics reliably ($p<0.05$) differed between the two phenotypic groups.

Conclusion: None of the demographic, personality, or sleep-wake measures evaluated prior to sleep restriction predicted PVT responses to 5 nights of sustained sleep restriction (4h/night). Analyses are continuing evaluating other outcomes affected by SR.

Support: National Institutes of Health grant R01 NR-004281 and NIH CTRC UL1TR000003.

Stability of Trait-Like Vulnerability To Total Sleep Deprivation And Chronic Sleep Restriction In The Same Protocol

Frager N, Dinges DF, Goel N

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Introduction: Exposure to different types of sleep loss separated by 2-4 weeks reveals similar trait-like differential neurobehavioral vulnerability. We determined whether such trait-like responses are obtained after one bout of chronic sleep restriction (SR) and one bout of acute total sleep deprivation (TSD) separated by recovery sleep in the same protocol.

Methods: 63 healthy adults (ages 21-50y; 31f) completed 2 baseline (10h and 12h time in bed, TIB) nights followed by either 5 SR nights (4h TIB) or 36 hrs of acute TSD. Subjects then received 4 recovery (12h TIB) nights followed by either 5 SR nights or 36 hrs of acute TSD, in a counterbalanced manner to the initial sleep loss condition. Neurobehavioral testing included the 10-min Psychomotor Vigilance Test (PVT), Digit Span (DS), Digit Symbol Substitution Test (DSST), Karolinska Sleepiness Scale (KSS), and Profile of Mood States (POMS) every 2h during wakefulness. The intraclass correlation coefficient (ICC) for each measure was computed as the ratio of between-subjects variance to the sum of the between- and within-subjects variances using data from 0800h/1000h to 2000h after the fifth night of SR and data from 2200h/0000h to 2000h of TSD.

Results: Subjects who displayed vulnerability to SR also displayed vulnerability to TSD, as evident by high ICCs: PVT lapses + false starts, ICC=0.741; PVT response speed, ICC=0.892; DSST correct, ICC=0.913; DS correct, ICC=0.938; POMS fatigue, ICC=0.763; and KSS, ICC=0.828. Sleep loss order did not affect ICCs.

Conclusion: Neurobehavioral vulnerability to SR and TSD, separated by 4 nights of recovery, showed trait-like stability in performance and subjective measures, as evident in the stability of substantial inter-individual variance (74%-94% across measures). These data confirm the stability of phenotypic neurobehavioral responses to SR and TSD regardless of the order of sleep loss configuration and are critical for understanding individual neurobehavioral responses across different forms of commonly experienced sleep loss.

Support: Work funded by the Department of the Navy, Office of Naval Research (Award No. N00014-11-1-0361 to NG) and CTRC UL1TR000003.

Keywords: Chronic Sleep Restriction, Individual Differences, Total Sleep Deprivation

Use of Mobile Electronic Devices in Bed Associated with Sleep Duration, Insomnia, and Daytime Sleepiness

Rebecca A. Gallagher MSEd, Michael L. Perlis PhD, Subhajit Chakravorty MD, Lauren Hale PhD, Marna Barrett PhD, Jesse Schuschu, Wailuddin S. Khadeer, and Michael A. Grandner PhD

INTRODUCTION: In recent years, mobile devices have become ubiquitous in bedrooms. The extent to which use of these devices is related to habitual sleep factors among adults is not well studied.

METHODS: Data from the Sleep and Healthy Activity, Diet, Environment, and Socialization (SHADES) study were used. Data were collected from surveys of adults age 22-60 in southeastern Pennsylvania (N=1007). Sleep duration was assessed using the NHANES item and was categorized as short (≤6h), normal (7-8h, reference), and long (≥9h). Insomnia was assessed using the Insomnia Severity Index (ISI) and was categorized as none (reference), mild, moderate, or severe. Sleepiness was assessed as scores of ≥10 on the Epworth Sleepiness Scale (ESS). Subjects were asked to rate the frequency of mobile electronic device use at night on a scale of 0 ("Never") to 4 ("Every night"). Variables included presence of device, any use, texting, emailing, browsing internet, calling, or social networking in bed, being woken by a call/text/email, being woken by device alarm, and checking device during the night. Since most use was among younger participants, age was restricted to 22-29 (N=473) and analyses were adjusted for age, sex, education, and race/ethnicity.

RESULTS: Simply having access to a device near the bed was not associated with short sleep, insomnia, or sleepiness, nor were most specific behaviors (e.g., calling or texting). Short sleep duration was associated with e-mailing "every night" (OR=2.95;p=0.003), browsing the internet (OR=5.73;p=0.003) and checking the device at night (OR=2.78;p=0.015). Being woken by a call "every night" was associated with moderate insomnia (OR=5.03;p=0.029), and checking the device was associated with mild (OR=4.25;p=0.001) and moderate (OR=17.69;p<0.0001) insomnia, as well as excessive sleepiness (OR=2.31;p=0.037).

CONCLUSIONS: Using the internet in bed was associated with shorter sleep duration and frequently checking the device at night was associated with less sleep, more insomnia, and excessive sleepiness.

SUPPORT: The SHADES study was funded by R21ES022931. Dr. Grandner is also supported by K23HL110216.

Short Sleep Duration, Insomnia, and Snoring Associated with Drowsy Driving

Rebecca A. Gallagher MSEd, Michael L. Perlis PhD, Indira Gurubhagavatula MD MPH, Subhajit Chakravorty MD, Lauren Hale PhD, Marna Barrett PhD, James Findley PhD, Jesse Schuschu, Wailuddin S. Khader, and Michael A. Grandner PhD

INTRODUCTION: Numerous studies have shown that sleep apnea and sleep loss are associated with motor vehicle accidents. Less well documented is whether habitual short sleep duration, insomnia, and/or loud snoring also constitute risk factors for drowsy driving. These associations are evaluated in the present study.

METHODS: Data from the Sleep and Healthy Activity, Diet, Environment and Socialization (SHADES) study was used. SHADES is a survey of adults age 22-60 in southeastern Pennsylvania (N=1007). Sleep duration was assessed with the NHANES item (typical weeknight sleep) and categorized as very short (≤4h), short (5-6h), normal (7-8h, reference), and long (≥9h). Drowsy driving in the past 30 days was self-reported using an item from an established national database (BRFSS). Insomnia was assessed with the Insomnia Severity Index (ISI) and categorized as none (reference), mild, moderate, or severe. Loud Snoring was assessed using the Multivariable Apnea Prediction (MAP) questionnaire item, as 0 ("Never", reference) to 4 ("Always"). Covariates included obesity (BMI≥30), age, sex, education, and race/ethnicity. Logistic regression analyses evaluated each sleep factor alone and after adjustment for the others (all included covariates).

RESULTS: Both very short (OR=3.99; p<0.0001) and short (OR=2.14; p=0.002) sleep duration were associated with drowsy driving, as was mild (OR=2.31; p=0.005), moderate (OR=3.14; p<0.0001), and severe (OR=6.61; p<0.0001) insomnia and snoring "Rarely" (OR=1.98; p=0.020), "Frequently" (OR=2.15; p=0.04) or "Always" (OR=4.59; p<0.0001). When sleep factors were adjusted for each other, unique effects were found for very short (OR=2.26; p=0.034) and short (OR=1.70; p=0.045) sleep, mild (OR=1.97; p=0032), moderate (OR=2.21; p=0.024), and severe (OR=3.42; p=0.010) insomnia, and loud snoring "Rarely" (OR=1.92; p=0.028) and "Always" (OR=3.62; p=0.001).

CONCLUSIONS: All 3 sleep risk factors were associated with drowsy driving. Notably, the effects of sleep duration overlapped with those of insomnia, attenuating results. These results show that short sleep, insomnia, and loud snoring are all independent risk factors for drowsy driving.

SUPPORT: The SHADES study was funded by R21ES022931. Dr. Grandner is also supported by K23HL110216.

Reduction in Unrealistic Sleep Expectations Mediates the Effect of Cognitive Behavior Therapy for Insomnia in Patients with Cancer

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Introduction: Insomnia is a prevalent and pernicious consequence of a cancer diagnosis and treatment. The presence and strength of dysfunctional sleep beliefs is related to the development, maintenance, and remission of insomnia. Previously, we demonstrated that Mindfulness-based Cancer Recovery (MBCR) was not inferior to Cognitive Behavior Therapy for Insomnia (CBT-I); however, the groups had differential effects on overall dysfunctional sleep beliefs. The objective of the present study was to examine whether changes in dysfunctional sleep beliefs mediate treatment outcomes of CBT-I relative to MBCR.

Methods: Participants were 72 adult post-treatment cancer patients who met criteria for insomnia disorder (MBCR n=40; CBT-I n=32). Mediation analyses were used to determine the indirect effects of total dysfunctional beliefs about sleep and the 4 subscales (i.e. unrealistic sleep expectations, worry about sleep, beliefs about the consequences of poor sleep, use of sleeping medication) in the relationship between treatment and insomnia severity adjusting for baseline scores. Bootstrapping was used to obtain biased corrected 95% confidence intervals for the indirect effects. Separate models were generated for each candidate mediator.

