CSCN research retreat

Chronobiology program

Monday, June 23, 2014

8:00 a.m. – 5:00 p.m.

Levy Conference Center
Penn Law School

Collaboration. Innovation. Inspiration.

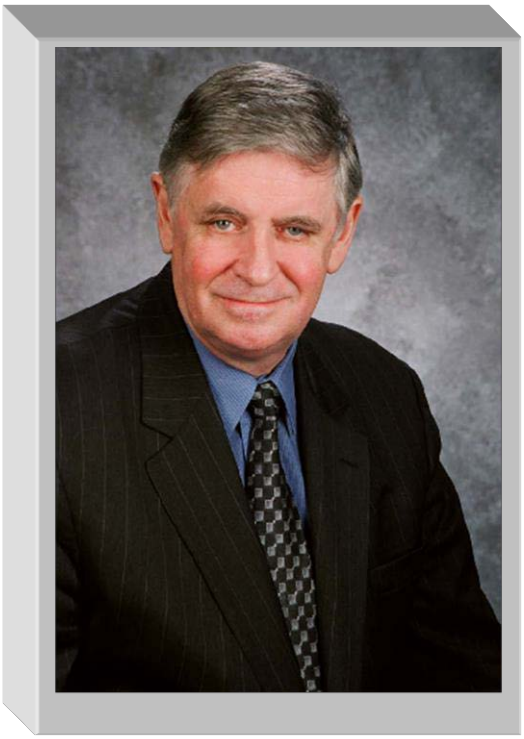
Perelman School of Medicine
University of Pennsylvania

CENTER FOR SLEEP AND CIRCADIAN NEUROBIOLOGY

2014 CSCN & Chronobiology Program Retreat Program
Monday, June 23, 2014
Levy Conference Center, Penn Law School

8:00 AM – 8:45 AM	Poster Mounting - Continental Breakfast will be served
8:45 AM – 9:05AM	Opening Remarks from the Center Director (Allan I. Pack, MBChB PhD)
9:05AM – 9:15AM	Welcome from the Retreat Planning Committee Chair (Michael A. Grandner, PhD)
9:15 AM – 10:30 AM	Session 1: SLEEP, HEALTH, AND ENVIRONMENTAL INFLUENCES Chair: Michael Grandner
	Michael A. Grandner "The Relationship between Sleep Duration and Cardiometabolic Risk Factors Depends on Race/Ethnicity and Whether Risk Factors Were Self-Reported or Objectively-Determined"
	Jesse Schuschu "The Relationship Between Race/Ethnicity and Sleep Duration Depends on Geographic Location"
	Mathias Basner "Inter-individual differences in the effects of aircraft noise on sleep fragmentation"
	Andrea Spaeth "Baseline Slow-Wave Sleep Negatively Relates to Energy Balance Responses during Sleep Restriction in Healthy Adults"
	Matthew Kayser "A Critical Period of Sleep for Development of Courtship Circuitry and Behavior in Drosophila"
10:30 AM – 11:00 AM	Break and Posters
11:00 AM – 12:00 PM	Session 2: ADVANCES IN SLEEP DISORDERS AND INTERVENTION RESEARCH Chair: Victoria Pak
	Sheila Garland " A Randomized Trial of Cognitive Behavior Therapy and Armodafinil to Treat Insomnia and Daytime Sleepiness in Cancer Survivors"
	Carole Marcus "Long-Term Effects of Caffeine Therapy for Apnea of Prematurity on Sleep"
	Renata Pellegrino "A Genome-wide Association Study of Apnea-Hypopnea Index in Children with Obstructive Breathing"
	McKinstry-Wu "Inhibition of the Locus Coeruleus Impedes Emergence from Alkylphenol Hypnosis"
12:00 PM – 1:00 PM	Lunch
1:00 PM – 1:30 PM	Posters
1:30 PM – 2:45 PM	Session 3: CIRCADIAN GENETICS Chairs: Robbert Havekes and Xianzhong Zheng
	Sarah McLoughlin "Diurnal changes in autophagy and the role of the clock"
	Heather Balance "Orchestrated Signal Transduction Unites Mammalian Circadian Metabolism Across Tissues"
	Brian Altman "Rev-erbα Modulates Myc-Driven Cancer Cell Growth and Altered Metabolism" Daniel
	Cavanaugh "Identification of a circadian output circuit for rest:activity rhythms in Drosophila" Shailesh
	Kumar "An ecdysone-responsive nuclear receptor impacts circadian rhythms in Drosophila"
2:45 PM – 3:00 PM	Break (Award Selection Panel meeting at this time)
3:00 PM – 4:00 PM	Adrian R, Morrison Keynote Address (introduction by Amita Sehgal, PhD) Michael Rosbash, PhD, Peter Gruber Endowed Chair in Neuroscience, Howard Hughes Medical Institute Investigator Brandeis University
4:00 PM – 5:00 PM	Awards and Reception

Welcome from Allan I. Pack, MBChB, PhD



We are pleased to present the 2014 Research Retreat by the Center for Sleep and Circadian Neurobiology. This year, we welcome the collaboration of the Chronobiology Program headed up by Amita Sehgal, PhD from the Department of Neuroscience.

Again this year the 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 return to the Levy Conference Center in the Law School for this on-day event. Our thanks once again to this year's Research Retreat Committee, chaired by Michael Grandner and joined by committee members Sam Zheng, Robbert Havekes, Hengyi Rao and Victoria Pak in choosing an interesting program to be presented to you today.

For the second 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 legacy.

Words of Welcome from Amita Sehgal, PhD

We are delighted to host the first retreat of the new Penn Chronobiology Program in collaboration with the CSCN. The Chronobiology Program was created last year with the goal of bringing together researchers working in the very diverse areas impacted by circadian clocks. Our monthly research meetings include laboratories working on metabolism, cardiovascular biology, sleep and other behaviors. We are also recruiting new faculty in these areas, in an effort to further enhance the already strong circadian and sleep communities at Penn. This strength 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.

Dear Friends and Colleagues,

We would like to welcome you to the annual Center for Sleep and Circadian Neurobiology Retreat. This is our 11th year! This year the retreat also collaborates 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 and the School of Veterinary Medicine. We are also honored to welcome our guest speaker, Michael Rosbash, PhD. 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, Planning Committee Chair is currently an Instructor in the Department of Psychiatry and a member of the Behavioral Sleep Medicine Program. Dr. Grandner's research focuses on the adverse cardiometabolic effects of insufficient sleep duration and the social/behavioral determinants of sleep in the community.

Robbert Havekes, PhD is currently a Research Associate in the Department of Biology, under the supervision of Dr. Ted Abel. Dr. Havekes' research investigates the cellular and molecular mechanisms by which sleep loss leads to cognitive impairments with a focus on the mammalian hippocampus

Victoria M. Pak, MS, PhD is a Research Associate in Sleep Medicine, under the mentorship of Drs. Allan Pack and Barbara Riegel. Dr. Pak's research investigates the molecular mechanisms of sleepiness symptoms in sleep apnea and cardiovascular disease.

Hengyi Rao, PhD is a Research Assistant Professor of Neurology. Dr. Rao's primary research interests involve the use of multimodal functional brain imaging to study brain function before and after sleep deprivation, as well as neural mechanisms underlying inter-individual differences in cognition and behavior.

Xiangzhong (Sam) Zheng, PhD is a Research Assistant Professor in the Department of Neuroscience. Dr. Zheng's research focuses on the molecular and neurobiological basis underlying circadian behaviors, particularly sleep:wake cycle.

Today, we welcome keynote speaker **Michael Rosbash, PhD**

Dr. Rosbash is the Peter Gruber Endowed Chair in Neuroscience, Professor of Biology at Brandeis University. A Howard Hughes Medical Institute Investigator and recipient of the Gruber Prize in Neuroscience, Dr. Rosbash brings us his interest in RNA processing and the genes and mechanisms that underlie circadian rhythms. A member of the US National Academy of Sciences; his focus is on Molecular Genetics of RNA Processing and Behavior. His research group cloned the Drosophila period gene in 1984 and proposed the Transcription Translation Negative Feedback Loop for circadian clocks in 1990. In 1998, they discovered the cycle gene, clock gene, and cryptochrome photoreceptor in Drosophila through the use of forward genetics, by first identifying the phenotype of a mutant and then determining the genetics behind the mutation. Dr. Rosbash was elected to the National Academy of Sciences in 2003.

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Section II. Abstracts for Poster Session (posters for viewing)

Section I. Abstracts for Presentations (no posters)

Rev-erbα Modulateas Myc-Driven Cancer Cell Growth and Altered Metabolism

Brian J. Altman[1]; Annie Hsieh[1]; Arvin M. Gouw[1]; Zachary E. Stine[1], Anand Venkataraman[2]; David I. Bellovin[4]; Sharon J. Diskin[5], Wenyun Lu[7], Sisi Zhang[7], Dean W. Felsher[4]; John M. Maris[5], Mitchell A. Lazar[6], Joshua D. Rabinowitz[7], John B. Hogenesch[2]; and Chi V. Dang[1,3]

[1]Abramson Family Cancer Research Institute, [2]Department of Pharmacology, Institute for Translational Medicine and Therapeutics, [3]Division of Hematology-Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania; [4]Division of Medical Oncology, Departments of Medicine and Pathology, Stanford School of Medicine; [5]Center for Childhood Cancer Research, Children's Hospital of Philadelphia; [6]The Institute for Diabetes, Obesity, and Metabolism, Perelman School of Medicine, University of Pennsylvania; [7]Lewis-Sigler Institute for Integrative Genomics, Department of Chemistry, Princeton University

Circadian rhythms are regulated by feedback loops comprising a network of factors that regulate Clock-associated genes. Chronotherapy seeks to take advantage of altered circadian rhythms in some cancers to better time administration of treatments to increase efficacy and reduce toxicity. While many cancers have perturbed expression of core circadian rhythm genes, the molecular basis underlying these perturbations and their functional implications in oncogenesis are still poorly understood, and so it is impossible to predict which cancers have altered circadian rhythms and would best benefit from chronotherapy. We have observed in cancer cell models of osteosarcoma, hepatocellular carcinoma, and neuroblastoma that the c-Myc and N-Myc oncogenic transcription factors disrupt oscillation of the circadian clock by specifically upregulating the circadian rhythm gene and nuclear hormone receptor *NR1D1* (Rev-erbα). Interestingly, while Rev-erbα has not been previously recognized as an oncogene, data from The Cancer Genome Atlas revealed that it is amplified in many forms of human cancer, and we also observed that Rev-erbα was upregulated in primary human neuroblastoma and associated with poor prognosis. Therefore, we hypothesized that Rev-erbα is a novel oncogene downstream of Myc and is important for cancer cell growth.

Here we show that Rev-erbα is specifically essential for the growth of Myc-driven hepatocellular carcinoma cells, as the related protein Rev-erbβ did not strongly influence growth. While knockdown of Rev-erbα expression by siRNA slowed growth, it did not cause cell death or canonical cell cycle arrest. Rev-erbα modulates circadian rhythm by downregulating the central circadian regulatory protein Bmal1, but this pathway did not play a central role in Rev-erbα control of cell growth. Additionally, while Rev-erbα has a well-described role in heme metabolism and subsequent support of mitochondria respiration, this pathway was not directly altered in Myc-driven liver cancer cells. Rather, knockdown of Rev-erbα was associated with decreased glycolytic activity characterized by a decrease in intracellular lactate and extracellular lactate production as well as an increase in certain glycolytic intermediates. In addition to these glycolytic changes, the maximum respiratory capacity of cells lacking Rev-erbα increased, as measured by oxygen consumption. These data suggest a novel role for Rev-erbα in promoting the growth of cancer cells through modulation of glucose metabolism and a shift towards increased respiration, and imply that cancers with upregulated Myc and Rev-erbα may be good candidates for chronotherapy.

We thank the following funding sources: NIH R01CA57341, LLS 6106-14.

Trainee Award Eligible

Orchestrated Signal Transduction Unites Mammalian Circadian Metabolism Across Tissues

Ballance H., Zhang R., Lahens N., Hughes M.E., and Hogenesch J.B.

University of Pennsylvania

The circadian clock is known to play a critical role in maintaining metabolic homeostasis throughout the body, with clock dysfunction contributing to metabolic syndrome, obesity, and diabetes. How the clock regulates coordinated metabolic homeostasis across multiple organs is an important unanswered question in chronobiology. To address this issue our research team has created an atlas of circadian RNA expression in 12 mouse organs at a resolution of 2 hours every 48 hours using Affymetrix 1.0 ST Arrays. RNA transcript expression is profiled in the brain: hypothalamus, brainstem, and cerebellum, and peripheral metabolic tissues: adrenal gland, aorta, brown adipose, heart, kidney, liver, lung, skeletal muscle, and white adipose tissue. Our data show that over 7,000 genes have circadian expression in at least one organ. We furthermore find that transcripts cycling in multiple organs are highly enriched for all stages of signal transduction, proceeding from ligand and receptor expression and extending through down-stream second messenger signaling to gene regulation. For example, we find circadian expression of ligands POMC and adiponectin, as well as transcripts for their respective receptors MC4R and AdiopoR2, which cycle in multiple organs. We also found rhythmic genes mediating down-stream signaling are also represented in the data, including MAPK, AKT, and MTOR as well as gene transcription pathways. This panoply of regulatory mechanisms now shown to be regulated by the clock at a systems level offers clues as to how the clock orchestrates diverse metabolic functions in multiple organs, including cholesterol, lipid, protein and carbohydrate metabolism, which we also found to be enriched across tissues. The richness of our high through-put data in many tissues allows us to uncover for the first time the intricate organization of clock coordination of activities in the brain and peripheral tissues.

Trainee Award Eligible

Inter-individual differences in the effects of aircraft noise on sleep fragmentation

Mathias Basner[1], Sarah McGuire[1], Uwe Müller[2], and Eva-Maria Elmenhorst[2]

[1]Division of Sleep and Chronobiology, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania , Philadelphia, PA, USA

[2]Division of Flight Physiology, Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany

Environmental noise exposure has been shown to disturb sleep and impair recuperation, and may contribute to the increased risk for (cardiovascular) disease. Noise policy and regulation are usually based on average responses, although substantial inter-individual differences in the effects of traffic noise on sleep have been demonstrated even in relatively homogeneous and healthy populations. In this analysis, we investigated what percentage of the total variance in noise-induced awakening reactions can be explained by stable inter-individual differences. It is based on 72 healthy subjects (age range 18-71 years, 32 male) who participated in a polysomnographic laboratory study on the effects of traffic noise on sleep and were investigated for 11 consecutive nights. This analysis concentrates on 4 exposure nights where subjects were exposed to 80 noise events form air, road, and/or rail traffic noise with maximum sound pressure levels varying between 45 and 65 dB(A). Mixed-effects models of variance controlling for age, gender, study phase, study night, noise exposure in the previous night, and awakening probability in noise-free nights showed that 53.7% of the total variance was explained by inter-individual differences. The results thus demonstrate that a considerable amount of the variance observed in noise-induced sleep disturbance can be explained by inter-individual differences that cannot be explained by age, gender, or specific study design aspects. It will be important to identify those at higher risk for noise induced sleep disturbance. Furthermore, the custom to base noise policy and legislation on average responses should be re-assessed based on these findings.

