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# Chronobiology

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## ABSTRACTS

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Guest Editors

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## A1

**The Effect of Systematic Light Exposure to Reduce Cancer-Related Fatigue (CRF) in Women Treated for Breast Cancer: A Randomized Controlled Trial of Circadian Active versus Inactive Light Stimulation**

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**Background:** Cancer-related fatigue (CRF) is among the most common and distressing late effects in women treated for breast cancer. Unfortunately, there is no standard treatment available for CRF. It has been hypothesized that circadian disruption may be an underlying pathophysiological mechanism of CRF and emerging evidence has shown that circadian stimulating light can be effective in reducing CRF in long-term cancer survivors.

**Study Aim:** The aim of the present study was to investigate the efficacy of circadian stimulating light to treat CRF in women recently treated for breast cancer.

**Methods:** Eligible women were screened for CRF at two months post-radiotherapy. Clinically fatigued (FACIT-Fatigue $\leq$ 33) and consenting participants were randomized to either 4 weeks of circadian active morning white light (10,000 K, 1500 lux) or a red light comparison condition. Assessments were undertaken at pre-intervention (T1), two weeks after (T2), immediately post-intervention (T3), and two months later (T4). Assessments included questionnaires, actigraphy, saliva sampling, blood draws, neuropsychological assessments, and structural MRI scans. Only questionnaire data are included in the present analyses. Mixed linear models (MLM) were used to examine the primary outcome (FACIT-Fatigue). The study was preregistered at ClinicalTrials.gov (NCT02661308) and approved by the Regional Committee on Health Research Ethics.

**Results:** Based on power analyses, 72 women were recruited and enrolled in this trial. Mean baseline fatigue was 27.96 (SD = 6.19). No baseline differences were observed between comparison groups on age, education, cancer treatments, or CRF (all  $ps > 0.05$ ). MLM revealed a statistically significant main effect of time on CRF ( $p < 0.0001$ ; T1: 27.96, SE = 0.72; T2: 32.81, SE = 0.81; T3: 35.33, SE = 0.83; T4: 36.82, SE = 0.85). No statistically significant time-by-group interaction was observed for CRF ( $p = 0.52$ ). Sixty-eight percent of participants experienced clinically meaningful reductions in CRF.

**Conclusions:** Light exposure resulted in large and clinically meaningful reductions in CRF. No differences were observed between light conditions. The overall improvements in CRF could be attributed to spontaneous recovery during the study period, placebo effects, specific therapeutic effects common to both conditions, or a combination of these factors. We are currently in the process of recruiting a post-hoc treatment-as-usual comparison group to further investigate these potential explanations.

## A2

**Synchrony of Sleep-Wake Cycles with Lunisolar Gravitational Force Changes in a Rapid-Cycling Bipolar Patient**

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**Background:** In a previous paper we described the synchrony of a bipolar patient's sleep wake cycles with the lunar tidal cycles. However, in that report, estimates of the actual gravitational forces were not made. Study aim. We sought to reanalyze the data using a computer program (ETIDE) that accurately calculates the gravitational forces at any time and place on earth.

**Methods:** We used the ETIDE program to calculate the lunisolar gravitational forces for Seattle, Washington, USA, from August 1 to Nov 30, 2004 when the bipolar patient kept a sleep log. We plotted the times of the highest (HGrav) and lowest (LGrav) gravitational forces for each day as well as the times of the maximum rates of negative change (MaxNeg) for each day in relation to the sleep log data.

**Results:** The sleep durations varied from 0 to 12 hours with a 14.8-day periodicity, which is similar to the period of the spring-neap tidal cycles. Over 9 spring-neap cycles, the sleep onsets would gradually phase delay for about 7.5 days and then phase advance for about 7.5 days; the wake onsets would phase delay for 7.5 days and then advance for about 7.5 days. The phase delays of LGrav preceded and correlated with the phase delays of the wake onsets. The phase delays of HGrav and MaxNeg preceded and correlated with the phase delays of the sleep onsets.

**Conclusions:** These data are consistent with the hypothesis that the synchrony seen between the mood switches and sleep changes seen in rapid-cycling bipolar patients and the lunar tidal cycle are mediated through changes in gravity. Future research can explore what types of changes in gravity might predispose bipolar patients to switches.