Results: CBT-I had significantly greater pre-post reductions in unrealistic sleep expectations than MBCR (B = -1.30 SE = .47 p = .008) and this predicted improved insomnia symptoms (B = .58 SE = .24 p = .019). Mediation analyses showed that changing unrealistic sleep expectations mediated the decrease in insomnia severity in CBT-I (ab = -.76 SE = .51, 95% CI -1.92: -.04). The proportion of variance in change in insomnia severity predicted by the indirect effect of modified sleep expectations was large (R^2 = .20). Total dysfunctional sleep beliefs and the remaining subscales failed to add significantly beyond the contribution of expectation modification.

Conclusion: These results suggest that sleep expectations may be a specific mechanism of CBT-I (relative to MBCR) in improving insomnia severity.

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Comparing Different Methods of Assessing Habitual Sleep Duration for Epidemiologic Research

Michael A. Grandner PhD, Rebecca A. Gallagher MSEd, Subhajit Chakravorty MD, Lauren Hale PhD, Marna Barrett PhD, Jesse Schuschu, Wailuddin S. Khadeer, and Michael L. Perlis PhD

INTRODUCTION: Large-scale survey studies tend to use single, non-validated items to assess sleep duration. It is unclear to what extent the different items produce different estimates of sleep duration and whether they predict outcomes in the same way.

METHODS: Data from the Sleep and Healthy Activity, Diet, Environment, and Socialization (SHADES) study was used. SHADES is a community-based study of adults in southeastern Pennsylvania (N=1007). Habitual sleep duration was assessed in four ways. The question from the National Health and Nutrition Examination Survey (NHANES) assessed hours of sleep on a typical weeknight, the question from the Behavioral Risk Factor Surveillance System (BRFSS) assessed typical hours of sleep in 24h, the question from the Pittsburgh Sleep Quality Index (PSQI) assessed sleep duration on a typical night, and the Sleep Timing Questionnaire (STQ) computed typical weeknight sleep from self-reported bed and wake times. These were evaluated continuously and categorized as short (≤6h), normal (7-8h, reference), and long (≥9h). Correlations among continuous (Pearson r) and categorical (Spearman R) variables were computed. Further, all variables were used to predict obesity (BMI≥30;N=236), sleepiness (ESS≥10;N=325), and depression (PHQ9;N=332) using logistic regression.

RESULTS: All sleep duration items were significantly correlated (all $p<0.0001$): NHANES-PSQ I($r=0.78$; $R=0.59$); BRFSS-PSQI ($r=0.51$; $R=0.36$); PSQI-STQ ($r=0.49$; $R=0.31$); NHANES-BRFSS ($r=0.47$; $R=0.48$); NHANES-STQ ($r=0.42$; $R=0.32$); and BRFSS-STQ ($r=0.30$; $R=0.21$). Of those who identified as normal sleepers on NHANES, most also identified as normal sleepers on PSQI (89%), BRFSS (78%), and STQ (71%). Short sleep was associated with obesity using questions from NHANES (OR=2.35; $p<0.0001$), BRFSS (OR=2.32; $p<0.0001$), PSQI (OR=2.45; $p<0.0001$), and STQ (1.66; $p<0.0001$). Short sleep was associated with sleepiness using questions from NHANES (OR=2.30; $p<0.0001$), BRFSS (OR=2.14; $p<0.0001$), PSQI (OR=2.33; $p<0.0001$), and STQ (2.29; $p<0.0001$). Short sleep was associated with depression using questions from NHANES (OR=2.09; $p<0.0001$), BRFSS (OR=1.98; $p<0.0001$), PSQI (OR=2.08; $p<0.0001$), and STQ (1.59; $p=0.001$).

CONCLUSIONS: Sleep duration items were correlated only moderately, but they similarly associate with outcomes when categorized. Thus, even though they do not overlap perfectly, they may be interchangeable in some cases.

SUPPORT: The SHADES study was funded by R21ES022931. Dr. Grandner is also supported by K23HL110216.

Relationships Among Habitual Sleep Duration, Race/Ethnicity, and Cardiometabolic Disease Outcomes: Data from >450,000 US Adults from the 2013 Behavioral Risk Factor Surveillance System

Michael Grandner, Michael Perlis, PhD, Megan Petrov, and Girardin Jean-Louis PhD

INTRODUCTION: Habitual sleep duration is associated with race/ethnicity and cardiometabolic disease risk. Previous studies have been limited in terms of which groups were examined. Also, few previous studies have explored whether cardiometabolic risks depend on race/ethnicity. Finally, the degree to which disparities in health outcomes are mediated by sleep duration has generally not been explored.

METHODS: The 2013 BRFSS was used (N=483,495). Habitual sleep duration was categorized as "Very Short" (≤4h), "Short" (5-6h), "Normal" (7-8h,reference), and "Long" (≥9h). Cardiometabolic outcomes assessed were self-reported hypertension, diabetes, and obesity. Covariates included age, sex, race/ethnicity, education, income, smoking, BMI (except for obesity) and overall health. Weighted regression analyses examined whether sleep duration categories were disproportionately distributed among race/ethnicity groups and whether sleep duration was associated with cardiometabolic outcomes. Interaction terms were computed for sleep by race/ethnicity interactions. To test whether sleep mediates race differences in obesity/diabetes/hypertension, regression models with these outcomes and race/ethnicity as predictor tested sleep as a mediator. Sobel tests evaluated partial mediation.

RESULTS: Very short sleep was more prevalent among Blacks/African-Americans (OR=1.96; p<0.0001), Native-Americans (OR=1.82; p<0.0001), Others (OR=1.85; p<0.0001), and Multiracial (OR=2.08; p<0.0001), and less prevalent among Hispanics/Latinos (OR=0.7; p<0.0001). Short sleep was more prevalent among Blacks/African-Americans (OR=1.69; p<0.0001), Asians (OR=1.34; p<0.0001), Native-Americans (OR=1.28; p<0.0001), Others (OR=1.54; p<0.0001), and Multiracial (OR=1.48; p<0.0001). Long sleep (≥9h) was more prevalent among Blacks/African-Americans (OR=1.53; p<0.0001), Native-Americans (OR=1.27; p<0.05), and Multiracial (OR=1.42; p<0.05), and less prevalent among Hispanics/Latinos(OR=0.84; p<0.0001). Very short, short, and long sleep were associated with obesity, diabetes, and hypertension, and all race/ethnicity interactions were significant (p<0.0001). Partial mediation was found for many relationships between race/ethnicity and cardiometabolic outcomes. For example, Black-White differences were significantly partially explained by sleep duration for hypertension (7.3%), diabetes (8.4%), and obesity (9.7%), and 16% of Hispanic/Latino-White differences in hypertension are explained by sleep duration.

CONCLUSIONS: Very short, short, and long sleep duration were associated with cardiometabolic risk, and this relationship depended on race/ethnicity. Further, several relationships between race/ethnicity and outcomes were partially mediated by sleep duration.

K23HL110216, R21ES022931

Understanding Recurrent Posttraumatic Nightmares: Variables Contributing to Nightmare Symptomatology

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Introduction:

Although sleep disturbance is a prominent feature of PTSD, its phenomenology and factors associated with posttraumatic nightmares, in particular, are not well understood. Prior research has identified higher PTSD severity, vigilance, lower unit support and reduced distraction skills as predictive of more severe general sleep disturbance. This study examined factors that may characterize those Veterans with persistent nightmare symptoms.

Methods:

Participants were 108 male and female (14%) OEF/OIF/OND Veterans with PTSD, insomnia, and recurrent nightmares in a RCT of sleep and nightmare treatments. We assessed baseline independent variables (clinician-rated PTSD severity adjusted for nightmare symptoms, depression, deployment-related experiences, demographics) to predict nightmare symptoms: frequency (NFQ) and distress (NDQ).

Results:

Nightmare frequency was significantly associated with PTSD severity, combat exposure ($r = .27, .28$, $p < .01$), and decreased post-deployment social support ($r = -.20$, $p < .05$). Nightmare distress was significantly correlated with PTSD, depression, perceived threat during deployment, combat exposure and post-deployment stressful events ($r = .32, .30, .33$, $p < .01$; $r = .21, .22$, $p < .05$, respectively). After adjusting for demographics, PTSD ($B = .08$, $SE = .03$, $p = .01$) and combat exposure ($B = .31$, $SE = .15$, $p = .05$) were significant predictors of nightmare frequency; depressive symptoms ($B = .15$, $SE = .087$, $p = .03$) significantly predicted nightmare distress in regression analyses. These factors accounted for 25% of the variance in nightmare frequency and 28% in nightmare distress.

Conclusion:

Nightmare frequency and nightmare distress had different predictors. While nightmare frequency was associated with PTSD severity and combat exposure, nightmare distress (the common impetus for treatment-seeking) was predicted only by the depression severity. Results emphasize the importance of distinguishing between nightmare frequency and nightmare distress. Results also suggest that alleviating nightmare distress may improve posttraumatic mood disturbance and treating depression may reduce nightmare distress.