Identification of a circadian output circuit for rest:activity rhythms in Drosophila

Daniel J. Cavanaugh[1], Jill D. Geratowski[1], Julian R. A. Wooltorton[1], Jennifer M. Singh[3], Clare E. Hector[5], Xiangzhong Zheng[1], Erik C. Johnson[5], James H. Eberwine[3,4] and Amita Sehgal[1,2]

[1]Departments of Neuroscience

[2]Howard Hughes Medical Institute

[3]Department of Pharmacology

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University of Pennsylvania, Philadelphia PA 19104, USA

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The circadian system is composed of clock neurons, which contain molecular clocks, input pathways, which synchronize these clocks to external signals such as light, and output pathways, which couple clock cells to overt behaviors. Though much is known about the core clock neurons and the underlying molecular clock, little is known about the downstream neuronal populations that comprise the output pathway. Through a screen for circadian-relevant neurons in the Drosophila brain, we identify here specific subsets of cells of the pars intercerebralis (PI), a functional homologue of the mammalian hypothalamus, as necessary components of the circadian output pathway for rest:activity rhythms. Temporally and spatially restricted activation of PI neurons induces behavioral arrythmicity without affecting the molecular clock, and genetic deletion of PI neurons also renders flies arrhythmic. Notably, the circadian relevant PI neurons are distinct from those expressing the insulin-like peptide, dilp2, which are known to be involved in sleep and metabolic functions in the fly, suggesting that molecularly-distinct subsets of PI neurons couple to different physiological outputs. We further use GFP Reconstitution Across Synaptic Partners (GRASP) to trace a circuit that extends from the master pacemaker clock cells, through dorsal clock neurons, and finally to cells of the PI, thus identifying an anatomical substrate through which the PI could receive circadian signals. Finally, we use single cell RNA sequencing of PI neurons to identify the corticotropin releasing factor (CRF) homologue, DH44, as a potential signaling molecule through which the PI may communicate with downstream locomotor control areas, and demonstrate that RNAi-mediated knockdown of DH44 degrades rest:activity rhythms. Together these studies establish the PI as an integral component of the Drosophila circadian output pathway for rest:activity rhythms, delineate an anatomical circuit that underlies the circadian control of these PI neurons, and pinpoint a specific output molecule that is expressed by PI neurons and is necessary for the full display of locomotor rhythms.

Trainee Award Eligible

A RANDOMIZED TRIAL OF COGNITIVE BEHAVIOR THERAPY AND ARMODAFINIL TO TREAT INSOMNIA AND DAYTIME SLEEPINESS IN CANCER SURVIVORS

Sheila N. Garland, Holly Barilla, James Findley, Philip Gehrman, Michael Perlis

University of Pennsylvania

INTRODUCTION: Insomnia and fatigue are the most frequently reported side effects associated with cancer. Although cognitive behavioral therapy for insomnia (CBT-I) is effective in addressing difficulty initiating and maintaining sleep, it frequently results in (short-term) sleepiness and fatigue. This may make it difficult for cancer patients to adhere to treatment. This study examines whether a combination of CBT-I and a wake-promoting medication (armodafinil) results in greater overall improvement in insomnia and fatigue symptoms among cancer survivors.

METHODS: Eighty-eight patients were randomized to one of four treatment conditions: 1) CBT-I + placebo (CBT+P), 2) CBT-I + armodafinil (CBT+M), 3) Placebo only (P) and 4) armodafinil only (M). CBT-I was delivered in 7 weekly one-hour individual therapy sessions (3 in person, 4 via telephone). Pre-post findings on sleep diary-measured sleep latency (SL), wake after sleep onset (WASO), total sleep time (TST), and daytime sleepiness measured by the Epworth Sleepiness Scale (ESS), are reported.

RESULTS: The mean age of the group was 56yrs, 88% were female and the majority of patients (68%) had breast cancer. All analyses were adjusted for baseline severity. Compared to the placebo group, patients in the CBT+P and CBT+M groups reported a significant reduction in SL with effect sizes of 0.67 and 0.58, respectively. There was a significant reduction in WASO in the CBT+M group only (p=.02). TST increased in the M group, but not in the CBT+P or CBT+M groups. There were no statistically significant reductions in daytime sleepiness (ESS) observed for any of the groups.

CONCLUSION: CBT-I alone and in combination with armodafinil was able to produce statistically and clinically significant improvement in self-reported sleep. The addition of armodafinil did not appear to enhance the effect of CBT-I via a reduction in daytime sleepiness. Analyses are ongoing to examine the impact of armodafinil on CBT-I compliance.

Trainee Award Eligible

The Relationship between Sleep Duration and Cardiometabolic Risk Factors Depends on Race/Ethnicity and Whether Risk Factors Were Self-Reported or Objectively-Determined

Michael A. Grandner PhD[1,2], Subhajit Chakravorty MD[1,2,3], Michael L. Perlis[1,2] PhD, Linden Oliver MS[1], and Indira Gurubhagavatula MD MPH[2,3,4]

[1]Behavioral Sleep Medicine Program of the Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA; [3]Philadelphia Veterans Affairs Medical Center, Philadelphia, PA; [4]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Phila delphia, PA

INTRODUCTION: Sleep duration is associated with cardiometabolic disease risk factors including hypertension, hyperlipidemia, diabetes and obesity. Not only are short and long sleep duration disproportionately experienced among race/ethnicity groups, but these cardiometabolic risks are as well. It is possible that the relationship between cardiometabolic disease and sleep depends on race/ethnicity. Also, this may depend on whether cardiometabolic risk is self-reported vs objectively-determined.

METHODS: We analyzed adult 2007-2008 National Health and Nutrition Examination Survey (NHANES) data (N=5,649). Average self-reported nightly sleep duration was reported and categorized as either ≤4h, 5-6h, 7-8h, or ≥9h. Self-reported as well as objectively-determined obesity, diabetes, hypertension, and hyperlipidemia were recorded. Binary logistic regression analyses, stratified by race/ethnicity, were performed using cardiometabolic factor as the outcome variable, and sleep duration category as the predictor variable, after adjusting for age, sex, acculturation, education, access to insurance, food security, home ownership, smoking, and caffeine use.

RESULTS: Significant sleep*race/ethnicity interactions existed for all cardiometabolic outcomes using both measurement approaches (all $p<0.005$). Among non-Hispanic Whites, ≤4h was associated with self-reported hypertension(OR=1.91;95%CI[1.18,3.09];p=0.009), hyperlipidemia(OR=2.10;95%CI[1.33,3.32];p=0.002), and diabetes(OR=2.40;95%CI[1.27,4.52];p=0.007), and objectively-determined hyperlipidemia(OR=1.62;95%CI[1.03,2.54];p=0.035), and ≥9h was associated with objectively-determined hyperlipidemia(OR=1.55;95%CI[1.07,2.25];p=0.020). Among Blacks/African-Americans, ≤4h was associated with self-reported hypertension(OR=2.12;95%CI[1.25,3.61];p=0.005) and obesity(OR=1.91;95%CI[1.20,3.05];p=0.007). Among Mexican-Americans, 5-6h was associated with self-reported hypertension(OR=1.93;95%CI[1.25,2.96];p=0.003) and obesity(OR=1.45;95%CI[1.04,2.04];p=0.030) and ≥9h was associated with less self-reported hyperlipidemia(OR=0.41;95%CI[0.20,0.85];p=0.016). Among other Hispanics/Latinos, ≤4h was associated with self-reported(OR=3.53;95%CI[1.50,8.29];p=0.004) and objectively-determined(OR=2.86;95%CI[1.21,6.73];p=0.016) hypertension and 5-6h was associated with less objectively-determined diabetes(OR=0.45;95%CI[0.23,0.89];p=0.022). Among Asians/Others, ≤4h was associated with self-reported(OR=11.50;95%CI[2.30,59.10];p=0.003) and objectively-determined(OR=3.74;95%CI[1.16,12.03];p=0.027) hyperlipidemia.

CONCLUSIONS: The relationship between sleep duration and cardiometabolic risk factors depended on race ethnicity for each risk factor assessed, though the patterns differed. Also, whether hypertension, hyperlipidemia, diabetes and obesity were assessed via self-report or by objective measures dictated results in some cases. Future studies should carefully consider these factors in determining individual and population-level risk.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

A Critical Period of Sleep for Development of Courtship Circuitry and Behavior in Drosophila

Matthew S. Kayser, Zhifeng Yue, and Amita Sehgal

University of Pennsylvania

Most animals sleep more early in life than in adulthood, but the function of early sleep is not known. Using Drosophila, we find that increased sleep in young flies is associated with elevated arousal threshold and resistance to sleep deprivation. The cellular basis of excess sleep in young flies resides in a specific circuit wherein reduced dopamine signaling to the dorsal fan shaped body (dFSB) permits higher activity of this sleep-promoting region. Experimental hyperactivation of this circuit only during a critical developmental window results in sleep loss and lasting deficits in adult courtship behaviors. These deficits are accompanied by impaired development of a single olfactory glomerulus, VA1v, which is unique in displaying extensive sleep-dependent growth in young flies. Ongoing work examines if growth of VA1v reflects addition of new synapses, and whether sleep loss during this time impairs synaptogenesis. Our results demonstrate that sleep is required for normal brain development and an adult behavior critical for species propagation, and suggest that rapidly growing regions of brain are most susceptible to sleep perturbations early in life.

Trainee Award Eligible

An ecdysone-responsive nuclear receptor impacts circadian rhythms in Drosophila

Shailesh Kumar[1], Dechun Chen[1], Christopher Jang[1], Alexandra Nall[1], Xiangzhong Zheng[1] and Amita Sehgal[1,2]

[1]Department of Neuroscience, [2]Howard Hughes Medical Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

Summary

Both circadian clocks and steroid hormone signaling are important for normal physiology, but little is known about molecular links between these processes. Through a gain-of-function screen for novel circadian rhythm genes, we identified a circadian function for a nuclear receptor, Ecdysone Induced Protein 75 (Eip75 or E75) that is induced by steroid signaling. We found that overexpression or knockdown of the E75 gene in clock neurons disrupts rest:activity rhythms and dampens oscillations of the PERIOD (PER) protein. Effects of E75 on the circadian clock are mediated in part through its direct repression of the gene encoding the transcriptional activator, CLOCK (CLK). Furthermore, we found that PER inhibits the activity of E75 on the Clk promoter, thereby providing a mechanism for a previously proposed de-repressor effect of PER on Clk transcription. The ecdysone receptor, upstream of E75 signaling, is also expressed in central clock cells and manipulations of its expression levels are similar to the effects of E75 on circadian rhythms. We find that E75 allows maintenance of rhythms under stressful conditions (nutritional and temperature), suggesting an important function for steroid signaling in the maintenance of circadian rhythms.

Trainee Award Eligible

Long-Term Effects Of Caffeine Therapy For Apnea Of Prematurity On Sleep

Carole L. Marcus, M.B.B.Ch.; Lisa J. Meltzer, Ph.D.; Robin S. Roberts, M.Sc.; Elizabeth Asztalos M.D.; Gillian Opie, M.D.; Lex W. Doyle, M.D.; Sarah N. Biggs, Ph.D.; Gillian M. Nixon, M.D.; Indra Narang, M.D.; Barbara Schmidt, M.D., for the CAP-S study group

Introduction

Apnea of prematurity is a common condition that is usually treated with caffeine. Caffeine is an adenosine receptor blocker that has powerful influences on the central nervous system. However, little is known about the long-term effects of caffeine on sleep in the developing brain. In particular, it is not known whether neonatal caffeine administration has permanent adverse effects on sleep architecture and ventilatory control, resulting in an increased prevalence of sleep disorders such as insomnia and obstructive sleep apnea. We hypothesized that neonatal caffeine use resulted in long-term abnormalities in sleep architecture and breathing during sleep.

Methods

201 ex-premature (500-1,250 gm) children aged 5-12 years who participated as neonates in a double-blind, randomized clinical trial (Caffeine for Apnea of Prematurity [CAP]) of caffeine versus placebo underwent sleep questionnaires, actigraphy and full ambulatory polysomnography.

Results

There were no significant differences in sleep quality or quantity based on actigraphy and questionnaires between the caffeine group vs placebo. Total recording time and total sleep time on polysomnography were longer in the caffeine group, but there was no difference in sleep efficiency between groups. Obstructive sleep apnea (apnea hypopnea index >2/hr) was common (8.2% of caffeine group vs 11.0% of placebo) compared to normative literature. Further, 24% of the caffeine and 29% of the placebo group had either obstructive sleep apnea on polysomnography and/or a history of adenoidectomy/tonsillectomy. However, neither the apnea hypopnea index nor the proportion of children with obstructive sleep apnea differed between groups. The proportion of subjects with elevated periodic limb movements was high (17.5% in caffeine vs 11% in placebo) but did not differ significantly between groups.

Conclusions

Therapeutic neonatal caffeine administration has no long-term effects on sleep pathology during childhood. However, preterm infants are at risk for obstructive sleep apnea and periodic limb movements in later childhood.

Support: NIH R01HL098045 and Philips Respironics

Inhibition of the Locus Coeruleus Impedes Emergence from Alkylphenol Hypnosis (note: 2 page abstract)

McKinstry-Wu A, Chalifoux M, Moore JT, Woll K, Eckenhoff RG, Kelz MB

Department of Anesthesiology and Critical Care, University of Pennsylvania

Introduction: Despite extensive use over the past thirty years both to induce and maintain states of anesthesia, the neuronal mechanisms by which the prototype alkylphenol anesthetic, propofol, works to produce hypnosis remain unknown. The locus coeruleus (LC) is a wake-active adrenergic center with widespread ascending projections to cortex and thalamus. The LC is known to modulate the hypnotic effects of alpha-2 agonists, GABAergic, and volatile agents, and LC neurons are inhibited by clinically-relevant concentrations of propofol. We here investigate the contribution of the LC to alkylphenol hypnosis using the photoadductible propofol analog, azi-propofol-m (aziPm), which in the presence of UVA light, is converted to a reactive carbene which covalently binds nearby targets.

Methods: LC neurons were identified using morphologic characteristics in intact brain slices continuously bathed in aCSF, taken from adult B6/C57 mice. After patching on and establishing baseline characteristics of a cell, the slice was bathed in 10 µM aziPm for 3 minutes followed by a washout. After returning to a baseline firing rate, cells were reexposed to 10 µM aziPm for 3 minutes with UVA illumination for the final minute. 12-20 week B6/C57 male mice were implanted with 5-lead EEG and EMG, and chronically indwelling bilateral cannulae stereotactically targeted to the LC. After 2 weeks recovery, systemic aziPm was administered intravenously (IV) by bolus (100 mg/kg) and infusion (10 mg/kg/min over 10 minutes) with or without fiberoptically-delivered 375 nm laser light (UVA) at 5 mW/mm2 via the cannulae. After a 1-week recovery the animals were group switched and re-exposed. After another week recovery, mice were given an IV bolus and infusion of propofol (25 mg/kg followed by 2.5 g/kg/min for 10 minutes) with and without laser exposure and then group switched after another week recovery. For all experiments EEG was continuously recorded and time to return of righting reflex noted. Temperature was maintained within 1.0 degrees of baseline using a heating pad and lamp, monitored via chronic subcutaneous implant. Cannula placement was confirmed histologically post-mortem.

Results: AziPm exposure to LC neurons in slice caused a significant decrease in firing rate (38±10 % of baseline) with subsequent recovery within 5 minutes of washout (Figs 1A, B.) When neurons were reexposed to aziPm in the presence of UVA, they exhibited long-term inhibition without recovery over 35 minutes of recording. Following within-subjects randomization, our preliminary data demonstrates that mice with cannulae that accurately targeted the LC exhibited a significant doubling in the duration of hypnosis upon photoadduction (aziPm + UVA: 902 ± 17 seconds) as compared to the duration of hypnosis in the same animals exposed to the anesthetic without photoadduction (aziPm – UVA: 457 ± 17 seconds), as well as a significant increase in hypnotic duration over placement control mice with photoadduction (aziPm + UVA: 389 ± 36, Fig 1C.) In those same nearby placement control mice with cannulae that missed the LC, there was no effect of UVA photoillumination on the duration of hypnosis. Control studies using propofol±UVA targeting the LC, reveal no effect of the laser itself (Fig 1D).