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**A3****Health Effects of Year-Round Daylight Saving Time: Would It Create More Circadian Desynchrony?***David Avery*

Psychiatric Medicine Associates, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, USA

**Background:** Year-round Daylight Saving Time (DST) has been proposed in both the United States and the European Union; it is important to consider the health effects, especially effects on circadian rhythms, sleep, and mood.

**Methods:** PubMed articles were reviewed if they contained "Daylight Saving Time".

**Results:** The transition from Standard Time (ST) to DST usually has more adverse health effects than the transition from DST to ST. However, few studies have assessed the effects of year-long DST. In Russia, year-round DST was started in 2011, but was revoked in 2014. During those three years, compared to the years before and after the year-round DST, there were more symptoms of winter depression, social jet lag, and poorer academic performance in children and adolescents. In other settings in which the social clock created a later sunrise in the morning, life expectancy rates are lower, cancer mortality rates are higher, rates of winter depression are higher, and academic test scores of high school students are lower.

**Conclusions:** While there can be adverse effects of the current biannual time changes, one cannot assume that year-round DST would have fewer adverse health effects. Most people have endogenous circadian rhythms with  $\tau$ s greater than 24 hours which are synchronized by morning light. Morning bright light has been found effective for both seasonal and non-seasonal depression. Year-round DST would reduce the natural morning bright light for much of the fall and winter; for most, circadian rhythms would phase-delay relative to sleep, creating circadian desynchrony. There is very little evidence that year-round DST has fewer adverse health effects compared to year-round ST or the current biannual time change system. Year-round DST would be a large-scale experiment with uncertain health benefits and probable adverse health effects.

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**A4****A Randomized, Double-Blind Controlled Clinical Trial of Light Therapy for Pregnant Women with Major Depressive Disorder***Babette Bais*

Erasmus MC University Medical Center, The Netherlands.

**Background:** Generally, 5–10% of pregnant women suffer from depression. Children who have been exposed to maternal depression during pregnancy have a higher risk of adverse birth outcomes and more often show cognitive, emotional and behavioral problems. Therefore, early detection and treatment are necessary.

Bright light therapy (BLT) is a promising treatment, for it combines direct availability, sufficient efficacy, low costs and high safety, for both mother and child.

**Study Aim:** We studied the effects of BLT on depression during pregnancy.

**Methods:** We randomly allocated 67 pregnant women (12–32 weeks pregnant) with a DSM-V diagnosis of depressive disorder to one of the two treatment arms: 33 women received treatment with BLT (9.000 lux) and 34 received treatment with dim red light therapy (100 lux). Both groups are treated for 6 weeks at home on a daily basis for 30 minutes, within 30 minutes of habitual wake-up time. Follow-up takes place weekly during the intervention, after 6 weeks of therapy, 3 and 10 weeks after end of therapy, at birth and 2, 6 and 18 months postpartum. Primary outcome is the average change in depressive symptoms measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version and the Edinburgh Postnatal Depression Scale. Changes in rating scale scores of these questionnaires over time will be analysed using generalized linear mixed models. Ethical approval was obtained.

**Results:** At the conference, we will present our findings, which yet have to be analyzed.

**Conclusions:** If BLT reduces depressive symptoms in pregnant women, it will provide a safe, low cost, non-pharmacological and efficacious alternative treatment for psychotherapy and antidepressants in treating antepartum depression, without any expected adverse reactions for the unborn child.

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**A5****Effects of Extended Darkness on Daytime and Nighttime Melatonin Production in Normotensive and Spontaneously Hypertensive Rats***Mikhail Blagonravov<sup>1</sup>, Anna Bryk<sup>1</sup>, Evgenia Medvedeva<sup>1</sup>, Vyacheslav Goryachev<sup>1</sup>, Sergey Chibisov<sup>1</sup>, Sergey Syatkin<sup>1</sup>, Tatyana Zotova<sup>1</sup>, Galina Varvanina<sup>2</sup>*

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**Background:** Hypertension is often accompanied by disorders of biological rhythms which may also be affected by environmental factors, in particular, a deficiency of daytime light. People living in northern latitudes might be at higher risk. However there is still little data concerning melatonin production under prolonged length of darkness in case of hypertension.

**Study Aim and Objectives:** We investigated daytime and nighttime secretion of melatonin in normotensive and hypertensive rats under extended darkness.