Support: Department of Defense

Poor Sleep Quality Associated with Lower Work Performance and Greater Healthcare Costs: Longitudinal Data from Kansas State Employee Wellness Programs

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INTRODUCTION: Several studies show sleep disorders and poor sleep quality to be associated with adverse occupational outcomes. Few studies, though, have examined whether worsening of sleep over time leads to worsening of outcomes. In particular, few studies examine sleep quality and its change relative to healthcare expenditures.

METHODS: Data from the Kansas State Employee Wellness Program from 2008 (N=11,698) and 2009 (N=5,636) were used. Sleep quality was assessed as "Trouble Sleeping" with categories of "Never," "Seldom," "Sometimes," "Often," or "Always." Absenteeism was recorded as full or partial workdays missed. Work performance over the past 4 weeks was rated in a 10-point scale and applied to both the self and typical workers in that position (relative performance was [self]-[others]). Healthcare costs were evaluated objectively in dollars. Analyses were adjusted for age, sex, race/ethnicity, education, income, and overall health.

RESULTS: Poor sleep quality was cross-sectionally and longitudinally associated with absenteeism, poor work performance, and increased healthcare costs. For example, poor sleep "Always" (vs "Never") was associated with greater likelihood of missing 7 or more full days (OR=5.58, p<0.0005), partial days (OR=5.37, p=0.004), and total days (OR=6.02, p<0.0005), lower self-rated performance (B=-0.36, p<0.0005), lower relative performance (B=-0.24, p=0.004), and higher healthcare costs (B=$3,461.89, p<0.0005). Longitudinally, each 1-category worsening of sleep quality over 1 year was associated with a further increase in missed full days (B=0.07, p=0.007), partial days (B=0.09, p=0002), and total days (B=0.15, p<0.0005), lower self-rated performance (B=-0.05, p=0.006), lower relative performance (B=-0.08, p=0.001), and $189.46 more healthcare expenditures (p=0.041).

CONCLUSIONS: Poor sleep quality was associated with greater absenteeism, worse work performance, and increased healthcare expenditures. Further, worsening sleep over 1 year led to exacerbations in these domains. Workplace health interventions should address problems of poor sleep quality, which may not only improve health but also improve work productivity and reduce costs.

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The Role of Poor Sleep Quality in Motivating and Maintaining Healthy Behavior: Data from the Kansas State Employee Wellness Program

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INTRODUCTION: Using the Transtheoretical Model of behavioral change, this study evaluates the relationship between sleep quality and the motivation and maintenance processes of healthy behavior change.

METHODS: Data collected in 2008 from the Kansas State employee wellness program (N=13,322). Sleep quality was assessed by describing the frequency of "Trouble Sleeping" as "Never," "Seldom," "Sometimes," "Often," or "Always." Stage of change was assessed with the question, "Right now, are you planning to make any of the following changes to keep yourself healthy or improve your health?" with the following behaviors: "Limiting the amount of alcohol," "Increase physical activity or exercise," "Quit or cut down smoking," "Cope or deal with stress better," and "Lose weight." Stage of change was coded as precontemplation, contemplation, preparation, action, or maintenance. Multinomial logistic regression analyses were adjusted for age, sex, race/ethnicity, education, and income.

RESULTS: Poor sleep quality was generally associated with an increased likelihood of contemplation, preparation, and in some cases action when engaging in the health behavior change process, but generally a lower likelihood of maintenance of healthy behavior. For example, poor sleep quality "Always" (vs "Never") was associated with greater likelihood of contemplation for managing stress (OR=3.32, $p<0.0001$), weight (OR=4.99, $p=0.0006$), and smoking (OR=2.70, $p=0.0026$), relative to precontemplation. Poor sleep "Always" (vs "Never") was associated with preparation and action for managing stress (OR=2.47, $p<0.0001$; OR=2.04, $p=0.0006$; respectively) and weight (OR=3.45, $p=0.0076$; OR=2.94, $p=0.0204$; respectively). Contrastingly, it was associated with decreased likelihood of maintenance of behaviors aimed to improve stress (OR=0.64, $p=0.0375$) and physical activity (OR=0.41, $p=0.0024$).

CONCLUSIONS: Poor sleep quality was associated with an elevated likelihood of contemplating or initiating behavior change, but a decreased likelihood of maintaining healthy behavior change. It is important to include sleep improvement as one of the lifestyle management interventions offered in wellness programs to comprehensively reduce health risks and promote health.

SUPPORT: Dr. Hui is supported by the National Cancer Institute (R03CA159903). Dr. Grandner is supported by the National Heart, Lung and Blood Institute (K23HL110216) and the National Institute of Environmental Health Sciences (R21ES022931). We also thank Drs. Ellerbeck, Shireman at University of Kansas Medical Center, and Ms. Cheryl Miller

The G-protein coupled receptor DMSR-1 mediates the somnogenic effects of RFamide neuropeptides following cellular stress in *C. elegans*

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Trainee Award Eligible

Although sleep is conserved among animals, the function of sleep is poorly understood. One possibility is that sleep plays an important role in recovery from cellular stress. The study of cellular stress effects on sleep in a simple organism such as the nematode *C. elegans* offers the opportunity to get at the core function of sleep. In addition, *C. elegans* contains only 302 neurons which makes it feasible to study sleep circuitry with single neuron resolution. *C. elegans* sleeps after exposure to cellular stressors. For example following heat stress, the worm transiently stops feeding and moving (Hill et al. *Current Biology* 2014). This stress-induced-sleep is dependent on the release of FLP-13 neuropeptides from ALA, a single neuron (Nelson *Current Biology* et al. 2014). FLP-13 peptides belong to a family of peptides containing an Arginine-Phenylalanine-amide (RFamide) motif at the C-terminus. RFamide are found in all animals, including humans, yet their function is not understood.

In this study, we report the identity of the FLP-13 receptor, which we identified using a forward genetic discovery approach. We made use of the strong somnogenic effects of FLP-13 over-expression. We searched for mutagenized animals that remained awake despite FLP-13 over-expression. We identified 12 mutants that were resistant to the somnogenic effects of FLP-13. By a combination of genetic complementation testing and whole genome sequencing, we found that 7 of these mutants contain mutations in the gene *dmsr-1*, which encodes a G-protein coupled receptor. *In vitro* experiments using cells transfected with DMSR-1 show that FLP-13 is a potent agonist of this receptor with an EC50 of 6 nM. We conclude that DMSR-1 acts as the receptor for FLP-13 to promote sleep induced by cellular stress. We thus have identified a novel molecular signaling module for sleep regulation.

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Serum Micronutrient - Status Associated with Sleep Duration in Adolescents

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Introduction: The role of serum micronutrient levels in habitual sleep duration during adolescence represents an underexplored pathway linking nutrition, sleep and health. The aim of this study was to examine serum levels of iron, zinc and copper in relation to sleep duration in adolescents.

Methods: This study represents a sub analysis of the China Jintan Child Cohort Study of 269 adolescents (12.03 ± 0.39 years old) enrolled from June to July 2013. Venous blood samples were collected and analyzed for iron, zinc, and copper concentrations, with the reference range of 75-175 ug/dl, 67-186 ug/dl, and 80-120 ug/dl respectively. Micronutrient concentrations below or above the reference ranges were categorized as low or high micronutrient level. Both adolescents and their parents were asked to fill in the question of habitual sleep duration on weekdays.

Results: The prevalence rates of insufficient (< 8 hours), borderline (8-9 hours) and optimal sleep duration (>=9 hours) in adolescents were 33.46% (n=89), 40.23% (n=107) and 26.32% (n=70) respectively. After adjusting for age, gender, co-sleep status, family income and habitual sleep duration in parents, low iron level (OR=0.80, P=0.001) and high copper level (OR=0.40, p=0.00) in serum were negatively associated with sleep duration levels in adolescents, indicating a decreased likelihood of optimal sleep duration relative to the reference range of iron and copper respectively. In contrast, adolescents with high iron level (OR=1.72, p=0.00) and low copper level (OR= 1.94, p=0.007) were more likely to have optimal sleep duration. Although serum zinc status (p=0.60) was not significantly correlated with sleep duration levels, the ratio of serum iron and zinc concentration showed a negative effect (OR=0.69, p=0.00) on the levels of sleep duration. Additionally, the ratios of serum iron and copper, as well as zinc and copper were not significantly associated with sleep duration levels in adolescents.

Conclusion: Our findings suggest that levels of serum micronutrient contribute to adolescent sleep duration. Future research is needed to examine the possible role of micronutrients in adolescent sleep in order to inform the future interventions for the interrelated health issues of nutrition and sleep during adolescence.

Support: Support for this research was provided by NIH/NIEH R01-ES018858 and K02ES019878 to Dr. Jianghong Liu at the University of Pennsylvania

Daytime Cognitive Function Associated with Habitual Sleep Duration

Wailuddin S. Khader and Michael A. Grandner PhD

INTRODUCTION: Sleep duration has been associated with adverse cardiometabolic outcomes. Sleep deprivation has been shown to impair cognitive function in the laboratory, but few studies have examined associated between sleep duration and cognitive function at the population level. This is relevant because poor cognitive function could lead to accidents, decreased functioning, and other adverse outcomes. It is possible that habitual sleep duration confers risk in this domain as well.