Discussion: Increased time to return of righting following alkylphenol photoadduction in the LC suggests that the LC reactivation is one mechanism necessary for prompt emergence. These studies are also consistent with inhibition of LC permitting entry into a state of anesthesia.

References:

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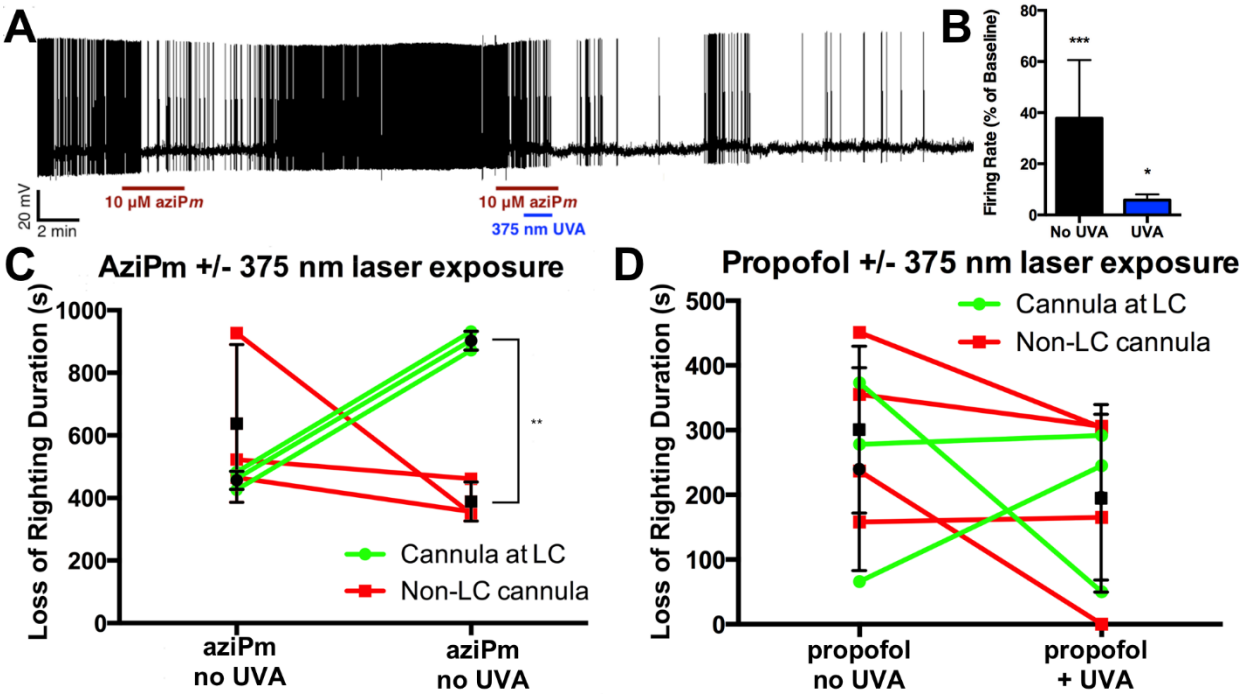

5.

Figure 1. Prolonged inhibition of the LC by UVA light + alkylphenols delays emergence. A Spontaneously active LC neuron is slowed by a 3 min bath application of 10µM aziPm. In the absence of UVA light, aziPm effects washout within 5 min. Re-exposure to 10µM aziPm plus UVA light causes a long-lasting inhibition of LC activity that does not recover over 35 min washout. B Summary of firing changes at LC with aziPm +/- UVA. C&D: In vivo OptoAnesthesia C Two-way ANOVA showed a significant interaction ($p<0.05$) between cannula location and UVA exposure in mice exposed to aziPm, and Sidak's multiple comparisons test demonstrated a significant difference ($p < 0.01$) in LoRR duration between cannula targeted to LC versus nearby placement controls. D There was no significant effect of placement nor UVA exposure in mice receiving propofol infusions.

Diurnal changes in autophagy and the role of the clock

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Autophagy is a cellular process whereby the cell digests its own components as a means of removing defective organelles, providing a source of amino acids or lipids in times of need, controlling inflammation and defending against invading pathogens. Reduced autophagy is implicated in a variety of conditions ranging from neurodegenerative diseases to cancer. In vivo, autophagy is increased during the sleep phase and reduced during the active phase, while the transcription of autophagy genes is rhythmic in many tissues. The control of this diurnal variability is not fully understood and the relevance of a day/night pattern in autophagy to human health and disease is unknown. Here, we investigate circadian expression of autophagy genes with the aim of further understanding the role of the circadian clock in autophagy. We show autophagy-related genes that cycle in vivo, including ulk1, atp6v1d, gabarpl1, cebp/b, atg7, p62 and atg2a, do not exhibit such cycling in entrained cells in culture with robust clocks including U2OS cells, bone-marrow derived macrophages and peritoneal macrophages. However, we also show that autophagy is altered in macrophages lacking Bmal1 and that the promoters of several autophagy genes contain E-boxes, indicating that the clock machinery may play a role in autophagy. We propose that a robust circadian clock is not sufficient to drive circadian rhythms in autophagy gene transcription in cultured cells and that Bmal1 contributes to autophagy function.

Trainee Award Eligible

A Genome-wide Association Study of Apnea-Hypopnea Index in Children with Obstructive Breathing

Renata Pellegrino*, PhD; Enda Byrne*, PhD, Lee Brooks, MD, Allan Pack, MD, PhD; Hakon Hakonarson, MD, PhD

***First authors**

Obstructive sleep apnea syndrome (OSAS) is a complex sleep disorder that imposes a large burden on our society in terms of morbidity, quality of life, and healthcare costs. Childhood OSAS is characterized by habitual snoring, disturbed sleep and problems with daytime neurobehavioral functioning. OSAS appears to result from diverse gene-gene interactions and association with environment changes. There have been no published GWAS in children for OSAS. The identification of genetic variants associated with increased risk for OSAS could potentially translate into earlier recognition and treatment with reduced morbidity, and may also serve to identify potential targets for novel therapies. Here we present a genome-wide association study of the Apnea-Hypopnea Index measured in a cohort of children referred to the sleep clinic at the Children's Hospital of Philadelphia for suspected obstructive breathing. Our aim was to identify common genetic variants that increase OSAS severity in children with sleep difficulties. A total of 2,473 children participated in the sleep study. The primary reason for referral was for suspected OSA and they had a Polysomnography (PSG) exam performed. 1,782 children in the sample were given a potential diagnosis of OSA prior to the sleep study. Also, a total of 1201 children were listed as having at least one mental disorder. All participants were genotyped using either the Illumina HumanHap550 or 610 Quad arrays. The association between the natural log of the Apnea-Hypopnea Index (AHI) and SNP was assessed using a linear model in PLINK. Principal components for each individual were calculated using GCTA, and the first 5 PCs were fitted as covariates in the analysis along with age, gender, BMI and total sleep recording time. No SNPs in the study passed the threshold for genome-wide significance ($p < 5 \times 10\text{-}8$), either within the ethnic groups separately, or in the meta-analysis of both groups. However, many of the marginally significant SNPs are located in or near genes that have shown evidence of association with related traits such as waist circumference and C-reactive protein, suggesting they may become useful biomarkers as we grow our sample size.

Trainee Award Eligible

The Relationship Between Race/Ethnicity and Sleep Duration Depends on Geographic Location

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

INTRODUCTION: Sleep duration is associated with health, and this may disproportionately affect minority groups. It is plausible that changing social-environmental factors (e.g., geographic region) would alter these relationships.

METHODS: Data from respondents age ≥18 from the 2012 Behavioral Risk Factor Surveillance System were used from Alaska(n=4,092), Kansas(n=5,646), Nevada(n=4,429), and Oregon(n=4,810). Self-reported sleep duration was assessed as total sleep within a typical 24-hour period. Responses were categorized as very short(≤4h), short(5-6h), normal(7-8h), and long(≥9h). Race/Ethnicity was categorized as White, Black/African-American, Hispanic/Latino, Asian-American, Native-American/Alaskan-Native, or Other. Population-weighted multinomial regression analyses examined the relationships between race/ethnicity and sleep duration category, relative to 7-8h. Analyses were adjusted for age, sex, education, income, body mass index, and smoking.

RESULTS: Across-state results were consistent with previous epidemiological studies, with very short sleep more likely among Black/African-American(OR=2.56,95%CI[1.34,4.89],p=0.005) and Other(2.16[1.35,3.43],p=0.001) adults, short sleep more likely among Black/African-American(1.89[1.36,2.62],p=0.0001) and Other(1.63[1.29,2.0],p=<0.0001) adults, and long sleep less likely among Asian-American(0.54[0.29,0.99],p=0.048) and more likely among Other(1.42[1.10,2.10],p=0.012) adults, versus White. A significant race*state interaction was found(p<0.0001). Analyses were then stratified by state. In Alaska, short sleep was more likely among Blacks/African-Americans(2.67[1.09,6.55],p=0.033) and long sleep was more likely among Asian-Americans(2.95[1.28,6.80],p=0.011) versus Whites. In Kansas, very short sleep was more likely among Others(3.55[1.21,10.39],p=0.021), short sleep was more common among Native-Americans/Alaskan-Natives(3.52[1.47,8.45],p=0.005) and Others(2.56[1.30,4.76],p=0.006), and long sleep was more likely among Others(3.61[1.48,8.80],p=0.005). In Nevada, Hispanics/Latinos were less likely to be very short sleepers(0.41[0.19,0.87],p=0.020), short sleep was more likely among Blacks/African-Americans(1.89[1.18,3.03],p=0.008) and Others(2.21[1.35,3.62,p=0.002), and long sleep was less likely among Hispanics/Latinos(0.60[0.37,0.97],p=0.036) and Asian-Americans(0.24[0.07,0.86],p=0.029). In Oregon, very short sleep was more likely among Blacks/African-Americans(9.00[2.26,35.85],p=0.002), Asian-Americans(5.87[1.07,32.14],p=0.041), and Others(2.82[1.31,6.09],p=0.008), short sleep was less likely among Hispanics/Latinos(0.51[0.30,0.85],p=0.010) and more likely among Others(1.51[1.05,2.18],p=0.026), and long sleep was more likely among Others(1.74[1.07,2.83],p=0.026).

CONCLUSIONS: Results demonstrated profound differences in the relationship between sleep duration and race/ethnicity, depending on state. This may be due to regional differences in social-environmental factors.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

Trainee Award Eligible

Baseline Slow-Wave Sleep Negatively Relates to Energy Balance Responses during Sleep Restriction in Healthy Adults

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Introduction: Sleep restriction (SR) leads to increased daily caloric intake, late-night eating and weight gain. However, not all subjects respond to SR to the same degree (some gain a significant amount of weight while others maintain or lose weight). The amount of time spent in sleep stages 3 or 4 (slow-wave sleep [SWS]) is stable and trait-like within individuals but highly variable between individuals. The current study examined if individual differences in baseline SWS associated with energy balance responses to SR.

Methods: N=36 healthy subjects (31.1±8.3y, 25.8±2.7 BMI, 20 females) participated in a laboratory protocol including 2 baseline nights (BL1-2; 10-12h time in bed [TIB]/night) followed by 5 consecutive SR nights (4h TIB/night). Polysomnography was recorded on BL2 and scored using standard criteria. Duration of each sleep stage was calculated as a percent of total sleep time (%TST). Weight was measured at admittance and discharge. Food/drink consumption was ad libitum and recorded daily. Partial correlations controlling for age, gender, race and BMI were used for analyses.

Results: Subjects consumed 20.8% more calories during SR than during BL, ate/drank 507.3±274.9 calories during late-night hours (2200h-0400h) and gained 0.61±1.88 kg during the study. Baseline SWS ranged from 1.6-28.8% of TST and was negatively correlated with increased caloric intake during SR (r=-0.45, p=0.011), late-night intake (r=-0.41, p=0.03) and weight gain (r=-0.48, p=0.006). No other sleep variables were significantly related to all three energy balance variables; however, stage 1 %TST was positively associated with increased caloric intake during SR (r=0.41, p=0.02), sleep efficiency was negatively related to late-night intake (r=-0.39,p=0.03) whereas sleep latency was positively related to late-night intake (r=0.38, p=0.04), and stage 2 %TST was positively associated with weight gain (r=0.39, p=0.03).

Conclusion: Adults with less slow-wave sleep may be more vulnerable to increased daily caloric intake, late-night eating and weight gain during sleep restriction.

Support: NIH R01 NR004281, F31 AG044102; CTRC UL1RR024134; ONR N00014-11-1-0361

Keywords: Caloric Intake, Slow-Wave Sleep, Individual Differences

Trainee Award Eligible

Section II. Abstracts for Poster Session

PAGE NUMBERS ARE POSTER LOCATION INDICATORS

Mammalian Circadian Rhythm Requires Glutamine Metabolism

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Circadian rhythms are twenty-four hour physiologic cycles present in all eukaryotes that control a variety of organismal processes, including metabolism. Peripheral clocks such as those present in the liver control metabolic pathways such as glucose metabolism and respiration as well as amino acid metabolism. It has been recently demonstrated that the availability of the metabolite NAD (nicotinamide adenine dinucleotide) can feed back to control circadian rhythm. There is much interest in targeting glutamine metabolism in cancer, but it is still unknown how inhibition of glutamine metabolism affects normal circadian rhythm. Here we show using U2OS osteosarcoma cells that glutamine withdrawal block proper circadian oscillation. Glutamine withdrawal led to distinct and dramatic changes in circadian gene expression which could be rescued by addition of the cell permeable TCA-intermediate α-ketoglutarate. Despite this, cells withdrawn from glutamine did not show signs metabolic stress or impairment of the mTOR pathway. While alterations to histone modifications possibly stemming from impairment of αKG-dependent enzymes were observed, these did not explain the observed alterations in circadian rhythm. Rather, glutamine withdrawal led to the strong downregulation of several genes involved in reactive oxygen species (ROS) defense and neutralization, and addition of cell permeable antioxidants rescued the disruption of circadian oscillation in the absence of glutamine. Together, these data suggest that glutamine availability and metabolism are critical to support circadian rhythm and gene expression through modulation of intracellular ROS.

Trainee Award Eligible

Changes in Upper Airway Anatomic Structures and Adiposity in Apneics After Bariatric

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Introduction: OSA is a common disease with a pathophysiology dependent on obesity and enlarged soft tissue structures surrounding the upper airway. Currently, there is limited knowledge about the effects that volumetric changes in upper airway soft tissue structures and adipose domains (neck and submental fat) have on OSA severity. We hypothesized that: 1) weight loss through bariatric surgery would decrease the volume of upper airway anatomic structures, neck fat, and submental fat; and 2) reductions in the size of these soft tissue structures and fat deposits would decrease the severity of OSA.

Methods: Subjects (11 (female=10, male=1); mean age = 50.9 ± 6.3 years; mean BMI 45.0 ± 5.2 kg/m2; mean AHI = 24.5 ± 14. 2 events/hour) underwent MR imaging of the upper airway on a Siemens Sonata 1.5T system. Subjects returned 6 months after their bariatric surgery to complete a follow-up weigh-in, PSG, and MRI. AMIRA 4.1.2 software was used to analyze upper airway soft tissue structures, airway measures, neck fat, and submental fat. Paired t-tests were used to compare changes in AHI, soft tissue structures, and adipose domains. Associations between AHI and anatomic structures were examined using Spearman correlations.