**Methods:** Experiments were carried out on Wistar-Kyoto rat (n = 5) and spontaneously hypertensive rat – SHR (n = 5) strains. The animals were kept under three light-dark schedules: 12 hour light:12 hour darkness (12 h:12 h), 20 hour darkness:4 hour light (20 h:4 h) and 24 hour darkness (24 h:0 h). Melatonin secretion was assessed by measuring concentrations of 6-Sulfatoxymelatonin (6-SMT) in daytime and nighttime urine using ELISA kit for

6-Sulfatoxymelatonin (Buhmann Laboratories AG, Switzerland). The study was approved by the authors' institution local ethical committee.

**Results:** Under 20 h:4 h schedule neither daytime nor nighttime urinary concentrations of 6-SMT were different compared with 12 h:12 h schedule. The difference between daytime and nighttime concentrations of 6-SMT was seen both under 12 h:12 h and 20 h:4 h schedules. However in case of 24 hour darkness daytime concentrations of 6-SMT significantly decreased in comparison with 12 h:12 h pattern in both groups of animals. But nighttime values had no differences between 12 h:12 h and 24 h:0 h schedules in both groups.

**Conclusions:** 24 hour darkness has a negative effect on daytime melatonin production both in cases of normal blood pressure and under hypertension. Nighttime melatonin secretion and its circadian rhythm are not affected.

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## A6

### Are We Still in the Dark? A Systematic Review on Light Exposure, Sleep and Mood in the General Population

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**Background:** We are told that light exposure is essential for health. Bright light therapy is prescribed as treatment for mood and sleep disorders, and is proven to be effective in treating these disorders. But what is the relationship of personal light exposure, sleep and mood in the general population? The current systematic literature review aims to answer this question.

**Methods:** Five electronic databases were searched up to November 2017, with light exposure-, mood- and sleep related search terms. Personal light exposure had to be measured during the waking day of the participants and had to be included in the analyses with sleep and/or mood outcomes. Quality of all included articles were assessed.

**Results:** The search resulted in 6990 references, of which a total of 21 were included in this review. Three studies received an overall "good" quality rating, 13 studies were rated as "fair" and five studies were rated as "poor". Personal light exposure was most often measured using a wrist worn light cell. Weak to no relationships were found for personal light exposure and sleep architecture, bedtimes, sleep duration, sleep onset latency, depression and affect. The only consistent relationship was found between more personal light exposure and less waking after sleep onset, better sleep quality and less sleep disturbances.

**Conclusions:** The studies included in this review are methodologically weak, and results on the relationship between personal light exposure, mood and sleep in the general population are inconclusive. Previous statements about the effects of light on health are based on results of intervention studies in clinical

populations, but do not seem to generalize to the general population. Better studies on this topic in the general population are needed.

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## A7

### Bright-Study: The Effect of Dynamic Indoor Lighting on Sleep and Mood in Elderly with Intellectual Disabilities Living in Group Home Facilities

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**Background:** The circadian sleep-wake rhythm of elderly with intellectual disabilities (Elderly-ID) is unstable and fragmented. Light exposure is essential for the circadian sleep-wake rhythm. Daytime light exposure in elderly-ID is however low. In the Bright-study, dynamic indoor lighting was installed in 6 group home facilities for elderly-ID. The effect of the lighting on the sleep-wake rhythm, sleep and mood in the residents was studied.

**Methods:** 54 participants (63.42 ± 8.6 years, 65% female) of 6 group home facilities were included. All participants had 3 baseline measurements in week 1, 5 and 9 of the study. Lighting was installed in study week 10 and intervention measurements took place in study week 12, 17 and 24. Stability (IS) and fragmentation (IV) of the circadian sleep-wake rhythm and sleep (total sleep time, waking after sleep onset) were measured using actigraphy (GeneActiv, ActivInsights, UK). Depressed mood was measured using the Anxiety, Depression and Mood Scale (ADAMS).

**Results:** Preliminary analyses showed a decrease in ADAMS depression scores from baseline to intervention measurements. Actigraphy variables of the sleep-wake rhythm and sleep did not change over time. The final results are expected in June 2019.

**Conclusion:** Preliminary results suggest that dynamic indoor light is effective in improving mood in elderly-ID. The intervention may not be effective to improve the sleep-wake rhythm, or such improvements take longer to develop.