METHODS: Data from the 2013 Behavioral Risk Factor Surveillance System (BRFSS) was used. The BRFSS is a phone-based survey conducted annually by the CDC. N=390,959 adults age ≥18 provided complete data. Sleep duration was assessed as habitual sleep within 24 hours and was categorized as very short (≤4h), short (5-6h), normal (7-8h, reference), and long (≥9h). Daytime cognitive dysfunction was operationalized with, "Because of a physical, mental, or emotional condition, do you have serious difficulty concentrating, remembering, or making decisions?" Covariates included age, sex, education, income, race/ethnicity, overall health, and days poor physical and/or mental health in the past month. Logistic regression analyses were weighted for representativeness to the US population.

RESULTS: In unadjusted analyses, daytime cognitive function was more frequently endorsed in very short (OR=8.07; 95%CI[7.48,8.71]; p<0.0001), short (OR=2.20; 95%CI[2.09,2.32]; p<0.0001), and long sleep (OR=2.72; 95%CI[2.52,2.93]; p<0.0001). After adjustment for demographics and socioeconomics, these were attenuated somewhat for very short (OR=5.52; 95%CI[5.09,6.00]; p<0.0001), short (OR=2.03; 95%CI[1.92,2.14]; p<0.0001), and long sleep (OR=2.09; 95%CI[1.93,2.26]; p<0.0001). After including overall, physical, and mental health, these relationships were further attenuated but still significant for very short (OR=2.32; 95%CI[2.10,2.57]; p<0.0001), short (OR=1.44; 95%CI[1.35,1.52]; p<0.0001), and long sleep (OR=1.72; 95%CI[1.58,1.87]; p<0.0001).

CONCLUSIONS: Short and long sleep duration are associated with cognitive dysfunction, even after accounting for demographics, social factors, and physical and/or mental health problems. Population-level concerns about the adverse impact of sleep duration should consider cognitive as well as cardiometabolic risks.

K23HL110216, R21ES022931

CBT-I for Veterans with Psychosis: Study Design

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Project Background: Insomnia is highly prevalent among individuals with psychotic disorders and confers significant long-term negative impacts on their physical, emotional, psychosocial, and cognitive recovery. Many behaviors that contribute to insomnia (e.g., poor diet, exercise, substance use, smoking) are associated with harmful medical conditions that are highly prevalent among Veterans with psychosis (e.g., obesity, cardiovascular disease). Improving sleep may improve these medical conditions, yet Veterans with psychosis are largely not provided with CBT-I, the current first-line treatment for insomnia.

Project Objectives: The proposed research will develop guidelines for the clinical tailoring of CBT-I for Veterans with psychotic disorders and study the preliminary feasibility, acceptability, and utility of the resulting program in improving sleep and associated functional outcomes. The first step of this research will involve an iterative process of review of the extant literature, analysis and integration of information on sleep problems gathered through pilot work, and input from Veteran clients, expert consultants, mentors and VA treatment providers to develop guidelines and materials for the clinical tailoring of CBT-I for Veterans with psychotic disorders. Using qualitative procedures, we will complete an initial acceptability trial of CBT-I with six Veterans with psychosis and insomnia for further refinements of the guidelines. Finally, the proposed study will use a small randomized controlled feasibility and preliminary efficacy trial comparing CBT-I (n=30) to a Health and Wellness control intervention (n=30) to assess rates of recruitment, initial intervention engagement, attendance at intervention sessions, and therapist fidelity. Outcomes include insomnia symptoms and functioning (e.g., health-related quality of life, physical functioning, role limitations, life activities, social interactions, participation in society, and cognitive functioning). We will explore whether baseline clinical and sleep characteristics, physical comorbidities, and other health behaviors (e.g., smoking, caffeine use, physical activity) moderate the impact of CBT-I on insomnia and functional outcomes, improve as a result of participation in CBT-I, or mediate the effect of CBT-I on functioning. In addition, we will assess the durability of effects of CBT-I on insomnia symptoms and functioning at a 3 month follow-up visit.

Project Methods: This project will include developing educational materials and guidelines for the clinical use of the CBT-I protocol, conducting an open trial of CBT-I in a small sample, and completing an RCT with 60 participants. We will monitor fidelity, feasibility, and acceptability; study Veterans' experiences; measure symptom and functional outcomes at post-treatment and 3-month follow-up; and evaluate potential moderators and mediators.

Anticipated Impacts on Veteran's Healthcare: Insomnia is a critical obstacle to the rehabilitation and recovery of Veterans with psychotic disorders. The VHA has made treatment of insomnia a high priority and has initiated a nationwide dissemination of Cognitive Behavioral Therapy for Insomnia (CBT-I) – an evidence-based practice and the first-line standard of care for insomnia – across the VHA system, but it is largely not provided to Veterans with psychosis and insomnia. This study involves developing empirically-derived guidelines for the clinical tailoring of CBT-I for Veterans with psychosis and insomnia, and testing the acceptability, feasibility, and preliminary efficacy of CBT-I for improving sleep-related functional outcomes. This work will yield a well-specified behavioral intervention that has the potential to improve not only sleep but also physical health functioning more broadly. *Funding: This study will be supported by a VA Research Career Development Award-2 (VA Rehabilitation Research and Development Service)*

Wake-related Lingual Muscle Activity Is Suppressed in Rats with Circadian Rhythm Disrupted by Constant Lights-on Condition

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Introduction: Obstructive sleep apnea (OSA) patients have elevated lingual muscle activity during wakefulness which helps them to maintain the upper airway open when they are awake. This adaptation is diminished during sleep and, as a result, sleep in OSA patients can be severely disrupted and misaligned relative to the normal circadian cycle. The impact of such disruption and misalignment on upper airway muscle tone is unknown. To fill this gap, we used rats to study how lingual EMG levels quantified in different behavioral states vary across the normal circadian cycle and how they are altered when the normal circadian rhythm of sleep is disrupted.

Methods: In 7 chronically instrumented Sprague-Dawley rats, we recorded lingual and nuchal EMGs, cortical EEG and motor activity. After habituation, one 24 h-long recording was collected under 12:12 light-dark (L-D) cycle (lights on at 7 AM) and another after at least 14 days of housing with lights continuously on which disrupts the circadian rhythm of sleep-wake and motor activity. EMGs were quantified in successive 10 s intervals, sorted by different sleep-wake states, and their root mean squares were normalized by the mean level during wakefulness recorded between 4 AM and 7 AM under the normal L-D cycle.

Results: Under the normal L-D cycle, the average levels of lingual and nuchal EMGs during wakefulness and slow-wave sleep (SWS) were significantly higher during the active (dark) phase than during the rest phase of the circadian cycle. In contrast, the magnitude of twitching activity that characterizes lingual EMG during rapid eye movement sleep (REMS) was lower during the active phase than during the rest phase. Under the constant lights-on condition, sleep-wake state amounts and motor activity (light beam breaks) quantified in successive 3 h intervals over 24 h were nearly constant at mid-levels relative to their peaks and nadirs recorded under the normal L-D cycle. In contrast, the average levels of lingual and nuchal EMG measured during wakefulness and SWS settled at levels close to their nadirs recorded under the normal L-D cycle, rather than at intermediate levels between the peaks and nadirs measured under the normal L-D conditions.

Conclusions: In rats, disruption of the normal circadian cycle of sleep and motor activity is associated with a suppression of spontaneous activity of the muscles of the tongue (and also those maintaining an upright head posture). In OSA patients who require elevated lingual EMG, sleep disruption and its circadian misalignment may exacerbate problems with maintaining the airway open during both wakefulness and SWS. (Supported by NIH grant HL-116508.)

(The results were first presented and published as an abstract at the Annual Meeting of the Associated Professional Sleep Societies, Seattle, WA, June 6-10, 2015.)