Results: A significant decrease was seen in AHI, BMI, and weight in apneics after weight loss (Table 1). There was also a significant reduction in the mean volume of the tongue, retroglossal lateral walls, neck fat (total, subcutaneous, and visceral) and submental fat in these subjects. Additionally, a significant increase was seen in the lateral width of the retroglossal airway. Decreased retroglossal lateral wall volume had a strong association with decreased AHI (rho=0.54, p=0.1). Increased lateral width of the retroglossal airway also had a significant association with decreased AHI (rho= -0.65, p=0.05). No significant associations were seen between any of the fat domains and AHI.

Conclusions: Weight loss through bariatric surgery decreases the volume of neck fat, submental fat, retroglossal lateral wall, tongue and AHI. Lower lateral wall volumes and greater lateral airway width in the retroglossal region were closely associated with decreased AHI. Decreased volumes of neck and submental fat showed little association with reduced AHI. These findings suggest that the reduction of retroglossal lateral wall volume in conjunction with an increase in the lateral width of the retroglossal airway may be important in mediating the improvement of OSA in weight loss subjects.

Table 1: Mean Differences in Weight Loss Group				
	Mean (SD) Before Weight Loss	Mean (SD) After Weight Loss	p-value	Δ
AHI (event/hour)	24.5 ± 14.2	6.1 ± 5.7	p<0.01	-18.4 ± 14.3
BMI (kg/m^2)	45.0 ± 5.2	36.6 ± 4.0	p<0.001	-8.8 ± 4.2
Weight (lbs)	275.3 ± 36.0	224.5 ± 29.8	p<0.001	- 50.8 ± 25.4
Total Neck Fat (mm^3)	879.7 ± 222.4	577.1 ± 152.8	p<0.01	-302.6 ± 277.5
Visceral Neck Fat (mm^3)	273.9 ± 87.9	183.5 ± 62.1	p<0.05	-90.3 ± 104.8
Subcutaneous Neck Fat (mm^3)	605.8 ± 170.6	393.5 ± 117.2	p<0.01	-212.3 ± 187.3
Submental Fat (mm^3)	88.4 ± 24.9	64.55 ± 26.3	p<0.001	-23.9 ± 13.2
Tongue (mm^3)	88914.6 ± 14796.5	83861.7 ± 15705.2	p<0.05	-5053 ± 6116.3
Retropalatal Lateral Walls (mm^3)	10776.3 ± 7429.9	10410.1 ± 3125.5	p=0.33	-366.2 ± 1140.8
Retroglossal Lateral Walls (mm^3)	10060.3 ± 2971.8	9098.2 ± 3293.0	p<0.1	-962.7± 1434.3
Retropalatal Airway Volume (mm^3)	3250.1 ± 1182.2	3699.0 ± 1272.3	p=0.19	448.9 ± 1012.6
Retroglossal Airway Volume (mm^3)	6257.4 ± 3026.9	6614.9 ± 2744.4	p=0.63	357.5 ± 2273
Anteroposterior Width of Retroglossal Airway (mm)	13.81 ± 2.6	12.25 ± 3.4	p<0.1	-1.6 ± 1.8
Lateral Width of Retroglossal Airway (mm)	15.03 ± 6.2	17.44 ± 5.9	p<0.1	2.4 ± 3.7

This abstract is funded by: NIH P01HL094307

New Likelihood Ratio Metric for the Psychomotor Vigilance Test and Implications for the Choice of a Primary Outcome Metric

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The Psychomotor Vigilance Test (PVT) is a widely used assay of behavioral alertness sensitive to the effects of sleep loss and circadian misalignment. However, there is currently no accepted PVT outcome metric that captures response slowing, attentional lapses, as well as compensatory premature responses typically observed concurrently in sleep deprived subjects. We developed a novel Likelihood Ratio Metric (LRM) that is based on relative frequency distributions in 50 categories of response times in alert and sleep deprived subjects. LRM scored the second highest effect size (1.91; 95% confidence interval CI 1.53-2.63) in a 33 hour total sleep deprivation protocol (outranked only by response speed, effects size 1.93; 95% CI 1.55-2.65) and the highest effect size (1.22; 95% CI 0.98-1.57) in a 5 nights with 4 hour sleep opportunity partial sleep restriction protocol (followed by response speed, effect size 1.21; 95% CI 0.94-1.59). Standardized LRM scores agreed well with standardized response speed scores, and less well with 5 other common PVT outcome metrics. In conclusion, the new LRM is a sensitive PVT outcome metric with high statistical power that takes subtle sleep loss related changes in the distribution of response times (including false starts) into account, uses most of the available information, is not prone to outliers, and can easily be calculated and interpreted. Congruence between and similar performance of LRM and PVT response speed support the use of response speed as the primary, most sensitive, and most parsimonious PVT outcome metric.

The Relationship between Television Viewing and Sleep Duration

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Introduction: Television viewing has been associated with both short and long sleep duration. The relationship between television viewing and habitual sleep duration is complex and likely depends on sociodemographic characteristics as well as the time-of-day and duration of television viewing.

Methods: Analyses are based on a representative sample of Americans 15 years and older participating in the 2003-2011 American Time Use Surveys (N=124,517).

Results: When adjusting for age, gender and race, long sleepers (≥11h/night) spent more time watching television compared to average (>6h and <11h) and short (≤6h/night) sleepers. When examining time-of-day, long sleepers spent more time watching television during daytime hours (i.e., 1000h-1900h). Although short and normal sleepers did not differ in terms of time spent watching television in a 24 h period, short sleepers spent more time watching television during late-night/early-morning hours (i.e., 2200h-0530h) compared to normal sleepers. When adjusting for a host of demographic variables we found that individuals who were not currently working (i.e. absent from work, unemployed, retired, or not in the labor force) were at increased odds for being a long sleeper.

Conclusion: Consistent with previous studies, although short sleepers do not watch more television in a given 24h period, these individuals do watch more television during late-night/early-morning hours. Reducing time spent watching television during this time may lead to longer sleep durations and a reduction in sleep debt. The relationship between long sleep duration and greater television viewing does not suggest that viewing more television will lead to more sleep. Rather it is likely that long sleepers have more discretionary time and spend that time viewing television and sleeping. Indeed, additional time spent viewing television occurred during daytime hours and individuals not in the work force were more likely to be long sleepers.

Support: NIH NR004281, NSBRI NASA NCC 9-58. ATUS was sponsored by: Bureau of Labor Statistics and conducted by: U.S. Census Bureau.

Sleep Duration is Associated with Access to Healthcare but Relationships Depend on Race/Ethnicity

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INTRODUCTION: Short sleep duration is associated with many adverse health outcomes, as well as demographic and socioeconomic factors. Sleep may represent a modifiable factor linking minority and/or low socioeconomic status with poor health. One potential reason for health outcomes associated with sleep duration may be healthcare access, and this may depend on race/ethnicity.

METHODS: Data from the 2009 Behavioral Risk Factor Surveillance System was used. N=26,765 adults provided data on sleep and healthcare access. Sleep duration was assessed as total sleep in a typical 24-hour period and coded as ≤4, 5, 6, 7, 8, 9, and ≥10hrs. Access to any medical insurance(yes/no) and having foregone medical care in the past 12 months due to cost(yes/no) were also assessed. Population-weighted, binary logistic regression analyses assessed associations between sleep (reference=7hrs) and healthcare access outcomes, adjusted for age, sex, race/ethnicity, education, employment, overall health, and state-of-residence.

RESULTS: Lack of health insurance was more likely among ≤4hr(OR=1.75;95%CI[1.24,2.45];p=0.001) and 5hr(OR=1.43;95%CI[1.07,1.90];p=0.015) sleepers. A significant sleep*race/ethnicity interaction(p=0.001) was found. Among non-Hispanic Whites, this pattern was maintained for ≤4hrs(OR=2.42;95%CI[1.62,3.63];p<0.0001) and 5hrs(OR=1.51;95%CI[1.10,2.06];p=0.011). No relationships were seen among other groups. Foregoing medical care (even after adjustment for access to health insurance) was more common among ≤4hrs(OR=2.17;95%CI[1.52,3.09],p<0.0001), 5hrs(OR=1.48;95%CI[1.13,1.95]=p<0.005) and 6hrs(OR=1.40;95%CI[1.14,1.70];p=0.001). Again, this relationship depends on race/ethnicity(interaction p=0.0002). Among non-Hispanic Whites, this relationship was maintained for ≤4hrs(OR=2.32;95%CI[1.60,3.34],p<0.0001), 5hrs(OR=1.98;95%CI[1.47,2.67];p<0.0001), and 6hrs(OR=1.54;95%CI[1.23,1.92];p<0.0001). However, among Blacks/African-Americans, increased likelihood was found for ≤4hrs(OR=2.16;95%CI[1.17,4.03];p=0.014), among Hispanics/Latinos, decreased likelihood was found for 5hrs(OR=0.27;95%CI[0.09,0.79];p=0.017) and 9hrs(OR=0.10;95%CI[0.03,0.34];p<0.0001), among Asians/Others, increased likelihood was found for 6hrs(OR=2.94;95%CI[1.19,7.27];p=0.019), and among Multiracial respondents, decreased likelihood was found for 9hrs (OR=0.02;95%CI[0.002,0.22];p=0.002).

CONCLUSIONS: Short sleep duration was associated with decreased healthcare access and foregoing medical care due to cost, but this relationship depended on race/ethnicity. Non-Hispanic Whites may show a more robust relationship between short sleep and healthcare access/utilization. Other factors may be more prominent in other groups.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

Do Sleep Disturbances Influence General Functioning After PTSD Treatments?

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Introduction: Chronic insomnia and recurrent nightmares are prominent features of posttraumatic stress disorder (PTSD). There is evidence that these sleep disturbances do not respond to trauma-focused therapies for PTSD and are associated with poor functional outcomes. Little is known about the effects of trauma-focused treatment on sleep disturbance and general functioning in adolescents with PTSD. The present study examined the effects of trauma-focused therapy on sleep-related PTSD symptoms, and the effect of disturbed sleep on general functioning.

Methods: Sixty-one adolescent females, ages 13-18 (M = 15.34, SD = 1.54), seeking treatment at a rape crisis center for sexual assault-related PTSD participated in a single-blind randomized clinical trial of prolonged exposure for adolescents (PE-A; n = 30) compared to client-centered therapy (CCT; n = 31). Both treatments consisted of fourteen 60-90 minute sessions. The Child PTSD Symptom Scale-Interview (CPSS-I) was used to assess the severity of PTSD symptoms including insomnia and nightmares; it was completed at baseline, post-treatment, and at 6- and 12- month follow-ups. The Children's Global Assessment Scale (CGAS) was used to assess general functioning. The CPSS-I and CGAS were administered by independent evaluators who were blind to participants' treatment condition.

Results: General Linear Model (GLM) repeated measures analyses were conducted on insomnia and nightmare symptoms with treatment condition (PE-A/CCT) as the between subjects variable. No significant time by condition interactions were found; however, statistically significant effects of time ($p < .001$) were found for the severity of insomnia and the intensity of nightmares, with symptoms decreasing from baseline to post-treatment. Both nightmare and insomnia symptoms significantly predicted general functioning and accounted for 20.3%-28.9% of the variance in this measure over time. Further, participants continued to endorse insomnia and nightmare symptoms over time.

Conclusions: Both treatments produced significant improvements in sleep-related PTSD symptoms. However, neither sleep symptom remitted after PTSD treatment. Additionally, both sleep symptoms continued to impact general functioning over time. Given these findings, future interventions targeting PTSD should take into account sleep disturbance in order to improve overall functional outcomes.

Support: This study was supported by the National Institute of Mental Health (R01

MH074505) PI: Edna Foa.

Sleep Duration Associated with Depressive Symptoms in a Population Sample: Potential Pathway to Poor Physical Health

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INTRODUCTION: Short sleep duration is associated with many adverse health outcomes. Some studies have shown associations with clinical depression. No previous studies have used a population sample to assess relationships between sleep duration and specific depressive symptoms, over and above general depressed mood and poor sleep quality (both associated with both sleep duration and symptoms in general).

METHODS: Data from the 2010 Behavioral Risk Factor Surveillance System (BRFSS) was used. The BRFSS is a state-based survey conducted annually by the CDC. A total of N=14,730 participants were asked questions about both sleep duration and depressive symptoms. Sleep duration was assessed as habitual sleep within a typical 24 hour period and coded as very short (≤4 hours), short (5-6 hours), normal (7-8 hours), or long (≥9 hours). Depressive symptoms were assessed as number of days in the past 2 weeks where the following symptoms were experienced: (1) depressed mood, (2) anhedonia, (3) poor sleep quality ("difficulty falling asleep, staying asleep, or sleeping too much"), (4) low energy, (5) appetite dysregulation, (6) feelings of failure, (7) difficulty thinking/concentrating, and (8) psychomotor agitation or slowing. Responses were coded as 0-14 days and categorized as none (0/14 days), mild (1-6/14 days), or moderate/severe (7-14/14 days). Population-weighted multinomial logistic regression analyses adjusted for age, sex, race/ethnicity, education, employment, smoking, body mass index, depressed mood, and poor sleep quality. To assess the role of depression in the relationship between sleep and health, a mediation model was tested, with days poor physical health in the past month as outcome, sleep duration category as predictor, and depressed mood as mediator.

RESULTS: After adjustment for covariates, including poor sleep quality and overall depressed mood, very short sleep was associated with mild psychomotor symptoms (OR=2.01,p=0.020), and moderate/severe anhedonia (OR=2.21,P=0.011), appetite dysregulation (OR=3.61,p<0.0001), low energy (OR=7.38,p<0.0001), feelings of failure (OR=3.03,p=0.014), difficulty thinking/concentrating (OR=3.44,p=0.0006), and psychomotor symptoms (OR=7.81,p<0.0001). Short sleep was associated with mild low energy (OR=1.21,p=0.046), feelings of failure (OR=1.31,p=0.048), and psychomotor symptoms (OR=1.48,p=0.012), and moderate/severe appetite dysregulation (OR=1.68,p=0.0001), low energy (OR=2.53,p<0.0001), feelings of failure (OR=1.75,p=0.009), and difficulty thinking/concentrating (OR=1.50,p=0.0495). Long sleep was associated with moderate/severe psychomotor symptoms (OR=2.34,p=0.019). In a mediation analysis, depressed mood (as a continuous variable 0-14) was a significant partial mediator of the relationship between sleep duration category and overall physical health, explaining 28.9% of the relationship, though this is reduced to 11.0% when accounting for the overlap between overall physical and mental health.

CONCLUSIONS: Overall, short sleep duration was generally associated with depressive symptoms over and above any contributions of depressed mood and/or poor sleep quality. Further, depression represents one potential pathway linking short sleep and overall health.

Surface EMG Activity During REM Sleep in Parkinson's Disease Correlates With Disease Severity

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Objective: To examine characteristics of manually-quantitated surface EMG activity during REM sleep in mentalis and limbs in PD and to determine whether the extent of this EMG activity is associated with measures of Parkinsons Disease (PD) and REM sleep behavior disorder (RBD).