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A8

**The Impact of a Wrist Worn Activity Monitor on Heart Rate, Pulse Pressure, Self-Reported Stress and Mindfulness Among Low-Income African-American Women with a History of Depression**

Inger Burnett-Zeigler

Northwestern University, USA

**Background:** Low-income African-American women are disproportionately exposed to chronic stress which is associated with physiological changes such as rapid breathing, increases in blood pressure and heart rate. Mindfulness-based interventions have been associated with decreases in blood pressure, heart palpitations, and heart rate among patients with cardiovascular issues and healthy individuals. The objectives of this study were to: 1) Compare physiological measures of stress including heart rate and pulse pressure collected via a wrist worn activity monitor with self-report assessments of mindfulness, stress, depression and trauma symptoms and 2) Assess pre-post changes in physiological and self-report measures of stress among participants in a pilot mindfulness maintenance intervention.

**Methods:** Thirty-nine African-American women with depressive symptoms who previously participated in an eight-week mindfulness group intervention enrolled in the study and wore an activity monitor for eight-weeks. Heart rate and pulse pressure were continuously collected via the activity monitor. Mindfulness, stress, depression and trauma symptoms were collected via self-report surveys at baseline and 8-weeks. Participants were instructed to practice mindfulness skills when the activity monitor notified them that they were stressed (standard deviation of pulse pressure). Data analysis was performed on the 19 participants who wore the watch for 50% of the days for four or more hours per day.

**Results:** There were no significant changes in the physiological measures or on the self-report measures of stress, depression, post-traumatic stress and mindfulness from baseline to eight-weeks. However, those who were high on the non-judge mindfulness subscale had a lower standard deviation pulse pressure and spent less of their time stressed.

**Conclusion:** More research is needed to explore how activity monitors may be used to increase mindfulness practice and reduce physiological indicators of stress in a high stressed population.

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A9

**Chronobiology and Sleep, Non-Image Forming Aspects of Light**

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**Background:** The discovery of melanopsin (OPN4), a photopigment maximally sensitive to the short-wavelength spectrum of light (peak sensitivity at 480 nm) and expressed in a subset of photosensitive retinal ganglion cells (pRGCs) in the eye, has paved the ground to better understand the non-image forming (NIF) effects of light. Besides photic resetting of the circadian clock, artificial light striking the retina between dusk and dawn impacts on neurons that regulate sleep-wake cycles, by inhibiting sleep-promoting neurons and activating arousal-promoting orexin neurons in the hypothalamus.

**Methods:** A substantial body of literature now confirms involvement of melanopsin in producing these changes in sleep:wake systems and driving other NIF responses. However, the retinal cells that contain melanopsin also receive input from rod and cone photoreceptors and these conventional photoreceptors can also contribute to NIF responses. It is thus currently unclear whether merely changing the activity of melanopsin would be sufficient to regulate the effects of light on human behavior and physiology.

**Results:** Here we discuss recent studies and unpublished data on the significance of different physical characteristics of artificial light (i.e. illuminance, melanopsin contrast, daylight-mimicking spectral components, and temporal dynamics) on human sleep, circadian physiology and neurobehavioral performance.

**Conclusions:** The overall aim of a proper lighting is to selectively modulate the degree of melanopsin excitation without impacting either its color or effective brightness. Accordingly, besides vision as the primary goal, the second requirement for any smart lighting system or visual display is to support human circadian physiology and sleep.

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A10

**Neurocognitive Assessment – Sensitivity to Chronotype and Time of Day**

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**Background:** Cognitive tests are a common part of cognitive examination and are key to determining cognitive deficit in neurological and neuropsychiatric disorders. As the patient might be tested at different times during the day, it is important to determine whether the time of the day when the test is performed and the patient's chronotype can affect performance to a clinically significant extent. The aim of this study was to determine whether chronotype affects cognitive functions, especially working memory,

attention and psychomotor pace in relation to time of testing in healthy volunteers of extreme chronotype.