Regulation of Sleep by Metabotropic Glutamate Signaling in *Drosophila Melanogaster*

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Trainee Award Eligible

Metabotropic glutamate receptors (mGluRs) modulate a wide range of processes in the central nervous system such as synaptic plasticity and neuronal signaling. Published and unpublished work from our labs has shown that proteins at the postsynaptic density (PSD) of glutamatergic synapses regulate sleep in both *Drosophila* and mice. mGluRs are part of a complex scaffold that physically links them to these sleep-regulating proteins. However, the direct involvement of mGluR signaling in sleep has not yet been established. In this study, we investigated the role of mGluR signaling in sleep and wake regulation in *Drosophila melanogaster*. We determined the behavioral sleep effects of pharmacologically and genetically inhibiting the single *Drosophila* mGluR – known as DmGluRA. We fed female wCS10 flies food containing LY341495, a type II mGluR antagonist and found that LY341495-treated flies display significant reductions in total sleep time across the day and night, suggesting that DmGluRA may generally serve as a sleep-promoting signal in the fly. To identify the brain-specific contributions of mGluR signaling to sleep, we employed the *Drosophila* UAS/GAL4 system to knock down DmGluRA in different cells and brain regions and assessed sleep behavior. Specifically, we expressed DmGluRA RNAi in neurons and various brain regions that are known to regulate sleep. Knockdown of neuronal DmGluRA recapitulated the sleep loss seen with pharmacological inhibition but only during the beginning of the night, while sleep was differentially affected by knockdown in different brain regions. Many of the sleep effects following genetic knockdown were isolated to the nighttime, suggesting that DmGluRA regulates sleep in a time-of-day-specific manner. To begin to characterize the molecular mechanisms of DmGluRA-mediated sleep regulation, we examined the binding dynamics of DmGluRA and Homer, a sleep- and wake-regulating adaptor protein that links mGluRs to ionotropic glutamate signaling at the PSD as well as to calcium signaling in the endoplasmic reticulum. Co-immunoprecipitation of DmGluRA and Homer confirm that DmGluRA and Homer physically interact in *Drosophila*. Furthermore, preliminary western blot analysis indicates that levels of Homer/DmGluRA protein interaction are higher during the day than during the night. Our results suggest that DmGluRA signaling modulates sleep in *Drosophila melanogaster* and suggests that its involvement in sleep regulation may be mediated by binding to Homer proteins. These results have important implications for our understanding of the molecular mechanisms underlying sleep and wake and provide a link between sleep and other biological processes in the brain that depend on mGluR and Homer signaling.

- Title: Sleep disruption-induced endoplasmic reticulum stress in locus coeruleus is associated with age-related memory impairment
- Introduction: Sleep fragmentation is a prevalent concern among the elderly, yet little is understood about how fragmentation affects the aging brain. We have shown previously that endoplasmic reticulum (ER) stress is induced in mouse cortex following sleep deprivation, and that this induction varies with aging. The present study addresses whether sleep fragmentation, a more physiological concern, induces age-dependent effects in wake-active area locus coeruleus (LC) and whether these effects are associated with cognitive changes.
- Methods: EEG recordings from 3-month-(young) and 12-month-old (aged) mice were collected over the 12-hour sleep phase during baseline and fragmented conditions. Fragmentation was induced by a rotating bar spanning the diameter of a circular chamber. Following fragmentation (or undisturbed conditions), one cohort of mice was perfused and brains were extracted for immunohistochemical analysis of ER stress markers in LC. Another cohort was tested for their ability to recognize a displaced object using visual cues.
- Results: At baseline, aged mice had fragmented sleep ($p<.001$), and also showed increased basal levels of ER stress marker CHOP ($p<.001$). Following 12-hour sleep fragmentation, young but not aged mice had robust induction of upstream marker p-PERK ($p<.01$) and CHOP ($p<.05$) expression. In correlation, young but not aged undisturbed mice were able to recognize a displaced object ($p<.05$), and this ability was lost in young mice following fragmentation.
- Conclusion: By 12 months of age, mouse sleep is fragmented, basal ER stress is increased in LC, and spatial memory is impaired. Furthermore, fragmentation causes ER stress and memory impairments in young but not aged mice. This indicates that baseline fragmentation in aged mice may induce protein dyshomeostasis that contributes to memory impairments in aging, consistent with data on sleep loss and aging in human subjects.
- Support: T32; P01 AG017628

Time-of-Day Variations in Brain Function: An ASL Perfusion Imaging Study

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Trainee Award Eligible

Introduction: Biological functions express rhythmic fluctuations across the 24-h day. However, circadian variations of neural activities in the human brain have been rarely examined using neuroimaging techniques. Arterial spin labeling (ASL) perfusion fMRI can non-invasively quantify regional cerebral blood flow (CBF) with excellent reproducibility, therefore providing a method to measure variations of human brain function at different times of day. We used ASL and examined time-of-day effects on brain function both at rest and during a 10-min psychomotor vigilance test (PVT).

Method: Nineteen healthy adults (8 females, 21-50y) were scanned during two separate in-laboratory sleep protocols. In one protocol the scan occurred in the morning following baseline sleep and in the other protocol, the scan occurred in the evening following baseline sleep. The median time between the two scans was 189 days. During both scans, a pseudo-continuous ASL sequence was used to acquire CBF data during the PVT as well as during resting states before and after the PVT. Data were analyzed using SPM8 and the Grocer toolbox.

Results: There were no differences in sleep duration or timing during the week prior to both protocols (assessed by wrist activity). PVT performance in the scanner (mean reciprocal reaction time, mean fastest 10% of reaction times, and mean number of errors), did not differ between morning and evening conditions. However, robust CBF differences between morning and evening were found in multiple brain regions during the PVT and at rest. During the PVT, evening scans showed lower CBF in the PCC, bilateral putamen, middle cingulate cortex and left inferior parietal gyrus and higher CBF in the right caudate. At rest, evening scans showed lower CBF in the left middle frontal and temporal gyrus, and pons, and higher CBF in the left parahippocampus and right medial frontal gyrus.

Conclusions: Although performance on the PVT did not differ between morning and evening, CBF differed significantly both at rest and during the PVT. These results demonstrate robust time-of-day variations of brain function without behavioral differences. Time-of-day effects must be considered in the interpretation of fMRI studies.

Support: Supported by NIH grants R01 HL102119, R01 NR004281, R21-DA032022, the PENN ITMAT-TBIC Pilot Project, the Department of the Navy, Office of Naval Research (Award No. N00014-11-1-0361), and National Space Biomedical Research Institute through NASA NCC 9-58.

Population Assessment of Sleep Duration, Chronotype and Body Mass Index

Susan Kohl Malone, Freda Patterson, Rose Lu, Alexandra L. Hanlon

Trainee Award Eligible

Obesity remains a leading cause of morbidity and mortality worldwide. Sleep may be a determinant of body mass index (BMI), whereby short sleep duration is predictive of weight gain. However, this relationship has not been found in all studies in adults. One reason for these inconsistent findings may be the failure to consider chronotype, which describes the extent to which an individual is a "morning" or an "evening" person. To address this gap, we conducted a descriptive examination of the association between sleep duration, chronotype and BMI in a population of 501,766 adults residing in the United Kingdom. Data were collected as part of the UK Biobank study. Fruit and vegetable consumption as well as number of days with moderate and vigorous physical activity in the last week were also examined. The majority of the sample was Caucasian (95%), 55% were female, 58% were employed and the mean age was 62.5 (SD=8.1) years. Mean BMI was 27.4 (SD=4.8). The average self-reported sleep duration was 7.2 hours per night (SD=1.1). The majority of the sample reported an intermediate chronotype (63.9%). The average number of servings of cooked vegetables per day was 2.7 (SD=1.9) while the average number of servings of raw vegetables per day was 2.2 (SD =2.2). On average, participants reported 3.5 days (SD=2.4) of moderate physical activity and1.8 days (SD=2.0) of vigorous activity per week. Longer sleep duration, morning chronotype, greater raw vegetable consumption, greater moderate physical activity, and greater vigorous activity were associated with a lower BMI. Eating more fresh fruit and cooked vegetables were associated with a higher BMI. Preliminary models suggest that the main effect of longer sleep duration on a lower BMI is greater for adults who report a morning chronotype as compared to an evening chronotype. This is the first population-based study to suggest that chronotype may moderate the relationship between sleep duration and BMI.

Associations among sleep duration, chronotype, and BMI in high school students using actigraphy measured sleep parameters

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Background: Support for an association between sleep and obesity in adolescents is inconsistent. These inconsistent findings may be explained by considering the synchrony between biological and behavioral processes, such as sleep/wake timing or circadian alignment. Circadian misalignment is associated with obesity in adults. This association has not been explored in adolescents. Yet, early high school start times coupled with developmental shifts towards later sleep/wake timing may contribute to chronic circadian misalignment. Chronotype (as a marker for circadian misalignment) may predict who is at greatest risk for obesity onset when exposed to short sleep.

Methods: This prospective cross-sectional study examined variations in sleep duration and chronotype among racially/ethnically diverse high school students and investigated whether chronotype modified the association between sleep duration and BMI. Sixty nine 9th and 10th grade high school students participated. Sleep duration, chronotype (midpoint of sleep), and social jet lag were estimated from seven days of actigraphy data. BMI and Waist to Height Ratios were estimated from height, weight, and waist measurements. General linear models were used to identify predictors of sleep duration, chronotype, and BMI.

Results: Greater social jet lag was associated with higher BMI z scores. Chronotype was not associated with BMI z scores.

Conclusions: Establishing regular sleep-wake patterns on school and free days may be more important than sleep duration for preventing obesity in adolescents. Delaying high school start times to align with developmental delays in sleep-wake times during adolescence may contribute to greater sleep-wake regularity between school and free days.

Predictions of Sleep Disturbance for Different Nighttime Airport Operation Strategies Using a New Markov State Transition Sleep Model

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Introduction: To balance benefits and costs of potential airport operation changes such as noise curfews, changes in flight schedules, or flight paths, models are needed which can predict the time varying nature of the effects of aircraft noise on sleep. While a Markov transition model has previously been developed which predicts the transitions between 6 sleep stages throughout the night (Wake, S1, S2, S3, S4, and REM), it has two limitations. The Markov model was developed based on data from a laboratory study, in which a greater probability of aircraft noise-induced awakenings was found compared to field studies. In addition, the model predicts the same probability of awakening for all aircraft events, regardless of the noise level.