Background: Over 40% of individuals with PD have RBD. This is associated with excessive sustained (tonic) or intermittent (phasic) muscle activity instead of the muscle atonia normally seen during REM sleep. To ascertain whether the extent of muscle activity during REM sleep is associated with specific clinical features we examined characteristics of manually-quantitated surface EMG activity in PD

Methods: In a convenience sample of outpatients with idiopathic PD, REM sleep behavior disorder was diagnosed based on clinical history and polysomnogram, and severity was measured using the REM sleep behavior disorder questionnaire (RBDSQ). Surface EMG activity in the mentalis, extensor muscle group of the forearms, and anterior tibialis was manually quantitated. Percentage of REM time with excessive tonic or phasic muscle activity was calculated and compared across PD and REM sleep behavior disorder characteristics.

Results: Among 65 patients, 31 had confirmed REM sleep behavior disorder. In univariate analyses, higher amounts of surface EMG activity were associated with greater age (srho=0.28; p=0.023), longer PD disease duration (srho=0.34; p=0.006), and greater disease severity (p<0.001). In a multivariate regression model, surface EMG activity was significantly associated with RBD severity (p<0.001) after adjustment for age and PD disease duration and severity.

Conclusions: Surface EMG activity during REM sleep was associated with severity of both PD and RBD. This measure may be useful as a PD biomarker and may aid in determining which PD patients warrant treatment for their dream enactment to reduce risk of injury.

The Association of Serum Lipids with Insomnia Symptoms and Alcohol Consumption

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Introduction: The aim on this current investigation was to investigate the relationship between individual serum lipid levels, insomnia symptoms and alcohol consumption in subjects from a nationally representative sample of Americans.

Methods: Data from adults, ≥ 21 years of age, from the 2005-2006 and 2007-2008 waves of National Health and Nutrition Examination Survey (NHANES) were used in this cross-sectional study. The final sample consisted of 4317 subjects out of the 10,732 subjects after excluding missing cases, and subjects without laboratory data on lipids levels. Data was evaluated for the following: a) serum lipids [Cholesterol, Triglycerides (TG), LDL cholesterol (LDL), and HDL cholesterol (HDL)]; b) insomnia symptoms [Sleep Latency (SL), Waking after Sleep Onset (WASO), Non-restful sleep (NRS)]; c) Alcohol consumption [Drinks per Day (DrPD), and Heavy Drinking Days (HDD)]; d) demographic and health-related covariates. Linear regression analyses evaluated for the association between log transformed lipid variables (dependent variable) and the interaction of insomnia variables and alcohol consumption variables, in unadjusted and fully adjusted models.

Results: The mean (SD) for the individual serum lipid levels were as follows: Sr. Cholesterol was 200 (41) mg/dl, Sr. TG was 140 (112) mg/dl, Sr. LDL was 116(35) mg/dl, and Sr. HDL was 53 (16) mg/dl. The frequency of insomnia symptoms reported 16/30 days were as follows: Initial insomnia (SL, 7.48%), middle insomnia (WASO, 7.59%), nonrestful sleep was 6.34%). Multiple interactions involving specific insomnia symptoms on alcohol consumption variables predicted specific Sr. Lipid levels, with the exception of Sr. LDL, were seen. Specifically, Sr. Cholesterol levels were predicted by the following interactions: sleep latency*HDD; WASO*HDD, NRS*HDD; Sr. TG was predicted by the following interactions: SL*HDD, WASO*DrPD, and WASO*HDD; NRS was predicted by NRS*DrPD.

Conclusion: Alcohol consumption may play a role in the propagation of the cardio-metabolic events among those who suffer from insomnia.

Psychosocial Problems Are Greater Among Alcoholics Who Complain of Insomnia

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Introduction: Psychosocial problems are known consequences of both pathological alcohol consumption and insomnia (which also frequently co-occur). It is unknown, though, whether an interaction exists, such that psychosocial problems among alcoholics are worse in the context of insomnia. Since psychosocial problems may increase treatment-related recidivism, if problems are worse with insomnia, this would strengthen the role of insomnia as a modifiable risk factor in alcoholism. The present study evaluates whether insomnia in alcoholics is associated with more psychosocial problems as compared to alcoholics without insomnia.

Methods: Alcoholics (N=123) were evaluated at baseline as part of a clinical trial using the following instruments: Short Index of Problems (SIP: psychosocial consequences of alcoholism); Addiction Severity Index (ASI: employment, social and legal problems); 3) Insomnia Severity Index (ISI: insomnia symptoms); Time Line Follow Back (TLFB: alcohol consumption). ANOVA and linear regression analyses evaluated the relationships between insomnia and psychosocial problems.

Results: The mean age was 44(SD=10) years and 83% were males. Rates of insomnia were 25% no insomnia, 29% mild, and 46% moderate-severe. The SIP sub-scale scores approximated the 5th decile in relation to normative data. Those with moderate-severe insomnia (versus without insomnia and mild insomnia) reported significantly greater problems on all SIP-recent sub-scales (social, intrapersonal, interpersonal, physical and impulse control; all $p<0.005$), 4 SIP-lifetime sub-scales (intrapersonal, interpersonal, physical and impulse control; all $p<0.02$); and the ASI (conflicts with friends/family, $p<0.03$). There were no differences in the alcohol consumption variables across the insomnia groups. Finally, ISI score predicted SIP-recent, and SIP-lifetime total scale scores in regression analyses.

Conclusion: Alcoholics with insomnia had more social conflicts and higher intensities of both recent and lifetime psychosocial problems. This may explain some of the unique challenges faced by this population. Future studies should clarify the relationship between insomnia and psychosocial problems in alcoholics, employing treatments for insomnia or for alcoholism.

Trainee Award Eligible

Patterns of Marijuana (Cannabis) Use and Sleep Symptoms in American Adults

Jilesh Chheda, Subhajit Chakravorty MD, and Michael A. Grandner PhD

University of Pennsylvania

INTRODUCTION: Cannabis is one of the commonly used drugs in the population, and with a higher prevalence of use in adolescents. Prior studies have associated cannabis use and insomnia, mainly in adolescents. It is possible that this relationship differs in adults, depends on age at first use, and differentially affects insomnia symptoms.

METHODS: Data from the 2007-2008 NHANES were used (N=3255 adults age 20-59 asked about drug use history). Cannabis use was assessed as (1)any history of use, (2)age at first use (<15yrs, 16-18yrs, >18yrs), and (3)number of times used in the past month (among N=1811 with history of use). Sleep symptoms included difficulty falling asleep, difficulty maintaining sleep, non-restorative sleep, and daytime sleepiness, coded as minimal(<5 days/month), mild(5-15 days/month) and severe(≥15 days/month). Population-weighted, multinomial logistic regression analyses examined whether marijuana use was associated with likelihood of sleep symptoms, after adjustment for age, sex, race/ethnicity, education, income, body mass index, and smoking.

RESULTS: Any history of cannabis use was associated with increased likelihood of mild(OR=1.39,p=0.045) and severe(OR=1.60,p=0.018) difficulty falling asleep, mild(OR=1.43,p=0.031) difficulty maintaining sleep, mild(OR=1.34,p=0.005) and severe(OR=1.74,p=0.001) non-restorative sleep, and mild(OR=1.53,p=0.006) daytime sleepiness. Regarding age at first use, relative to non-users, those who started at <15yrs were more likely to experience severe difficulty falling asleep(OR=2.28,p=0.001), mild(OR=1.60,p=0.026) and severe(OR=1.78,p=0.049) difficulty maintaining sleep, mild(OR=1.86,p<0.0001) and severe(OR=2.25,p<0.0001) non-restorative sleep, and mild(OR=1.60,p=0.016) and severe(OR=1.99,p=0.013) daytime sleepiness. For those who began at 16-18, effects were seen for mild difficulty falling asleep(OR=1.47,p=0.048), mild difficulty maintaining sleep(OR=1.50,p=0.043), mild non-restorative sleep(OR=1.39,p=0.047), and mild daytime sleepiness(OR=1.53,p=0.021). Those who began after 18yrs demonstrated no relationships except with severe nonrestorative sleep(OR=1.67,p=0.019). Among users, frequency of use was associated with severe difficulty falling asleep(OR=1.03,p=0.027).

CONCLUSIONS: Frequent cannabis use is associated with impaired sleep quality. Initiation of cannabis use in adolescence may impart a higher risk for subsequent insomnia symptoms.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

Case Series Review of Pre-Post CBT-I Outcomes

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Introduction: While there is a preponderance of clinical trial evidence that CBT-I is effective and that its clinical outcomes are moderate to substantial, little is known about the "real world" effects of the treatment. The prevailing assumption is that in-clinic effects are unlikely to exceed those of clinical trials given a variety of uncontrolled factors including: medical/psychiatric comorbidity, financial pressure to reduce the number or duration of sessions and/or the number of treatment components delivered, etc. The present study examined the efficacy of CBT-I utilizing a clinical sample.

Methods: Sixty patients (45% female; mean age=53±15.6 years) from the Philadelphia metropolitan area were evaluated and treated at the Penn Center for Sleep. None of the patients in the present analysis were using sleep medications. Intake interviews were conducted to establish ICSD diagnoses and clinical history. After a one-week baseline period, patients with insomnia were scheduled on a weekly basis for 4-8 sessions, during which five interventions were implemented: Sleep Restriction, Stimulus Control, Sleep Hygiene, Cognitive Therapy and Relapse Prevention. Sleep was monitored using sleep diaries for the duration of treatment.

Results: Baseline data were compared to 4 sessions of CBT-I (modal number of sessions) using paired t-tests. On average, patients that completed therapy were about 31% improved. This average corresponded to a 52% reduction in sleep latency (effect size = 0.70), 54% reduction in wake after sleep onset (effect size = 0.96), 27% reduction in number of awakenings (effect size 0.36), 4% increase in total sleep time (effect size = 0.16), and 19% increase in sleep efficiency (effect size = 1.23).

Conclusion: These findings suggest that "real world" CBT-I is effective. Analyses are ongoing and include: comparative efficacy, efficacy viz. number of sessions, outcomes with respect to medical/psychiatric comorbidities and hypnotic tapers (before vs. during CBT-I).

Trainee Award Eligible

A Comparative Analysis of Multiple Artifact Rejection Methods

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Introduction: It is widely assumed that EEG artifact rejection should be utilized prior to application of quantitative analysis methods (e.g., power spectral analysis). This assumption has not, however, been empirically tested. If artifacts occur relatively infrequently relative to hundreds or thousands of analytic windows, then their identification and rejection may not be necessary. The present study evaluates whether any of 3 artifact rejection strategies produces spectral profiles that are significantly different from raw EEG data.

Methods: Data from n=90 subjects were used (n=60 Primary Insomnia and n=30 controls matched on sex, age, BMI, and education). Power spectral analysis of 4-second windows was performed using C3-A2 placement, with 128Hz sampling and high-pass/low-pass filters set at 0.3Hz/100Hz. Three artifact rejection methods were compared to raw data using average Stage 2 and NREM/REM power spectral voltages. The first method utilized a 3-minute moving window that rejected epochs containing values that were 4*median in the 26.25-32Hz frequency range (Brunner et al., 1996). The second method employed the same algorithm with an alternate range (45-64Hz). The final method employed visual artifact rejection of 30-second windows.

Results: All three artifact rejection methods resulted in decreased power across all frequency bands for NREM/REM and Stage 2, compared to raw data ($p<0.0001$). Additionally, methods generally differed from each other. Visual rejected more data than Brunner and Alternate (by 12.9% and 11.7% respectively; $p<0.0001$). Across methods, more epochs were rejected in NREM versus REM ($p<0.001$), but methods did not differ from each other.

Conclusion: The systematic application of any artifact rejection procedure produces reliable differences that are small in absolute magnitude but statistically significant. A stronger test of the utility of artifact rejection would be whether its application enhances the ability to detect group membership or the effects of experimental manipulations. Analyses are ongoing regarding group differences.

Trainee Award Eligible

Sleepiness and Interference

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Introduction: Healthy sleep facilities the consolidation of newly learned memories. Evidence suggests that sleep after learning compared to periods of wakefulness improves declarative memory. However, these studies have primarily focused on healthy subjects. Sleep disturbance, in particular insomnia has been associated with significant daytime impairment and decreased cognitive function. The present study examined verbal declarative memory consolidation utilizing a future interference paradigm in individuals with insomnia and healthy controls.

Methods: Twenty-eight college students (60.7% Females, mean age = 19.6, SD = 1.51) were divided into two groups (n = 13, Insomnia group, n = 15, healthy controls). Participants in the insomnia group met Quantitative Research Criteria for insomnia and at least sub-threshold insomnia criteria on the Insomnia Severity Index (ISI). The Epworth Sleep Scale (ESS) was utilized to assess sleepiness and the Morning-Eveningness Questionnaire (MEQ) was used to measure chronotype. To assess declarative memory recall, 2 word-pair associate lists (A-B and A-C) created from the Toronto Word Pool were used, which were matched for frequency, concreteness, and imageability, and counter-balanced across participants (Friendly et al., 1982). Testing took place on 2 subsequent days. Recall was measured 3 times with cued-recall word-pair lists: immediate (on day 1), delayed (after 24-hours on day 2), and interference (after interference learning which directly followed the delayed recall task on day 2).

Results: Overall, both groups experienced significantly decreased delayed recall after interference testing; however, there were no significant group differences. Controlling for MEQ score, regression analyses showed that on day 1, ESS score was associated with immediate recall scores, but only for controls [adjusted analyses; β = -12.115, 95%CI (-22.228, -2.003); p=.023]. On day 2, sleepiness was not associated with delayed recall scores for either group. However, sleepiness was associated with interference recall scores for the control group only, [unadjusted and adjusted analyses; -37.313, (-68.436, -6.191); p=.023 and -34.375, (-65.342, -3.408); p=0.033; respectively].

Conclusion: The finding that sleepiness was associated with interference recall for the control group only suggests that the Insomnia group may be somewhat resilient to effects of sleepiness when faced with difficult tasks. This may have implications regarding further understanding students' ability to cope with daytime sequelae resulting from Insomnia symptoms.

Trainee Award Eligible

Prolonging obstructive apneas in a hospitalized patient – a potential harm of routine medical therapy

Eric M. Davis, MD

University of Pennsylvania

A type III unattended sleep study performed on an 85 year-old man during his inpatient hospitalization following cardiac arrest reveals an increase in the average apnea length from 27.9 to 52.2 seconds after the initiation of supplemental oxygen therapy. Representative 10-minute and 60-minute tracings are shown while the patient is on room air (Figure 1) and while on supplemental oxygen (Figure 2). By demonstrating a potential harm of a routine medical intervention, this case highlights arousal mechanisms involved in obstructive apnea events.

Figure 1

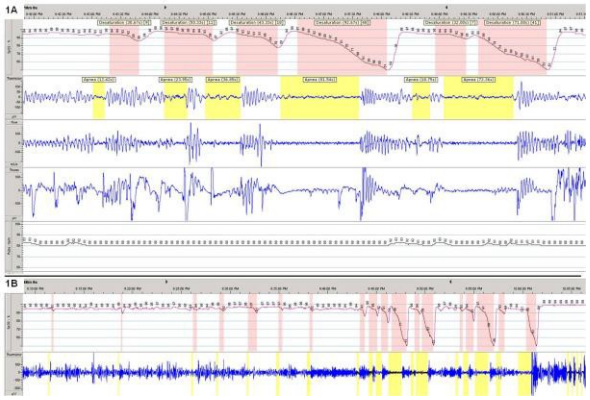
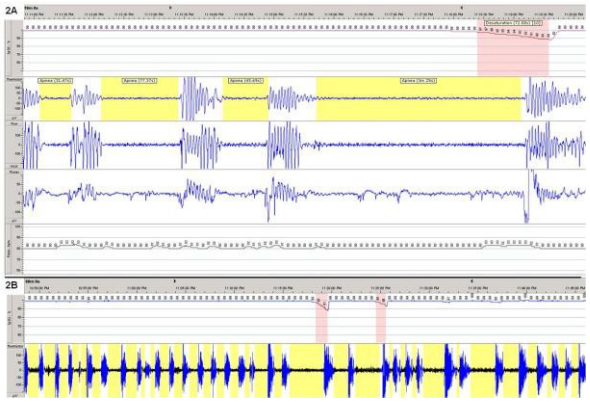


Figure 2



Trainee Award Eligible

Assessing treatment gaps for the un- or underinsured patients through community partnerships: a potential idea for cost effective care

Lourdes M. DelRosso, M.D.; Romy Hoque, M.D; Andrew L. Chesson Jr. M.D.