**Methods:** We enrolled 14 extreme morning types, 14 extreme evening types and 14 participants of intermediate chronotype on the Morningness Eveningness Questionnaire (MEQ). Participants received cognitive testing in the morning (8 AM) and evening (8 PM). Body temperature was assessed using iButton thermochrons and physical activity with wrist actigraphy. Performance on neurocognitive testing from the Stroop, subtests of WAIS III and digit span (WMS III), was evaluated. Participants were tested on two separate days during the weekend. Statistical analysis was performed using SPSS, GraphPad Prism, and Actilife programs. The study was approved by the Ethical Committee of the author's institution.

**Results:** We found differences in performance at subjective-preferred and non-preferred time based on chronotype. Number of tests sensitive to time, day and chronotype interactions were detected from the complete test battery.

**Conclusions:** There is a potential risk for misinterpretation of the results from neuro-cognitive assessment without prior knowledge of the patient's chronotype. Chronotype should be taken into account before cognitive testing.

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## A11

### The Effect of Systematic Light Exposure on Vigilance and Attention in Clinically Fatigued Women Recently Treated for Breast Cancer

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**Background:** Cancer-related fatigue (CRF) is among the most distressing symptoms both during and after breast cancer treatments. CRF is associated with neurobehavioral symptoms such as impairment of cognitive functions, including vigilance and attention, which are fundamental for higher-level cognitive processes. Evidence suggests that CRF may be associated with disrupted circadian rhythms and that exposure to circadian-active light can reduce CRF.

**Aims:** In the present, we investigate whether exposure to circadian-active morning bright light improves vigilance and attention in a group of clinically fatigued women recently treated for breast cancer.

**Methods:** Seventy-two women were screened for CRF with the FACIT-Fatigue scale (FFS) at two months post-treatment and allocated to an intervention of either 4 weeks of circadian-active morning white light (10.000 K, 1500 lux) or a comparison red light condition. Vigilance and attention were measured with a brief (5 minute) version of the psycho-motor vigilance test (PVT), a well-

established test of sleep- and fatigue-related cognitive deficits. All participants completed the PVT and FSS at pre-intervention (T1) and immediately after intervention completion (T2). Between-group differences across time (interactions) were statistically analyzed for the following PVT outcomes: mean and median reaction time (RT); minor lapses; speed (1/RT); and fastest 10% RT. The study was preregistered at ClinicalTrials.gov (NCT02661308) and approved by the Regional Committee on Health Research Ethics.

**Results:** Results revealed a statistically significant main effect for time on FSS and all of the selected PVT outcomes ( $p$ 's < 0.05) indicating improvements across time (e.g. T1-FSS = 28.1 [6.1]; T2-FSS = 35.4 [7.0]; T1-meanRT = 287.3 [49.6]; T2-meanRT = 270.8 [44.2]). However, improved performance on the PVT (mean RT) was not associated with reductions in CRF ( $r$  = -0.2,  $p$  = 0.12). No statistically significant between-group differences were observed from T1 to T2 on any of the PVT outcomes (all  $p$ 's > 0.05).

**Conclusions:** Our results suggest an overall improvement in vigilance and attention following light therapy, which was not associated with reductions in cancer-related fatigue. There were no differences in improvements on vigilance and attention between the light conditions. The observed overall improvements can be attributed to either retest and learning effects of repeated cognitive testing, placebo effects or real therapeutic effects of both light interventions.

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## A12

### A Close Look at Acute Diurnal Effects of Light Exposure

Yvonne de Kort

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**Background:** Acute diurnal effects are probably the least understood and least consistent among non-image forming effects. Whereas we have a quite good – although admittedly not complete – understanding of the mechanism behind circadian effects and can even predict effects multiple days ahead based on quite advanced mathematical models, the mechanism behind acute effects is still largely unknown and no modelling attempts have been made so far. Over the past year or so, we have seen three reviews of acute effects appear (Lok, Smolders, Beersma & de Kort, 2018; Souman, Tinga, Te Pas, Van Ee & Vlaskamp, 2018; Xu & Lang, 2018), all of which conclude that findings are inconsistent. Moreover, two attempts at constructing a dose response curve for daytime exposure have failed to deliver indications of required minimal light effects, or a saturation point (Lok, Woelders, Gordijn, Hut & Beersma, 2018; Smolders, Peeters, Vogels & de Kort, 2018).