Methods: To overcome the two limitations of the previous model, a new Markov transition model was developed using data from a total of 483 nights from 63 subjects who participated in a polysomnographic field study that was conducted around Cologne-Bonn Airport. Similar to the previous Markov model, transition probabilities between sleep stages were calculated using 1st-order autoregressive multinomial logistic regression models. In addition to elapsed sleep time, the maximum noise level has been added to the model as an explanatory variable.

Results: The Markov model was used to predict the number of awakenings and the time spent in each sleep stage for different nighttime noise mitigation strategies including different timing of events and flight patterns. The model predicts a decrease in slow wave sleep and an increase in time spent awake due to noise exposure which is dependent on the number, noise level, and distribution of the aircraft events during the night.

Conclusion: With further validation, this Markov model could be a useful tool for optimizing nighttime traffic patterns to reduce the impact of noise on sleep in communities.

Support: This study was internally funded by the German Aerospace Center (DLR).

Binge Drinking and Habitual Sleep Duration, and the Roles of Depression and Smoking: Data from the 2013 BRFSS

Sohaib A. Rana MBBS, Subhajit Chakravorty MD, and Michael A. Grandner PhD

INTRODUCTION: Several studies have shown that both alcohol binges and smoking can disturb sleep, and that substance use is commonly seen in the context of depression, which itself is associated with poor sleep. The present study sought to explore these relationships in a national sample with the goal of determining pathways linking binge drinking with sleep duration.

METHODS: Data from the 2013 BRFSS, a large survey conducted by the CDC, was used (N=199,009). Sleep duration was assessed as amount of sleep in typical 24h and was categorized as very short (≤4h), short (5-6h), normal (7-8h, reference), and long (≥9h). Binge drinking frequency was assessed as number of occasions in the past 30 days of ≥5 drinks. Smoking and depression were self-reported. Covariates included age, sex, race/ethnicity, education, income, marital status, and BMI. Multinomial logistic regression, with sleep duration as dependent variable, examined the role of binge drinking, smoking, and depression. Sobel tests examined the role of smoking and depression as mediators of relationships with heavy drinking.

RESULTS: In analyses adjusted for covariates, each binge episode was associated with increased likelihood of very short (OR=1.05; 95%CI[1.04-1.06]; p<0.0001), short (OR=1.02; 95%CI[1.01-1.02]; p<0.0001), and long (OR=1.03; 95%CI[1.02-1.04]; p<0.0001) sleep. Similarly, smoking was associated with very short (OR=2.38; 95%CI[2.21-2.57]; p<0.0001), short (OR=1.53; 95%CI[1.47-1.59]; p<0.0001), and long (OR=1.22; 95%CI[1.14-1.32]; p<0.0001) sleep. After adjusting for smoking and depression, effects for binge drinking were still significant for very short (OR=1.04; 95%CI[1.03-1.05]; p<0.0001), short (OR=1.01; 95%CI[1.01-1.02]; p<0.0001), and long (OR=1.03; 95%CI[1.02-1.04]; p<0.0001) sleep. In partial mediation analyses, smoking accounted for 29%, 36%, and 6% of the relationship between binge drinking and very short, short, and long sleep, respectively, and depression accounted for 14%, 10%, and 7% of these relationships.

CONCLUSIONS: Binge drinking and smoking are associated with very short, short, and long sleep duration. The relationship between binge drinking and sleep is partially mediated by smoking (especially for very short and short sleep) and depression.

K23HL110216, R21ES022931

Where Are the Sleep Duration Disparities? The Relationship between Sleep Duration and Race/Ethnicity Depends on State of Residence: Data from 50 States and the District of Columbia, BRFSS 2013

Jesse Schuschu, Wilfred Pigeon PhD, Girardin Jean-Louis PhD, and Michael A. Grandner PhD

INTRODUCTION: Several studies have shown that sleep duration is associated with race/ethnicity, and these associations may play a role in health disparities. It is plausible that different social/environmental contexts may reflect different relationships to sleep.

METHODS: Data from the 2013 BRFSS was used (N=484,401 with sleep duration data). The BRFSS is a state-based telephone survey conducted by the CDC. Data from 50 states and the District of Columbia were included. Sleep duration was assessed as habitual sleep in a typical 24 hours and was coded as short (6h or less), normal (7-8h, reference), or long (9h or more). Race/ethnicity was categorized as Non-Hispanic White (reference), Black/African-American, Hispanic/Latino, Asian/Pacific-Islander, Native-American, and Other/Multiracial. Covariates included age, sex, education, access to insurance, smoking, and BMI. Population-weighted multinomial logistic regression analyses examined the relationship between race/ethnicity and sleep duration in the complete sample, and stratified by state.

RESULTS: Overall, short sleep was more prevalent among Black/African-American (OR=1.74;95%CI[1.66-1.82];p<0.0001), Asian/Pacific-Islander (OR=1.40;95%CI[1.28-1.54];p<0.0001), Native-American (OR=1.38;95%CI[1.23-1.54];p<0.0001), and Other/Multiracial (OR=1.58;95%CI[1.44-1.74];p<0.0001) groups, and long sleep was more prevalent among Black/African-American (OR=1.65;95%CI[1.53-1.77];p<0.0001), Native-American (OR=1.45;95%CI[1.21-1.74];p<0.0001), and Other/Multiracial (OR=1.42;95%CI[1.17-1.72];p=0.0003) groups. Blacks/African-Americans exhibit greater prevalence of short sleep in 40 states and long sleep in 19 states. Hispanics/Latinos demonstrated increased short sleep in 9 states and increased long sleep in 3 states. Asians/Pacific-Islanders demonstrated increased likelihood of short sleep in 9 states, more long sleep in 1 state, and less long sleep in 7 states. Native-Americans demonstrated more short sleep in 14 states, more long sleep in 7 states and less long sleep in 1 state. Others/multiracial demonstrated more short sleep in 25 states, and more long sleep in 7 states.

CONCLUSIONS: The relationship between sleep duration and race/ethnicity varies by state of residence. It is possible that factors unique to different regions may exert differential influence over sleep as it relates to other factors such as race/ethnicity.

K23HL110216, R21ES022931

The Relationship between Sleep Duration and Obesity Depends on State of Residence: Data from 50 States and the District of Columbia, BRFSS 2013

Jesse Schuschu, Wilfred Pigeon PhD, and Michael A. Grandner PhD

Trainee Award Eligible

INTRODUCTION: Many studies have shown that short sleep duration is associated with obesity at the population level. Further, studies have shown geographic factors associated with both obesity and sleep. Thus, the relationship between sleep duration and obesity may vary geographically.

METHODS: Data from the 2013 BRFSS was used (N=484,401 with sleep duration data). The BRFSS is a state-based telephone survey conducted by the CDC. Data from 50 states and the District of Columbia were included. Sleep duration was assessed as habitual sleep in a typical 24 hours and was coded as short (6h or less), normal (7-8h, reference), or long (9h or more). Obesity (BMI≥30) was based on self-reported height and weight. Covariates included age, sex, education, access to insurance, smoking, and race/ethnicity. Population-weighted multinomial logistic regression analyses examined the relationship between race/ethnicity and sleep duration in the complete sample, and stratified by state. Holm-Bonferonni was used to adjust for Type-I error rate.

RESULTS: Overall, short sleep was associated with obesity (OR=1.35;95%CI[1.31-1.39],p<0.0001), as was long sleep duration (OR=1.10; 95%CI[1.05-1.16]; p=00002). Short sleep was associated with obesity in 41 states, in order from greatest to weakest association: MN (OR=1.73; 95%CI[1.48,2.03]; p<0.0001), MA, SD, RI, ME, ID, CO, NC, WA, NM, TX, IN, GA, KS, WY, AR, FL, TN, KY, CT, ND, VT, PA, NE, IA, VA, OH, NJ, AL, UT, MD, SC, IL, MT, WV, MS, NH, MI, OK, CA, and NY (OR=1.24; 95%CI(1.07-1.44); p=0.004). Note that no significant relationships were found in AK, AZ, DC, DE, HI, LA, MO, NV, OR, or WI. Long sleep duration was not associated with obesity in any state after Type-1 error adjustment and only in NC, IN, and NE (all OR=1.3; p<0.05) before adjustment.

CONCLUSIONS: Regional differences in social and environmental factors may play a role in the relationship between sleep duration and obesity.

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Abdominal Fat Differences Between Sexes in Lean and Obese Apneics

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Trainee Award Eligible

Introduction

Obesity is known to increase an individual's risk of sleep apnea (OSA); however specific fat distribution has been shown to vary between genders. Past studies have showed that men tend to store fat viscerally, while women tend to have increased subcutaneous fat distribution[1]. The etiology of OSA in lean individuals is also unclear. This study examined the differences of fat distribution in genders and apneic patients in both lean and obese groups.