Louisiana State University Health Sciences Center Shreveport

Introduction

The management of obstructive sleep apnea (OSA) in patients who cannot afford a CPAP device is challenging. Some charity organizations provide CPAP for uninsured patients but little is known about unique factors that affect adherence. We hypothesize that additional factors, besides the ability to purchase CPAP may uniquely affect adherence in uninsured patients.

Methods

CPAP devices were provided through an ASMF Humanitarian Grant to 30 uninsured patients, with OSA by Medicare criteria (group 1). 25 other uninsured patients with OSA (group 2) were provided contact options to obtain CPAP (local and national charity organizations, discounted or used CPAP). Both groups were followed at 3 months (further follow-up in process). Factors potentially affecting adherence included: timely acquisition, phone access, ability to come to the appointment (transportation), available electricity, discomfort due to mask or pressure and other medical conditions.

Results:

There were no significant differences between groups in gender (Group 1: 18 women, 12 men vs Group 2: 14 women and 11 men), age (47.7+9.4 [mean+SD] vs 46.4+10.7 yr), AHI (AHI 33.2+34.9 vs 37.3+38.2/hr) or CPAP pressure (12.6+3.6 vs 12.8±3.6 cmH2O). At 3-months, all Group 1 patients had received CPAP and 13 had returned for follow-up. 12 patients from group 2 had obtained CPAP devices and only 6 returned for follow-up. Factors that impeded follow-up included phone disconnection, not returning phone calls, incarceration, no transportation, comorbidities and relocation.

Conclusion:

The provision of CPAP devices to uninsured populations alone may not solve adherence problems. Other socioeconomic factors need to be assessed in such patients who already have high health care risks, and may need to be taken into consideration for charity programs to be effective

Funded in part by an American Sleep Medicine Foundation Humanitarian Grant

Prevalence of Obstructive Sleep Apnea and Barrett's esophagus in patients referred for Esophagogastroduodenoscopy due to reflux symptoms.

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Introduction

The relationship between obstructive sleep apnea (OSA) and gastroesophageal reflux (GERD) has been previously studied with mixed results. The arousals during obstructive sleep apnea (OSA) decrease the lower esophageal sphincter pressure, contributing to worsened nocturnal reflux. We hypothesize that the prevalence of OSA in those undergoing esophagogastroduodenoscopy (EGD) for evaluation of GERD is higher than in the general population.

Methods

Retrospective chart review was performed in 174 adult patients seen in a Family Medicine EGD clinic from 07/01/2011 until 07/01/2013 whose initial complaint was GERD related. Patients referred for melena, occult stool blood, gastrointestinal malignancy, Barrett's surveillance, or unexplained weight-loss were excluded. Data collected included: age, sex, body mass index (BMI), indication for EGD, and diagnosis following EGD. Three subgroups were analyzed: Group 1 had PSG with OSA. Group 2 were Stop-Bang questionnaire (SBQ) positive, but no PSG. Group 3 were SBQ negative.

Results

Across all groups 51(29.5 %) were men, 20(11.5%) had PSG with OSA, 49(28.1%) were SBQ positive. Group 1: age 52.5±9.3 (mean ± standard deviation); and BMI 31.6±4. Group 2: age 58.2±11; and BMI 35.5±10.4. Group 3: age 52.5±14.7; and BMI 28.7±8.1. All three groups had a similar prevalence of erosive esophagitis at 6%. Prevalence of gastritis, across all groups: 48(27.5%); Group 1: 6(30%); Group 2: 15(30%); and Group 3: 27(25%). Prevalence of Barrett's esophagus Group 1: 3(15%); Group 2: 7(14%); and Group 3: 11(10%).

Conclusions

The prevalence of OSA in patients undergoing EGD for evaluation of GERD symptoms is higher than in the general population. There is a statistically significant difference in BMI between patients with OSA and those without OSA. There was an increased prevalence of Barrett's esophagus in those with OSA or SBQ positive compared to those without OSA or SBQ negative.

Investigating impact of mating status on Drosophila sleep behavior

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Sensory perception directly impacts health and behavior in several species, including humans and Drosophila. Yet how external environmental cues and internal physiological states are sensed, integrated, and conveyed to appropriate behavioral circuits has yet to be resolved. Recent studies have shown that Drosophila Sex Peptide (SP), which is transferred from a male to a female during copulation, triggers stereotypical female post-mating behavioral responses including increases in egg laying and decreases in sexual receptivity; changes which are critical for reproductive success. Interestingly, while baseline amounts of daytime sleep are different in male and female flies, copulation further exacerbates this imbalance. These data support the idea that altering sleep:wake activity may also contribute to an adaptive reproductive response. However, it is unclear if the sensory and inter-neurons required for modifying sexual receptivity and egg laying are identical to the ones responsible for altering sleep. In one situation, the same set of neurons might receive SP and transmit this signal via a common pathway to divergent circuits in higher brain centers to elicit various behavioral responses. Alternatively, distinct sets of neurons may receive male mating cues thereby eliciting changes in behavior via parallel, non-overlapping circuits. Lastly, how these post-mating behaviors are ultimately coordinated is not understood. We are interested in uncovering the neuronal and molecular mechanisms responsible for eliciting changes in female post-mating sleep patterns. Additionally, we hope to gain insight into how an organism interprets external cues and internal states to tune its behavior in response to an ever-changing environment. We will report on the progress of these investigations.

Trainee Award Eligible

Predictors of Perceived Insufficient Sleep among Habitual Short Sleepers

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INTRODUCTION: Self-reported short sleep duration is associated with many adverse health outcomes. Some short sleepers perceive that their sleep is insufficient, whereas others do not. Previous studies have not characterized short sleepers who perceive impairment compared to those that do not.

METHODS: Data from adult (age≥18) respondents from the 2009 Behavioral Risk Factor Surveillance System were used. Number of days/month of insufficient rest or sleep was assessed. Those reporting 0 or 30 were categorized as never-insufficient or always-insufficient, respectively. Sleep duration was assessed as typical sleep per 24 hours; short sleep was defined as ≤6h. Potential factors included age(reference=80+), sex, race/ethnicity(reference=white), household size(continuous), suburban/rural(reference=urban), education(reference=college), marital status(reference=married), employment type(reference=sedentary), body mass index(reference=normal), days/month of poor physical and mental health(both continuous), overall health(reference=excellent), exercise(reference=none), and emotional support(reference=always). Population-weighted binary logistic regression analyses evaluated unadjusted and adjusted contributions of these factors in predicting always-insufficient status (vs never-insufficient) among short sleepers. N=7,648 respondents were short sleepers and N=7,098provided complete data on all variables.

RESULTS: In unadjusted analyses, short sleepers who were always-insufficient were more likely to be younger (18-24:OR=3.15,p<0.0001; 25-29:OR=3.67,p<0.0001; 30-34:OR=4.96,p<0.0001; 35-39:OR=4.18,p<0.0001; 40-44:OR=2.37,p<0.0001; 45-49:OR=1.97,p=0.0003; 50-54:OR=2.05,p=0.0001; 55-59:OR=1.73,p=0.004; 60-64:OR=1.57,p=0.017), report fair(OR=1.68,p=0.001) or poor(OR=3.71,p<0.0001) health and more days of poor physical(OR=1.05/day,p<0.0001) and mental(OR=1.08/day,p<0.0001) health, live in a larger household(OR=1.16/person,p<0.0001) or in a rural area(OR=1.27,p=0.039), report emotional support frequently(OR=1.90,p<0.0001), sometimes(OR=2.04,p<0.0001) or rarely(OR=2.77,p=0.0001), and were less likely to be male(OR=0.67,p<0.0001), Asian/Other(OR=0.63,p=0.010), or widowed(OR=0.52,p<0.0001). In adjusted analyses, this pattern was maintained for younger age groups (18-24:OR=3.99,p<0.0001; 24-29:OR=4.31,p<0.0001; 30-34:OR=5.50,p<0.0001; 35-39:OR=4.62,p<0.0001; 40-44:OR=2.48,p=0.0001; 45-49:OR=1.74,p=0.011; 50-54:OR=1.76,p=0.0052; 55-59:OR=1.57,p=0.029), men(OR=0.065,p<0.0001), Asians/Others(OR=0.55,p=0.003), poorer physical(OR=1.05/day,p<0.0001) and mental(OR=1.06/day,p<0.0001) health, fair health(OR=1.38,p=0.098), widows(OR=0.52,p<0.0001), exercisers(OR=1.34,p=0.013), unemployed(OR=0.57,p<0.0001), have larger households(OR=1.13/person,p=0.001), and report emotional support frequently(OR=1.82,p<0.0001), sometimes(OR=1.87,p=0.0001) or rarely(OR=2.33,p=0.0009).

CONCLUSIONS: At the population level, several characteristics distinguished short sleepers who perceived impairment from those who did not. Future studies may discern whether perceived insufficiency in the context of short sleep is a parker of risk.

EEG SPECTRAL ANALYSIS AND CHANGES IN DELTA POWER: THE EFFECTS OF TRIMESTER AND SLEEPDISORDERED BREATHING IN PREGNANCY

Izci Balserak B, Pack AI, Corbitt C, Maislin G, Keenan B, Perlis ML, and Pien G

Introduction: In nonpregnant population it has been shown that slow wave sleep (SWS) decreases in those with sleep-disordered breathing (SDB), compared to those without SDB. There are few electroencephalography (EEG) studies on sleep during pregnancy. Furthermore, the changes in EEG sleep parameters during pregnancy, and especially the possible changes in total SWS, are inconsistent. The aim of the study is to determine if SWS changes during pregnancy by using Power Spectral Analysis (PSA) and to test the hypothesis that a greater decrease in SWS during pregnancy occurs in women with SDB.

Methods: This is a secondary analysis of previous prospective study. Pregnant women (n = 103; mean age = 27.06 ± 7.22 yrs) completed sleep questionnaires and underwent full lab-polysomnography in the first and third trimesters. Ten and 27 women in the first and third trimesters, respectively, have AHI > 5. Average spectral profiles were created for each NREM cycle after removing waking and movement epochs and epochs containing micro or miniarousals. Linear regression was performed to explore relationships between delta power and changes between two trimesters. Using delta power changes between two trimesters as the outcome variable, AHI changes and demographic variables having a $p < 0.2$ in a bivariate analysis were reevaluated in full linear regression models as independent variables.

Results: Delta power changed significantly between two trimesters ($b = -0.06$, $p = 0.019$, but the significance disappeared after adjusting for BMI (kg/m2), total sleep time and frequency of naps per week ($b = -0.13$, $p = 0.051$). However, AHi changes between two trimesters were significantly associated with delta power changes, after adjusting for age, race, parity, BMI gain and changes in total sleep time between trimesters ($b = -0.019$, $p = 0.024$).

Conclusion: Delta power does not differ significantly between the first and third trimesters. However, PSG-confirmed obstructive sleep apnea (OSA) may alter the quantity of delta power between trimester.

Support (If Any): K99NR013187; K23HD041465.

DELTA POWER BE1WEEN GOOD AND POOR SLEEPERS IN PREGNANCY

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Introduction: Disturbed sleep and impaired sleep quality are common complaints during pregnancy. Sleep disturbances associated with decreased delta spectral power are potential risk factors for pregnancy complications. However, there are few electroencephalography (EEG) studies on sleep during pregnancy. In this study, we aimed to assess if delta power differs between good sleepers and poor sleepers across pregnancy. Thus, the power spectral analysis (PSA) of sleep EEG was performed in pregnant women in both the first and third trimester of pregnancy.

Methods: This is a secondary analysis of previous prospective study. Pregnant women (n = 103; mean age = 27 .06 ± 7 .22 yrs) completed sleep questionnaires including the Pittsburgh Sleep Quality Index (PSQI), and underwent full lab-polysomnography in both the first and third trimester of pregnancy. The PSQI is used to identify 'good sleepers' and 'poor sleepers'. Average spectral profiles were created for each NREM and REM cycle after removing waking and movement epochs and epochs containing micro or miniarousals. Random effect mixed linear regression analysis was used to explore relationships of delta power with sleep quality in NREM and REM cycles between two trimesters.

Results: Mixed models showed significant group (good sleepers vs. poor sleepers) differences in delta power between the first and third trimesters ($b = -0.064$, $p = 0.037$) after adjusting for age, objectively measured sleep efficiency, AHi, BMI, nap frequency, race and parity. Good sleepers had higher delta power than poor sleepers in both trimesters. Poor sleepers had lower delta power in the third trimester. However delta power in REM cycle did not differ between good and poor sleepers across pregnancy trimesters ($b = -0.041$, $p = 0.19$).

Conclusion: Women who are good sleepers had high delta power in both trimesters in comparison with women who are poor sleepers. Sleep disturbances modify delta power during slow wave sleep. Improving sleep quality may improve the outcomes of pregnancy which are associated with decreased delta power.

Ribosome profiling reveals an important role for translational control in circadian gene expression

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Physiological and behavioral circadian rhythms are driven by a conserved transcriptional/translational negative feedback loop in mammals. Although most core clock factors are transcription factors, post-transcriptional control introduces delays that are critical for circadian oscillations. Little work has been done on circadian translational regulation, and to address this deficit, we conducted ribosome profiling experiments in an autonomous human cell model. We found that most rhythmic gene expression occurs with little delay between transcription and translation. However, we also found genes that cycle translationally, without cycling at the transcriptional level by sequencing or array analysis. These genes were all phased to the same time of day. Unexpectedly, we also found that the clock regulates cytoplasmic processing body formation, suggesting a role for the clock in regulating general cellular mRNA metabolism.

Trainee Award Eligible

Obstructive sleep apnoea treatment and fasting lipids: a comparative effectiveness study

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Obstructive sleep apnoea (OSA) is associated with cardiovascular disease. Dyslipidaemia has been implicated as a mechanism linking OSA with atherosclerosis, but no consistent associations with lipids exist for OSA or positive airway pressure treatment. We assessed the relationships between fasting lipid levels and obesity and OSA severity, and explored the impact of positive airway pressure treatment on 2-year fasting lipid level changes.

Analyses included moderate-to-severe OSA patients from the Icelandic Sleep Apnoea Cohort. Fasting morning lipids were analysed in 613 untreated participants not on lipid-lowering medications at baseline.

Patients were then initiated on positive airway pressure and followed for 2 years. Sub-classification using propensity score quintiles, which aimed to replicate covariate balance associated with randomised trials and, therefore, minimise selection bias and allow causal inference, was used to design the treatment group comparisons. 199 positive airway pressure adherent patients and 118 non-users were identified.

At baseline, obesity was positively correlated with triglycerides and negatively correlated with total cholesterol, and low-density and high-density lipoprotein cholesterol. A small correlation was observed between the apnoea/hypopnoea index and high-density lipoprotein cholesterol. No effect of positive airway pressure adherence on 2-year fasting lipid changes was observed.