**Aim and Objectives:** So where do we go from here? All above mentioned papers call for investigating further individual differences, timing and duration dependency, and other task and condition characteristics. Some of those have or are already being made. In this presentation, I would like to explore some important questions to consider in continuing this line of research. Reviewing the current literature and their methodology, we should perhaps ask ourselves what we exactly should be looking at, and, equally important, when? Also, I will reflect on the question whether, in

spite of, or perhaps even inspired by, the many inconsistencies, we can attempt to draw some conclusions or hypotheses regarding underlying mechanisms.

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#### A13

### EEG Power Density as a Proxy for Objective Alertness Depends on Spectral Composition and Intensity of Light Exposures During Daytime

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**Background:** There are conflicting reports in the literature about alerting effects of light exposure during daytime. Some of these studies were performed after curtailment of previous sleep. Most studies analyzed subjective alertness measures, but only few have looked at the wake-EEG as an objective measure of alertness.

**Objectives:** The aim of this study was to determine how daytime polychromatic white light exposures that differed in the light spectrum and intensity affected the wake-EEG.

**Methods:** During four laboratory visits 72 healthy participants were exposed to polychromatic white lighting conditions and a control condition (in dim light) starting 3 hours after wake-up (48 female;  $24.4 \pm 2.7$  yrs; mean  $\pm$  SD; within-between-subject design). The lighting conditions differed in peak wavelengths in the shorter wavelength range of the light spectrum (peak at 435 nm or around 480 nm), or in light intensity (i.e. 100 lx, 200 lx, 600 lx, 1200 lx; randomized order). The color temperature was the same for all lighting conditions (= 3500 K) and they were designed to be metameric. Melanopic irradiance was calculated with the new CIE standard (CIE S 026, 2018) and varied between  $0.066 \text{ W/m}^2$  and  $1.513 \text{ W/m}^2$ . Hourly Karolinska Drowsiness Tests (KDT) were performed (5 min closed and 5 min open eyes; 0.5–25 Hz). The study was approved by the local Ethical Committee (Charité University Medicine Berlin, Germany). Analysis was performed by applying mixed linear regression models.

**Results:** Statistical significant differences in EEG power densities were found between lighting conditions of different peak wavelengths and intensities in the KDTs with open eyes (for the theta, alpha, sigma and beta ranges;  $p < 0.05$ ). At low light intensities (100 photopic lux) there was a stronger alerting effect (i.e. stronger reduction in the EEG alpha activity) depending on melanopic irradiance (main effect of light spectrum;  $F_{3,74} = 11.813$ ,  $p < 0.001$ ). At higher illuminance, the impact of spectral compositions and intensity of lighting on EEG power densities were more pronounced in the sigma and beta ranges, with higher melanopic irradiance showing lower EEG power density ( $p < 0.05$ ).

**Conclusions:** These findings show in a large sample size and under controlled laboratory conditions that even in well-rested participants lighting conditions can differentially affect objective alertness measures during daytime, depending on melanopic irradiance.

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#### A14

### Shift Work and Jet Lag: Management of Circadian Rhythm Misalignment with Bright Light, Dark and Melatonin

Charmane Eastman

Rush University Medical Center, USA

**Background:** Shift work and jet travel across time zones produce circadian misalignment because people are forced to sleep at the wrong times relative to their internal circadian rhythms. However, it is possible to trick the circadian clock into delaying (shifting later) or advancing (shifting earlier) to align with the new sleep schedule, and this will reduce or eliminate circadian misalignment.

**Methods:** Phase shifting is done by creating a new light-dark cycle using appropriately timed light boxes, sunlight (if available at the right time), sleep (in a dark room) and sunglasses (for going outside into daylight at the wrong time). Appropriately timed melatonin can also help increase the size of the phase shift.

**Results:** People often use bright light or melatonin at the wrong times for reducing jet lag, by timing them according to local time at the destination rather than the time of their internal circadian clocks. Example schedules for reducing or preventing jet lag will be shown, as will schedules for reducing circadian misalignment for night shift workers. Bright light during the night shift is often required for phase shifting the circadian clock and thus reducing circadian misalignment. Light can suppress melatonin which is secreted at night, and since melatonin is an antioxidant, light at night has been discouraged. But melatonin pills can be taken before the new sleep time allowing for the necessary bright light at night. When the circadian clock is shifted to align with daytime sleep, then melatonin can be secreted naturally. True circadian adaptation to night shift work requires permanent night work or very slowly rotating shift work schedules.