Methods

A total of 121 subjects underwent a sleep study and abdominal MRI at the Penn Sleep Center. Subjects were divided into controls (AHI ≤10 events/hour) or apneics (AHI ≥15) based on PSG, and into lean or obese groups using a waist measurement cutoff of 100 cm (Table 1). Volumetric analysis was conducted for subcutaneous and visceral fat volumes using Amira 5.4.3 (Visage Imaging Inc.). Stata 12 was used to conduct statistical analyses.

Table 1. Subject Demographics

	Age (years)	BMI (kg/m^2)	Controls		Apneics	
			Lean	Obese	Lean	Obese
Men (n = 90)	51.00 ± 7.11	31.89 ± 7.67	16	4	29	41
Women (n = 31)	57.20 ± 6.22	29.86 ± 4.33	9	3	5	14
Values presented as Mean ± SD						

Results

Differences in BMI were borderline significant between genders (p = 0.075) (Table 2). There were no significant differences found between groups with respect to race and ratios of men to women. Both age (p <0.0001) and waist measurements (p < 0.01) were significantly different between genders. Visceral fat distribution was significantly significant between genders after adjusting for age, waist, race, and BMI (p < 0.0001), and subcutaneous fat volumes were borderline significant between genders (p = 0.054). Total fat volumes were not different between genders (p = 0.63). Apneics showed greater visceral fat volumes than controls in lean subjects (p = 0.04) though subcutaneous (p = 0.9) and total abdominal fat (p = 0.49) volumes were not different (Table 3). Obese subjects showed no significant differences in subcutaneous, visceral, or abdominal fat volumes between apneics and controls.

Conclusions

This study shows that the biggest difference in fat distribution between genders was in visceral fat volume. Men showed greater abdominal visceral fat than women, and there was a trend for women to show greater subcutaneous fat volumes. In lean subjects, there was a borderline significant difference in visceral fat volumes between controls and apneics, while in obese subjects no differences were observed. These data suggest that in obese subjects, abdominal fat may have a lesser effect on OSA than other etiologies such as enlarged upper airway structures or increased tongue fat.

Sources

1. Blaak, E. (2001, November 4). Gender Differences in Fat Metabolism. Retrieved April 26, 2015, from http://www.ncbi.nlm.nih.gov/pubmed/11706283

Table 2. Differences Between Male and Female Measures

Measure	Male (n = 90)	Female (n = 31)	p	p†
BMI (kg/m^2)	31.89 ± 7.67	29.86 ± 4.33	0.075	
Age (years)	51.00 ± 7.11	57.20 ± 6.22	***	
Waist (cm)	106.06 ± 19.78	96.62 ± 9.65	**	
Subcutaneous Fat (cm^3)	6690 ± 4280	7280 ± 2700	NS	0.054
Visceral Fat (cm^3)	3850 ± 1820	2030 ± 1230	***	***
Total Abdominal Fat (cm^3)	10000 ± 5690	9300 ± 3300	NS	NS
†Adjusted for Age, BMI, Race, and Waist Measurement; *p<0.05; **p<0.01; ***p<0.0001; NS = Not Significant; Values presented as Mean ± SD				

Table 3. Differences Between Controls and Apneics within Lean and Obese Groups

Measure	Lean (n = 59)				Obese (n = 62)			
	Control	Apneic	p	p†	Control	Apneic	p	p†
BMI (kg/m^2)	26.83 ± 3.99	27.79 ± 3.67	NS		30.18 ± 3.85	35.81 ± 7.37	*	
Age (years)	50.52 ± 5.55	50.94 ± 5.98	NS		53.33 ± .891	54.38 ± 8.38	NS	
Waist (cm)	91.36 ± 13.63	95.63 ± 11.26	NS		110.17 ± 4.08	113.59 ± 18.83	NS	
Subcutaneous Fat (cm^3)	4740 ± 2050	4680 ± 1580	NS	NS	6900 ± 2190	8960 ± 4500	0.07	NS
Visceral Fat (cm^3)	1910 ± 1050	2910 ± 1330	**	*	2770 ± 1730	4350 ± 1900	0.06	NS
Total Abdominal Fat (cm^3)	6650 ± 2840	7300 ± 2270	NS	NS	9660 ± 2930	12600 ± 5860	*	NS
†Adjusted for Age, BMI, Race, and Waist Measure; *p<0.05; **p<0.01; NS = Not Significant; Values presented as Mean ± SD								

Chronobiology of Acute Aortic Dissection in Marfan Syndrome Patients: Insights from the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) and the International Registry of Acute Aortic Dissection (IRAD)

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Background: Marfan Syndrome (MFS) is an autosomal dominant connective tissue disease caused by mutations in *FBN1*. The most catastrophic phenotype associated with MFS is acute aortic dissection (AAD). Several cardiovascular conditions follow a chronobiological pattern in incidence, from myocardial infarctions to aortic dissections. We used two large registries that include MFS patients to investigate possible trends in the chronobiology of AAD in MFS.

Methods: We queried the International Registry of Acute Aortic Dissection (IRAD) and the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry to extract data on all patients with MFS who had suffered an AAD. The group included 257 patients with MFS who suffered an AAD between 1980 and 2012. Data on demographics, comorbidities, time, month and season of AAD were analyzed. Possible interactions with age, gender and medical comorbidities were also explored. Chi-square tests were used for statistical testing.

Results: Mean subject age at time of AAD was 38 years and 61% of subjects were male. 65% of patients suffered a Type A dissection. AAD was more likely in the winter/spring season (Nov-Apr) than the other half of the year (57% vs. 43%, p=0.05). Dissections were significantly more likely to occur during the daytime hours, with 65% of dissections occurring from 6AM to 6PM (p=0.001). Males were more likely to dissect during the daytime hours (6AM-6PM) than females (74% vs. 51%, p=0.01), with females dissecting more evenly across the day. Gender did not correlate with monthly/seasonal distribution of AAD. Type A dissections were more likely to occur during the day time (6AM-6PM) than Type B dissections (72% vs. 53%, p=0.03); Incidence of Type B dissections was more evenly distributed throughout the day and night. MFS patients with a history of hypertension (35% of cohort) or cigarette smoking (38% of cohort) did not seem to have a significantly different distribution of AAD incidence compared to those without these conditions (not significant).

Conclusions: This study may be the largest collection of MFS patients with AAD ever reported. By merging two large registries with no overlap, we were able to compile a large cohort of MFS patients to explore relationships between time and AAD. MFS patients were most likely to have an AAD during the winter months and during the first half of the day. Males with MFS were more likely to dissect during the day time compared to females. These insights offer a glimpse of the times of greatest vulnerability for MFS patients who suffer from this catastrophic event. Based on our analyses, the chronobiology of AAD in MFS reflects that of AAD in the general population. Therefore, it appears that the various factors driving the chronobiology of AAD are not disrupted by the underlying genetic predisposition for AAD exhibited in MFS. Additional investigations will help elucidate the environmental and molecular underpinnings of these patterns in the general and MFS populations. Furthermore, the use of medications and other risk factor modification during particularly high risk times may be tailored to minimize risk of AAD in this already vulnerable MFS population.

Resting Metabolic Rate Varies by Race and by Sleep Duration

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Trainee Award Eligible

Introduction: Short sleep duration is a significant risk factor for weight gain and obesity, particularly in African Americans and men. Increased caloric intake underlies this relationship but it remains unclear whether decreased energy expenditure is a contributory factor. The current study assessed the impact of sleep restriction and recovery sleep on energy expenditure in African American and Caucasian men and women.

Methods: Healthy adults (21-50y) participated in a controlled laboratory study. After two baseline sleep nights, subjects were randomized to an experimental (n=36; 4h time-in-bed (TIB)/night for 5 nights followed by 1 night 12h TIB recovery sleep) or a control condition (n=11; 10h TIB/night). Resting metabolic rate and respiratory quotient were measured using indirect calorimetry in the morning after overnight fasting.

Results: Resting metabolic rate—the largest component of energy expenditure—decreased after five nights of sleep restriction (-2.6%, p=0.032) and returned to baseline levels after recovery sleep. No changes in resting metabolic rate were observed in control subjects. Relative to Caucasians (n=14), African Americans (n=22) exhibited comparable daily caloric intake but a lower resting metabolic rate (p=0.043) and a higher respiratory quotient (p=0.013) regardless of sleep duration.

Discussion: Adults who are chronically sleep restricted due to having habitual short sleep durations may need to compensate for decreased morning resting metabolic rate by reducing caloric intake or increasing physical activity to prevent weight gain.

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Keywords: Sleep Restriction, Race, Energy Expenditure

Effect of Short-Term Fasting on Late-Night Neurobehavioral Performance during Sleep Restriction

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Introduction: Evidence suggests that caloric intake leads to decreased alertness and increased sleepiness. Healthy adults consume approximately 500 additional calories during late-night hours when sleep restricted. Late-night/early-morning hours are also when most sleep-restricted adults display pronounced decreases in alertness and neurobehavioral performance deficits. The objective of the current study was to assess if refraining from consuming late-night calories affects neurobehavioral performance during sleep restriction.