Results do not support the concept of changes in fasting lipids as a primary mechanism for the increased risk of atherosclerotic cardiovascular disease in OSA.

Evolutionarily-conserved role for a neuropeptide and its receptor in promoting an adaptive stress-induced sleep response in Drosophila

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Enhanced sleep in response to cellular stress is a conserved adaptive behavior across multiple species, but the mechanism of this process is unknown. Both Drosophila melanogaster (Kuo et al. 2010) and Caenorhabditis elegans (Hill et al., unpublished) exhibit increased sleep or quiescence following exposure that stresses cells. Prolonging sleep in response to septic injury increases survival during the infection (Kuo and Williams, 2014), suggesting that this evolutionarily conserved adaptive response is important for promoting survival.

Two genes, flp-13 and frpr-4, were recently identified as necessary for stress-induced quiescence in C. elegans (Nelson et al., unpublished), it is not yet known whether their Drosophila homologs function similarly in the adult fly. The neuropeptides encoded by flp-13, similar to Drosophila FMRFamide peptides, induce quiescence following heat stress by signaling through the G-protein coupled receptor FRPR-4, which is related to the FMRFamide receptor in Drosophila. Given the conserved nature of these peptides and receptors, we tested the hypothesis that FMRFamide and its corresponding receptor function to promote the stress-induced sleep response in Drosophila in an analogous manner.

Using the Drosophila Activity Monitoring System (DAM System, Trikinetics Inc.) to assess wake and sleep, we exposed FMRFamide receptor (FR) mutants and wild type controls to one of three types of stimuli: heat shock, sleep deprivation, or bacterial infection. Flies were subjected to heat shock or infection at ZT18 (6 hours into the dark phase of a 12h:12h light: dark cycle), because previous work showed that treatment at this time produced the most robust effects on sleep (Kuo et al , 2010). Compared to wildtype flies, FR mutants had a significantly dampened sleep response as well as decreased survival after stressful exposure. Animals over-expressing the gene encoding FMRFamide, the ligand for FR (Cazzamali and Grimmelikhuijzen, 2002 and Johnson et al., 2003), exhibited an enhanced sleep response compared to control groups. These findings support our hypothesis that FMRFamide and its receptor promote an adaptive increase in sleep following stress. We are currently performing additional genetic studies to verify the role of the FMRFamide/FR system in stress-induced sleep.

References:

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Trainee Award Eligible

Supported by NIH grants #R21 NS078582 to J.W. and #R01 NS064030 to D.R.

Recovery following exposure to three volatile anesthetics occurs differently as measured by performance in the y-maze memory paradigm in male mice.

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Despite being used in clinical settings for over 160 years, the neural mechanisms by which volatile anesthetics exert their hypnotic effects remain unknown. Additionally, the process by which the brain restores cognitive function upon exiting the anesthetic state remains poorly understood. Here, adult male C57Bl/6 mice (n=35) were trained using palatable rewards in the y-maze paradigm, a behavioral test that models hippocampal dependent spatial memory. Mice were placed in the starting arm and allowed to explore the maze in 2-minute trials 10x/day. Animals that met training criteria (n=30) entered the correct arm first in 8/10 trials during training. After ten days of training, mice were exposed to two hours of 1.2% isoflurane (n=9), 2.29% sevoflurane (n=10), or 0.97% halothane (n=9). Immediately following removal of the anesthetic, mice were placed on their back inside the y-maze and were monitored for regaining of righting reflex, a marker for return of conscious perception. Once mice regained their righting reflex, the time to restoration of memory was determined by measuring the latency for mice to approach their previously conditioned target area. We hypothesized that after adjusting for pharmacodynamic differences among the inhaled anesthetics, the latency to return of memory would be fixed as higher cognitive functions come back online. As expected and in accordance with the known differences in volatile anesthetic solubility, mice who were exposed to sevoflurane regained their righting reflex faster than mice exposed to an equipotent dose of isoflurane who regained their righting reflex faster than mice exposed to halothane. In contrast to our expected results, time for return of memory also correlated with anesthetic solubility as sevoflurane exposed mice recognized their environment and reached the target significantly faster than isoflurane-exposed mice, while isoflurane-exposed mice performed significantly better than halothane exposed animals. This study suggests that time to regain memory is not fixed, but rather depends upon the chosen anesthetic even after accounting for their distinct pharmacokinetic differences. This project will contribute to the understanding of the neuronal mechanisms through which anesthetics alter consciousness and the mechanism by which the central nervous system reintegrates as the brain emerges from anesthesia.

Trainee Award Eligible

Acute sleep deprivation suppresses aggression in Drosophila

Benjamin Mainwaring, Jonathan Levenson, Amita Sehgal, and Matthew S. Kayser

Sleep deprivation impairs cognitive performance and multiple physiological processes. In addition, sleep disruption can impinge on affective state and mood. A neurobiological basis for many of these effects remains unknown. Over the past decade, the model system Drosophila has been used to explore the genetic, molecular, and cellular basis for aggressive behaviors. Here, we use the fruit fly to investigate the effect of acute sleep deprivation on aggression. We find that total sleep deprivation for a single night results in a profound suppression of aggressive behaviors. This effect does not reflect widespread impairment of all behaviors, as courtship is unaffected. Moreover, the observed reduction in aggression is fully reversible with 1 day of recovery. Because of the intimate connection between sleep and circadian systems, we also investigated a role for the clock in regulating aggression. Unlike many other behaviors such as feeding and courtship, we detect no diurnal variation in aggression and find that this behavior is unaffected in the absence of a functional clock. Pharmacological experiments show that dopamine or octopamine receptor agonists differentially rescue suppressed aggression depending on the etiology of sleep deprivation. Other methods known to reduce aggression (such as group housing of flies) can be reversed by either of these agonists. Current work is focused on genetic approaches to rescuing suppressed aggression following acute sleep deprivation, and mapping the changes in specific neural circuits that couple sleep loss to changes in aggression.

Trainee Award Eligible

Refinement and validation of an ECG based algorithm for detecting awakenings

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The most sensitive method for measuring the impact of noise on sleep is electroencephalogram based polysomnography. However, this approach is somewhat invasive and has a high methodological expense as trained individuals are needed for both instrumentation and data analysis. An alternative, less intrusive and expensive approach that has been proposed is to use a single channel electrocardiogram to measure heart rate. An algorithm was previously developed which automatically identifies increases in heart rate associated with cortical arousals, greater than or equal to 3 seconds in duration. However, the EEG awakening (i.e., an activation greater than or equal to 15 seconds in duration) is currently the most agreed upon indicator of noise-induced sleep disturbance. Therefore, refinements have been made to the original algorithm in order to identify EEG awakenings. The data used for refining and validating the algorithm were gathered in field studies which examined the effects of aircraft noise on sleep. The changes made include the re-estimation of model parameters, the use of actigraphy data, and the addition of a sleep onset and offset algorithm. Awakenings detected with the algorithm were compared to awakenings identified visually using polysomnography data for 106 subject nights and agreement between the two approaches was high relative to conventional standards. Therefore, due to the high sensitivity in detecting awakenings this ECG based approach could be a useful method for examining noise-induced sleep disturbance in larger subject samples with lower methodological expense compared to polysomnography and more reliable and meaningful results compared to actigraphy.

Trainee Award Eligible

Ratio of Low to High Density Lipoproteins Associated with Insomnia in the American Population

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INTRODUCTION: Although high lipid levels tend to be associated with short sleep duration and poor sleep quality, it is unclear whether high levels of healthy lipids may be associated with better sleep. Few population-level studies have examined HDL cholesterol and LDL:HDL ratio relative to sleep duration and quality.

METHODS: Data from the 2007-2008 NHANES were used. Participants included individuals who provided blood for lipid assays and responded to sleep questions (N=2594). Sleep symptoms included self-reported difficulty falling asleep, difficulty maintaining sleep, non-restorative sleep, and daytime sleepiness, coded as minimal (<5 days/month), mild (5-14 days/month) or severe (≥15 days/month). Sleep duration and sleep latency were coded in whole numbers. Blood collections and assay procedures were standardized for NHANES; values were mg/dl. Population-weighted multinomial regression analyses examined relationships of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and LDL:HDL ratio to sleep symptoms, adjusting for age, sex, race/ethnicity, education and smoking. Body mass index was added in a separate model. Similar analyses using linear regression evaluated sleep duration and latency.

RESULTS: LDL levels were not associated with any sleep parameters (all $p>0.05$). HDL was negatively associated with severe difficulty falling asleep (OR=0.99,p=0.022), non-restorative sleep (OR=0.99,p=0.033), and daytime sleepiness (OR=0.98,p=0.004), as well as continuous sleep duration (B=0.003,p=0.030). LDL:HDL ratio was associated with severe difficulty falling asleep (OR=1.21,p=0.033). When BMI is added to models, significant relationships were only found between LDL:HDL ratio and severe difficulty falling asleep (OR=1.20,p=0.045).

CONCLUSIONS: HDL cholesterol (and LDL:HDL ratio) may be protective in development of cardiometabolic disease. The present analysis suggests that these are also associated with healthier sleep in the population.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

Trainee Award Eligible

Age-mediated relationship between Prostate Specific Antigen levels and Short and Long Sleep Duration: A cross-sectional study of the United States.

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INTRODUCTION: Prostate specific antigen (PSA) has emerged as a marker of prostate cancer risk among men over age 40. The correlation between PSA and cancer risk increases with age and has been linked to inflammation. Habitual sleep has also been associated with and age, inflammation, and (to a lesser degree) cancer risk; indicating that sleep may influence PSA levels.

METHODS: This study used representative data from the 2007-2008 NHANES. We restricted the sample to males ≥40 years old (N=1,479) who provided analyzed PSA samples and complete data for other covariates. PSA levels were assessed using standardized assays. Sleep duration was assessed using self-reported hours slept, categorized as ≤4, 5, 6, 7, 8, 9, and ≥10hrs. Age was grouped in 5-year bins from 41-80+. Covariates included race/ethnicity, education, income, smoking, body mass index, and log c-reactive protein levels. Population-weighted linear regression, with log PSA levels as outcome and sleep duration as predictor (reference=7h) were conducted across age groups.

RESULTS: The age*sleep duration interaction was significant (p<0.0001), justifying stratified analyses. Among those age 41-45, PSA was lower in 9h (B=-0.652;95%CI=[-0.997,-0.308];p<0.0001) and ≥10h(B=-0.311,95%CI=[-0.612,-0.011]p=0.042). PSA was higher in 9h (B=0.804;95%CI=[0.177,1.430];p=0.012) among those 46-50. Similarly, PSA was higher in 8h(B=0.478;95%CI=[0.010,0.947];p=0.045) and 9h(B=0.648;95%CI=[0.196,1.099];p=0.005) among those 51-56. PSA was lower in 9h (B=-0.648;95%CI=[-1.250,-0.047];p=0.035) for participants 56-60, and in 5h (B=-0.476;95%CI=[-0.946,-0.007];p=0.047) among participants 61-65. PSA was higher in ≥10h (B=0.814;95%CI=[0.131,1.496];p=0.020) among those 66-70, and those 71-75 (B=1.634;95%CI=[0.021,2.247];p<0.0001). No relationships were found among participants in 66-70 group.

CONCLUSIONS: The association between sleep duration and PSA differs across age groups. The most robust relationships were seen between longer sleep and higher PSA among those aged 66-75 but lower PSA in those ≤45. These could represent cohort effects in reporting, relationships with secondary variables, and changing risk profiles with age.

SUPPORT: This work was supported by the National Heart, Lung and Blood Institute (K23HL110216), the National Institute of Environmental Health Sciences (R21ES022931), and the University of Pennsylvania CTSA (UL1RR024134).

Trainee Award Eligible

The neuropeptidergic regulation of C.elegans sleep behaviors

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C. elegans is the simplest animal known to sleep. The worm grows from an embryo to adulthood in 2 days and possesses a mere 302 neurons. These facts coupled with powerful genetic tools make C.elegans a unique model for the dissection of sleep regulation with single cell resolution. We have identified a single neuron type, called RIA, that regulates the sleep/wake balance in C.elegans (Nelson et al. Nature Communications. 2014). Interesting, RIA has both sleep-promoting and wake-promoting functions. RIA expresses a somnogenic neuropeptide, NLP-22, and chronic removal of RIA, using a genetic ablation, results in reduced sleep. However, RIA also expresses NLP-2, deletion of which increases sleep and over-expression of which inhibits sleep; in addition, acute optogenetic activation of RIA promotes wakefulness. How can we reconcile a single neuron having both sleep- and wake-promoting properties? Hendricks et al have shown that dynamic calcium compartmentalization exists within RIA (Hendricks et al. Nature. 2013), emphasizing the signaling complexity within this single cell. We propose that RIA releases the two different neuropeptides under distinct physiological conditions and in response to different signaling pathways. Intriguingly, NLP-2 peptides are very similar to NLP-22 peptides, differing by only a few amino acids, suggesting that evolutionary changes in single amino acid residues can dramatically affect an animal's behavior. Also, surprisingly, both peptides can bind to the same G-protein coupled receptor, encoded for by the gene gnrr-3, in in vitro cell culture assays (Frooninckx L and Schoofs L, personal communication), suggesting a possible antagonistic relationship with the same receptor. Thus, the RIA neuron is a central component of sleep/wake regulation in C. elegans.

Trainee Award Eligible

Acute dietary alterations changes sleep/wake architecture in mice

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There is a strong association between sleep and metabolism, though most studies have focused on how sleep disruption impacts metabolic function. Exploring the reciprocal relationship-how acute dietary changes influence sleep architecture-will complete our understanding of the sleep and metabolism interaction and may provide novel therapies for patients with sleep disorders and metabolic syndromes, including obesity. In this study, we used a within-animal approach to investigate how acute dietary manipulations affect sleep/wake behavior. Briefly, adult mice were implanted with EEG/EMG electrodes and baseline sleep was recorded. Following baseline sleep recording, mice were randomized to either a 25-hour food removal (FR) or one week of high fat diet (HFD). Mice were then returned to regular chow for one week before being switched to the other dietary manipulation. Diet had differential and significant effects on total wake time in the dark phase ($p < 0.01$, Friedman), with FR trending towards increased wake ($p < 0.08$, Wilcoxon Rank). HFD mice displayed increased sleep fragmentation in the dark phase, evidenced by increased wake bout number and decreased wake bout length ($p < 0.02$ and $p < 0.04$, respectively). Additionally, the multiple sleep latency test showed a significant diet interaction for sleep propensity at the beginning of the dark phase ($p < 0.05$). Diet did not affect total wake and sleep time during the light phase. Taken together, this study provides a foundation for exploring molecular mechanisms and brain regions that influence diet-induced changes in sleep/wake architecture.

Trainee Award Eligible

Stability of Energy Balance Responses to Sleep Restriction over Long Time Intervals

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Introduction: We have recently shown that sleep restriction (SR) leads to weight gain, increased caloric intake and late-night eating. However, not all subjects respond to SR to the same degree (e.g., some gain a significant amount of weight while others maintain or lose weight). The aim of the current study was to examine if the weight gain and caloric-intake responses to SR are stable over time.

Methods: N=17 healthy subjects (22-50 y, 19-30 BMI, 8 females) participated in a protocol including 2 baseline nights (BL1-2; 10-12h time in bed [TIB]/night) followed by 5 consecutive SR nights (4h TIB/night) during two separate laboratory experiments. Of these subjects, caloric intake was measured during both occasions for n=10 (4 females). The duration between the two experimental exposures to SR ranged from 1.7 to 68.5 months (median=10 months). Weight was measured at protocol admittance and discharge. Food/drink consumption was ad libitum and the amount and time each item was consumed was recorded daily. 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.