Methods: Forty-four subjects (21–50y) had ad libitum access to food/drink during the first three days following sleep restriction (SR1-3, 4h time-in-bed/night, 0400-0800). Beginning at 2200 on the fourth day following sleep restriction (SR4), subjects assigned to the fed condition (n=20) continued to have ad libitum access to food/drink whereas subjects assigned to the fasted condition (n=24) were only allowed to consume water until bedtime. Each day, all subjects completed objective assessments of vigilant attention (Psychomotor Vigilance Test; PVT), working memory (Digit Span) and cognitive throughput (Digit Symbol Substitution Task) as well as subjective measures of sleepiness (Karolinska Sleepiness Scale), stress (Visual Analogue Scale) and mood (Profile of Mood States) at 0200h.

Results: On SR1-3, when all subjects were fed ad libitum, performance on the PVT (reaction time and lapses) did not differ between subjects in fed and fasted conditions (ps>0.46). However, on SR4, fasted subjects performed better than fed subjects on the PVT (faster reaction times and fewer lapses, ps<0.05). Furthermore, fed subjects exhibited significantly slower reaction times and more lapses on SR4 compared to SR3 (ps<0.05) whereas fasted subjects did not show this decline in performance (ps>0.18). There were no differences between subjects in fed and fasted conditions when examining working memory, cognitive throughput or subjective ratings of sleepiness, stress, and mood on SR1-4 (all p>0.15).

Conclusion: These results indicate that refraining from consuming calories during late-night hours may be a useful strategy for alleviating (but not eliminating) decreased vigilance during sleep restriction.

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Keywords: Sleep Restriction, Psychomotor Vigilance Test, Fasting

Vitamin E Intake Associates With Spatial Memory Performance During Sleep Restriction In Healthy Women

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Introduction: A previous study using a rodent model found that Vitamin E administration attenuated sleep deprivation-induced spatial memory impairment. The current study assessed if ad libitum Vitamin E intake associated with memory performance in healthy adults undergoing sleep restriction.

Method: Forty-one healthy adults (18 females, 21-50y) participated in one of two laboratory protocols and experienced two nights of baseline sleep (BL1-2, 10h/night, 2200h-0800h) followed by five nights of sleep restriction (SR1-5, 4h/night, 0400h-0800h). Subjects completed the Visual Object Learning Task (VOLT), a spatial working memory assessment, as part of a larger test battery each morning. Performance on the VOLT was assessed using a standard score that accounted for the accuracy and speed of responses. Food/drink intake was ad libitum and was recorded by trained monitors. Intake data were entered into a food processing program to obtain Vitamin E consumption.

Results: Performance on the VOLT varied significantly across protocol days ($p<0.001$). Subjects displayed improvement on the VOLT from BL2 to SR2 and then a decline in performance from SR2 to SR5. During baseline, Vitamin E intake was not related to VOLT performance in men or women ($ps>0.21$). During sleep restriction (mean SR1-SR5), Vitamin E intake was more strongly positively correlated with VOLT performance in women ($r=0.46$, $p=0.053$) than in men ($r=0.14$, $p=0.51$), albeit statistically not significant. A median split based on Vitamin E intake during sleep restriction showed that women who consumed higher levels of Vitamin E performed significantly better on the VOLT during sleep restriction than women who consumed lower levels of Vitamin E ($p=0.029$, Cohen's $d=1.13$).

Conclusion: Ingestion of Vitamin E, an antioxidant substance, may improve spatial memory performance during sleep restriction in women. Future research is needed to replicate these findings in a larger sample and to assess if other nutrients or vitamins are related to memory performance during sleep restriction.

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Brain response during sleep estimated from NMR metabolomics

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Sleep related disorders such as insomnia, parasomnias, sleep apnea, and narcolepsy could be better understood by studying Brain activity during sleep and wakefulness. Increasing evidence also points to the bidirectional interaction of sleep and metabolism. However, simple and quantitative test to estimate brain function related to sleep and metabolism is still absent. We profiled the blood serum metabolome of healthy individuals every 2 hours over a period of 48 hours that included regular sleep and wakefulness periods using NMR spectroscopy. Brain activity of the participants was monitored via overnight polysomnography. Multivariate regression modelling was used to correlate these two different data sets. Encouraging results were observed suggesting the possibility of estimation of brain activity during sleep. These results have the potential to uncover the connection of altered brain function and metabolic biochemistry in dysregulated sleep.

Anxiety Symptoms Predict Short Sleep Duration, but Only in Individuals Who are Not "Natural" Short Sleepers

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INTRODUCTION: Sleep duration may be, at least in part, mediated by anxiety. This may not apply, though, for individuals who are "natural" short sleepers.

METHODS: Data from the Sleep and Healthy Activity, Diet, Environment, and Socialization (SHADES) study was used. SHADES is a community-based study of adults in southeastern Pennsylvania (N=1007). Sleep duration was assessed using the NHANES question and was categorized as very short (≤4h), short (5-6h), normal (7-8h, reference), or long (≥9h). Subjects were also asked if they awaken naturally AND are satisfied with the amount of sleep they get (N=267/1007). Anxiety symptoms assessed using the GAD7 included nervousness, lack of control, worry, trouble relaxing, restlessness, irritability, and fearfulness. These items were scaled from 0 ("Not at all") to 3 ("Nearly every day"). Multinomial logistic regressions included sleep duration as dependent variable, anxiety symptoms as independent variable, and age, sex, education, and race/ethnicity as covariates, overall and stratified by "natural" sleep status.

RESULTS: Overall, very short sleep (≤4h) was associated with "nearly every day" reports of nervousness (OR=5.7,p<0.0001), lack of control (OR=6.1,p<0.0001), worry (OR=8.7,p<0.0001), trouble relaxing (OR=13.1,p<0.0001), restlessness (OR=7.3,p<0.0001), irritability (OR=7.9,p<0.0001), and fear (OR=5.2,p<0.0001). Short sleep (5-6h) was also associated with "nearly every day" reports of nervousness (OR=2.8,p<0.0001), lack of control (OR=3.4,p<0.0001), worry (OR=3.0,p<0.0001), trouble relaxing (OR=4.3,p<0.0001), restlessness (OR=2.3,p<0.0001), and irritability (OR=2.1,p<0.0001). When analyses were stratified by "natural" sleep, "natural" short sleepers did not show statistically significant associations compared to "natural" normal sleepers. In contrast, "non-natural" short sleepers (very short and short) exhibited strong associations between sleep duration and anxiety compared to "non-natural" normal sleepers.

CONCLUSIONS: Short sleep duration is associated with increased reporting of anxiety symptoms. However, these associations may only hold true for those who do not awaken "naturally" and report dissatisfaction with their sleep duration.

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Modeling Circadian Rhythmicity of Cardiac Arrhythmias

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Abstract: The cardiomyocyte circadian (~24-hour) clock influences multiple intracellular processes, including transcription and contractile function, and has recently been linked to ventricular arrhythmias in mice (Jerayaj *et al.* (2012) Nature 483:96-100). Circadian rhythms have also been observed in transient outward potassium current (I_{to}) – a current which dominates mice action potential (AP) repolarization. We used mathematical modeling to study the dynamical mechanisms underlying secondary oscillations during the repolarization phase of the AP. These oscillations, called early afterdepolarizations (EADs), have significance because they are associated with heart failure and arrhythmias. It can be shown numerically and analytically that EADs arise from a Hopf bifurcation and that this can occur for certain ranges of the I_{to} conductance (Zhao *et al.* (2012) Cardiovascular Research 95:308-316). We investigated how variation of calcium and I_{Ks} potassium conductances affects the range over which EADs occur. This allows us to predict the role circadian regulation of currents other than I_{to} could play in cardiac activity. Finally, we hope to compare our results on daily rhythms in EADs to existing data on the times of day that humans are most likely to suffer sudden cardiac death.

Degeneration in Arousal Neurons in Chronic Sleep Disruption Modeling Sleep Apnea

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Chronic sleep disruption (CSD) is a cardinal feature of sleep apnea that predicts impaired wakefulness. Despite effective treatment of apneas and sleep disruption, patients with sleep apnea may have persistent somnolence. Lasting wake disturbances in treated sleep apnea raise the possibility that CSD may induce sufficient degeneration in wake-activated neurons (WAN) to cause irreversible wake impairments. Implementing a stereological approach in a murine model of CSD, we found reduced neuronal counts in representative WAN groups, locus coeruleus and orexinergic neurons, reduced by 50% and 25%, respectively. Mice exposed to CSD showed shortened sleep latencies lasting at least 4wk into recovery from CSD. As CSD results in frequent activation of WAN, we hypothesized that CSD promotes mitochondrial metabolic stress in WAN. In support, CSD increased lipofuscin within select WAN. Further, examining the locus coeruleus as a representative WAN nucleus we observed increased mitochondrial protein acetylation and down-regulation of anti-oxidant enzyme and brain-derived neurotrophic factor mRNA. Remarkably CSD markedly increased tumor necrosis factor-alpha within WAN, and not in adjacent neurons or glia. Thus, CSD, as observed in sleep apnea, results in a composite of lasting wake impairments, loss of select neurons, a proinflammatory, pro-oxidative mitochondrial stress response in WAN, consistent with a degenerative process with behavioral consequences.

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