Results: Although there was considerable variability between subjects in terms of weight gained during the study and increased caloric intake during SR, there was considerable stability within subjects, as evident by high ICCs: weight change during the study (ICC=0.79), increased caloric intake during SR (SR intake – BL intake, ICC=0.70), and caloric intake during late-night hours (2200h-0400h, ICC=0.94).

Conclusion: As is true for neurobehavioral measures, the energy balance response to SR may be a trait-like characteristic: certain individuals more prone to weight gain, increased caloric intake and late-night eating than others. The results are relevant for predicting energy balance responses in individuals who are exposed to acute SR, chronically or intermittently, across months and years.

Support: NIH R01 NR004281, F31 AG044102; CTRC UL1RR024134; ONR N00014-11-1-0361

Proapoptotic signaling in young and aged locus coeruleus following chronic sleep fragmentation

Anna Stern and Nirinjini Naidoo PhD

Sleep disturbances are a common concern among the elderly population, with older individuals frequently reporting nocturnal awakenings and daytime sleepiness resulting in a fragmented sleep/wake cycle. However, little is known regarding the impact of sleep fragmentation on neuronal health over aging. Using a mouse model, we showed previously that aging impairs the adaptive component of the unfolded protein response (UPR) – a quality control mechanism that is critical for maintaining protein homeostasis – specifically in response to sleep deprivation. We also demonstrated a particular vulnerability of wake-active locus coeruleus neurons, which in aged but not young mice showed evidence of pro-apoptotic signaling in response to acute sleep fragmentation. Here, we extend these experiments to determine the effects of chronic sleep fragmentation on protein homeostasis and the unfolded protein response in aged locus coeruleus, with a particular focus on pro-inflammatory and pro-apoptotic signaling pathways.

Trainee Award Eligible

PREVALENCE OF PERIODIC LIMB MOVEMENTS DURING SLEEP IN NORMAL CHILDREN

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Introduction: There is a lack of community derived data regarding the prevalence of periodic limb movements during sleep (PLMS) in children. Previous studies based on clinical samples, such as children referred to sleep clinics or diagnosed with attention deficit-hyperactivity disorder, have estimated the prevalence of a PLMS index (PLMI) ≥ 5/hour between 1.2 and 11.9%. However, normative data based on the general population are unknown. Therefore, the aim of this study was to determine the prevalence of PLMS in a sample of normal children.

Methods: 195 healthy, non-snoring children aged 5-17 years recruited from the community for research purposes underwent polysomnography. Data were analyzed with descriptive statistics, t-tests and chi square tests as appropriate.

Results: The group age (mean + SD) was 12.4 + 3.1 years, BMI z-score was 0.6 + 2.6, and 58% were male. Sleep architecture was normal, and the obstructive apnea hypopnea index was 0.2 + 0.3/hour. PLMI median (range) was 0(0-35.5)/hour. Fifteen participants (12 male vs. 3 female, $p<0.0001$), aged 12.7 + 2.7 years had PLMI ≥ 5/hour, resulting in a prevalence of 7.7%. Five subjects had PLMI ≥ 10/hour. Results were further analyzed by age: 100 school-aged children (5-12 years) and 95 adolescents (13-17 years). Five school-aged children, all male, had PLMI ≥ 5/hour (prevalence 5%) vs. 10 (7 males, 3 females, prevalence 10.5%) adolescents ($p = 0.15$).

Conclusions: This study provides normative data to the field. Elevated PLMS were infrequent in this sample of normal children recruited from the community, but were more prevalent in males than females. However, there were no significant differences between younger and older children. Further research aimed at understanding the pathophysiology of PLMS in otherwise normal children is warranted.

Support: RedCap and everybody's grants,

CTRC: NIH UL1RR024134

AHA 10CRP376001

Regulation of feeding quiescence during sleep in C. elegans

Trojanowski N, Fang-Yen C, Raizen D

During sleep, feeding stops. In sleep-related eating disorder, humans eat during sleep time despite maintaining other features of sleep such as reduced responsiveness. Hence, feeding quiescence is a clinically-important and under-studied subprogram of sleep. We study feeding quiescence during sleep in the nematode Caenorhabditis elegans. The C. elegans nervous system, which contains 302 neurons whose connections are all known, communicates via neurochemicals remarkably similar to those used by mammalian neurons and regulates complex behaviors similar to those seen in mammals, including sleep. C. elegans sleep occurs during a larval transition period called lethargus and demonstrates behavioral and molecular genetic similarities to mammalian sleep (Raizen et al., Nature 2008). C. elegans feed on bacteria via pharyngeal contraction/relaxation movements, called pumps. The pharyngeal nervous system consists of 20 neurons of 14 types, and makes only one connection to the somatic nervous system. Pharyngeal pumping occurs continuously throughout the animal's life except during lethargus. The mechanism by which feeding is inhibited during C. elegans lethargus is unknown. The Raizen lab has recently identified three neuropeptides – NLP-22, NLP-29, and FLP-13 – that promote feeding quiescence when over-expressed. I focused initially on understanding the function of the C. elegans feeding circuit and then used this information to understand how feeding quiescence is regulated during lethargus and in response to somnogenic neuropeptide over-expression.

I developed an optogenetic approach to dynamically manipulate neural circuits at single neuron resolution in intact, behaving animals. I use a digital micromirror device to shine laser light onto individual neurons expressing light-sensitive ion channels and pumps and developed a machine vision approach to measure pumping rate in response to such optogenetic manipulations (Trojanowski et al, J. Neurophys., in press). I have shown that two pairs of bilaterally symmetric cholinergic neuron types, called MC and M2, directly stimulate pumping, and therefore can be considered motor neurons. I have further shown that the paired cholinergic I1 interneurons are excitatory to both MC and M2. These data are consistent with prior ultrastructural reconstructions of the pharyngeal nervous system: The MC and M2 neurons form gap junctions on each other and chemical synapses on the muscle, and the I1 interneuron forms chemical synapses on MC and M2.

To test whether feeding quiescence during lethargus is modulated at the level of the nervous system, I optogenetically stimulated the MC and M2 motor neurons during lethargus. Stimulation of neither neuron type resulted in pharyngeal pumping, indicating that the modulation of feeding quiescence during lethargus occurs downstream of motor neuron excitation, perhaps at the level of pharyngeal muscle. I used similar logic to identify the circuit point at which feeding is blocked by neuropeptide over-expression. I found that adult animals over-expressing either NLP-22 or NLP-29 behave much like wild-type animals in lethargus: optogenetic excitation of the pharyngeal motor neurons did not elicit pumps. By contrast, in animals over-expressing FLP-13, either MC or M2 excitation was sufficient to stimulate rapid pharyngeal pumping, indicating that FLP-13 acts on the nervous system. The effect of FLP-13 on the pharyngeal nervous system may be humoral and not synaptic because it persisted after I laser-ablated the single connection between the somatic and pharyngeal nervous systems.

A direct comparison of three sleep acquisition systems

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Abstract:

Sleep is conserved across phyla and can be measured through electrophysiology or behavioral hallmarks. The fruit fly, Drosophila melanogaster, provides an excellent model for investigating the genetic and neural mechanisms that regulate sleep. Multiple systems for precise measurement of fly behavior, including video analysis and single-beam infrared-based (IR) monitoring, have been reported. Video acquisition determines the precise location of flies, but requires resource- and labor-intensive analysis, while single beam infrared-based recording is commercially available and efficient, but reportedly overestimates sleep. Recently, a more sensitive IR-based monitoring system was developed. A direct comparison of acquisition methods for measuring complex variables associated with sleep, including aging, sleep-location preference, and feeding state has not been performed across all three acquisition systems. Here, we directly compare sleep in individual flies using a custom-built video-based acquisition system, and 1- and 17-beam based infrared tracking. Our results confirm previous findings, suggesting that single beam infrared-based recordings overestimate sleep, but find these inaccuracies are dramatically reduced using the 17-beam system. In addition, we find that single beam infrared-based recordings misrepresent other qualities of sleep such as number of sleep bouts and average bout length, and that the 17-beam system more accurately represents these aspects of sleep. Lastly, both 17-beam infrared-based monitoring and video monitoring add the benefit of being able to measure complex variables such as sleep-location preference. These findings provide the basis for choosing between different sleep acquisition systems in Drosophila.

Short Sleep Duration and Financial Stress: Pathways to Obesity

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INTRODUCTION: Many previous studies have linked habitual short sleep duration to obesity. Other studies have linked habitual sleep to food insecurity (food-related financial stress), which has itself been associated with inability to obtain nutritious meals, leading to obesity. Data is needed to further examine the relationship of sleep duration to financial stress and the possible role in obesity.

METHODS: Data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) was used. The BRFSS is a state-based telephone survey conducted by the CDC. Sleep duration was assessed as total 24-hour habitual sleep, coded as ≤4, 5-6, 7-8 (reference), and ≥9 hours. Housing-related financial stress was assessed with, "How often in the past 12 months would you say you were worried or stressed about having enough money to pay your rent/mortgage?" and food-related financial stress was assessed with, "How often in the past 12 months would you say you were worried or stressed about having enough money to buy nutritious meals?" Responses were coded as Never (reference), Rarely, Sometimes, Usually, or Always. Obesity was based on BMI ≥30. Logistic regression analyses examined relationships between sleep, housing-related and food-related financial stress, and obesity, adjusted for age, sex, race/ethnicity, education, employment, smoking, alcohol use, and state. A Sobel test examined partial mediation. All tests use BRFSSS sample weights.

RESULTS: Housing-related financial stress was associated with sleep duration. Those reporting problems "Rarely" were less likely to report ≥9hrs (OR=0.784,p=0.013), problems "Sometimes" were associated with ≤4hrs (OR=1.459,p=0.003) and 5-6hrs (OR=1.313,p<0.0001), problems "Usually" were associated with ≤4hrs (OR=2.615,p<0.0001) and 5-6hrs (OR=1.634,p<0.0001), and problems "Always" were associated with ≤4hrs (OR=4.121,p<0.0001), 5-6hrs (OR=1.666,p<0.0001), and ≥9hrs (OR=1.436,p=0.001). Food-related financial stress was also associated with sleep duration. Those reporting problems "Rarely" were more likely to report 5-6hrs (OR=1.202,p<0.0001), problems "Sometimes" were associated with ≤4hrs (OR=2.224,p<0.0001), 5-6hrs (OR=1.294,p<0.0001), and ≥9hrs (OR=1.209,p=0.021, problems "Usually" were associated with ≤4hrs (OR=2.907,p<0.0001) and 5-6hrs (OR=1.765,p<0.0001), and problems "Always" were associated with ≤4hrs (OR=5.250,p<0.0001) and 5-6hrs (OR=1.810,p<0.0001), and ≥9hrs (OR=1.436,p=0.001). When combined in the same model, both stress variables explained unique variance in sleep duration. Logistic regression analyses also showed that both financial stress variables were associated with obesity. Mediation analyses showed that housing-related financial stress explained approximately 1.7% of the relationship between sleep duration and obesity and food-related financial stress explained approximately 6.7% of the relationship (both Sobel p<0.0001).

CONCLUSIONS: Both housing-related and food-related financial stress are associated with sleep duration (mostly shorter sleep duration). Further, they both represent unique pathways through which short sleep duration is associated with obesity. Although the majority of the relationship may be due to physiologic pathways directly related to sleep, these findings may suggest independent, modifiable pathways linking short sleep duration and obesity.

The Relationship between Long Work Hours and Obesity is Partially Mediated by Sleep Duration

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INTRODUCTION: Identifying modifiable risk factors for obesity is a major public health concern. Recently, sleep duration and long work hours have both been shown to be related to obesity and other health problems. Despite studies showing long work hours being associated with short sleep duration, the role of sleep in the relationship of long work hours to health has not been explored.

METHODS: Data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) was used. The BRFSS is a state-based telephone survey conducted by the CDC. Data on sleep and work hours was available from Hawaii, Illinois, and Louisiana. A total of N=9,756 individuals provided complete data and were included in analyses. Sleep duration was assessed as total 24-hour habitual sleep, coded as a continuous variable (truncated at 4 and 10 hours) and categorically (≤4, 5-6, 7-8 (reference), and ≥9 hours). Average work hours per week was assessed continuously and categorically (<40, 40 (reference), 41-60, and >60 hours). Obesity was based on BMI ≥30. Logistic regression analyses examined relationships among sleep, work hours, and obesity, adjusted for age, sex, race/ethnicity, education, smoking, alcohol use, and state. A Sobel test examined partial mediation. All tests use BRFSSS sample weights.

RESULTS: Work hours were related to obesity. For each hour worked, risk of obesity increased (OR=1.010, 95%CI 1.006-1.015, p<0.0001); categorically, <40 hours was associated with decreased likelihood of obesity (OR=0.823, 95%CI 0.711-0.952, p=0.009) and >60 hours was associated with increased likelihood (OR=1.42, 95%CI 1.106-1.823, p=0.006). Sleep duration was related to obesity. For each hour of sleep reported, risk of obesity decreased (OR=0.906, 95%CI 0.879-0.934, p<0.0001); this was also seen categorically, with increased likelihood of obesity among those sleeping ≤4hrs (OR=1.928, 95%CI 1.495-2.485, p<0.0001) and 5-6hrs (OR=1.332, 95%CI 1.205-1.473, p<0.0001). Work hours predicted sleep duration. Each hour of work was associated with increased likelihood of ≤4hrs (OR=1.024, 95%CI 1.008-1.042, p=0.004) and 5-6hrs (OR=1.017, 95%CI 1.011-1.023, p<0.0001), and decreased likelihood of ≥9hrs (OR=0.972, 95%CI 0.959-0.985, p<0.0001). Categorically, those working <40hrs were more likely to be ≥9h sleepers (OR=2.081, 95%CI 1.441-3.004, p<0.0001), those working 41-60hrs were more likely to be 5-6h sleepers (OR=1.447, 95%CI 1.206-1.735, p<0.0001) , and those working >60hrs were more likely to be ≤4hr (OR=4.136, 95%CI 1.594-10.729, p=0.004) and 5-6hr (OR=3.110, 95%CI 2.100-4.604, p<0.0001) sleepers. When the models were combined, sleep duration accounted for 17.33% of the relationship between work hours and obesity (Sobel=3.448, p=0.0006).

CONCLUSIONS: Both long work hours and sleep duration are associated with obesity. Further, experiencing long work hours is associated with shorter sleep duration. The relationship between long work hours and obesity is partially explained by the relationship with short sleep duration.

A novel role of the ancient casein kinase 1 in synchronizing the circadian clock network

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Casein kinase 1, known as DOUBLETIME (DBT) in Drosophila, is a critical component of the circadian clock that phosphorylates and promotes degradation of the PERIOD (PER) protein. However, other functions of DBT in circadian regulation are controversial, in part because severe loss of dbt causes pre-adult lethality. Here we report the molecular and behavioral phenotype of a viable dbtEY02910 loss-of-function mutant. We found that most mutant flies display arrhythmic behavior, with a few showing weak, long period (~32h) rhythms. Peak phosphorylation of PER is delayed, and both hyper- and hypo-phosphorylated forms of PER and CLOCK proteins are present throughout the day. In addition, molecular oscillations of the circadian clock are dampened. In the central brain, PER and TIM expression is heterogeneous and decoupled in the clock neurons of the dbt mutants. These data thus demonstrate that overall reduction of DBT causes long and arrhythmic behavior and reveal an unexpected role of DBT in promoting synchrony of the circadian clock network.