**Conclusion:** Using these techniques for shift work requires changing the beliefs and demands of family, friends, employers, managers, etc. as well as changing the sleep schedules and light exposure of the individual shift worker.

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#### A15

### A Novel Retina-Thalamic Circuit Underlies the Effects of Light on Mood

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**Background:** Light exerts a range of powerful biological effects beyond conscious vision, including circadian regulation, sleep induction and mood control. Alterations in the regular lighting conditions lead to depressive symptoms. It is known that intrinsically photosensitive retinal ganglion cells (ipRGCs) drive photic information to modulate mood in mice; however, the central mediators are unknown.

**Aim:** Delineate the retina-brain circuit by which light affects mood.

**Methods:** Mice were housed for 2 weeks under an alternating cycle of light and dark exposure (3.5 hours each). We used genetic, anatomical and functional tools to define the circuits driving the effects of abnormal light on affective behavior.

**Results:** We revealed that the effects of abnormal light on mood are independent of the central pacemaker function. Moreover, we found that a previously unrecognized thalamic region, termed perihabenular nucleus (PHb), is both necessary and sufficient for driving the effects of light on affective behavior. Thalamic PHb receives dense ipRGC innervation and is integrated in a distinctive circuitry with mood-regulating centers, including the prefrontal cortex.

**Conclusions:** Our results provide evidence for a novel retina-brain circuit that mediates the effects of abnormal light on mood in mice. Mapping the neural circuits by which light affects behavior is a promising step towards new treatments for affective disorders associated with abnormal light exposure.

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## A16

### **Light and Vitality: Effects of Bright Office White Light on Workers' Performance, Well-Being, Sleep and Appreciation**

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**Background:** The study objective was to compare the effects between a dynamic pattern and a static situation as defined in offices' guidelines on workers' performance, well-being, sleep and appreciation.

**Methods:** After baseline measurements at a temporary working place and moving to renovated floors, data was collected for 3 consecutive weeks per condition, static versus dynamic, in a cross-over design fashion. The main differences between conditions resided in the morning boost: about 100 lux and 226 lux melanopic-EDI, respectively, in the absence of outdoor lighting and at eye level. Number of participants (depending on variable) varied between 11 and 33. A waiver was obtained from the Medical Ethical Committee.

**Results:** Compared to baseline, mood (1.7 score higher on a 10-point scale,  $p < 0.01$ ) and all visual related outputs improved after moving to the new situation. No significant differences were observed for any variable when comparing conditions. Independent of condition, a correlation between average daytime light exposure and subsequent sleep was found. For every extra log unit (between waking up and 6 pm) an expected increase of 1.7% in sleep efficiency and an advance of 0.16 h for sleep offset was predicted by a multilevel regression analysis.

**Conclusion:** Moving to a new environment with a high-quality lighting system improved mood and visual comfort, however the morning boost in the current study was not enough to improve any other output measured. However, higher light levels during the day (until 6 pm) were able to improve subsequent sleep. These findings are in favour of improving indoor office lighting with

higher light levels than the current standards to support well-being and health. Additional research is required to establish the most optimal lighting scheme for office applications.

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## A17

### **Shift Work and Chronotype: Health Consequences of Circadian Misalignment**

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**Background:** The master circadian clock is a group of cells in the brain producing rhythms with a period of approximately 24 hours. Actually, circadian clocks are found all over the body, in organs such as the liver, the heart, the kidneys etc. Circadian clocks do not need regular daily signals to keep on being rhythmic. However, the endogenous period is often slightly deviating from 24 hours and therefore clocks need signals (zeitgebers), such as light for the master-clock and meal timing for the liver clock, to keep in synch with the 24 h light dark cycle and with each other (entrainment).

Individuals differ in their exposure to zeitgebers and in the characteristics of their circadian clock, e.g. the endogenous period may be less than or more than 24 hours. This results in different phases of entrainment between endogenous rhythms and the outside world. In society we see the consequences as a large distribution of chronotypes; individuals sleeping either very early or very late. In extreme chronotypes, the observed rhythms of sleep and food intake are often very irregular and not in synch with endogenous rhythms. In other words there is circadian misalignment. An extreme case of circadian misalignment occurs in shift-workers, who shift their sleep and working time all over the 24 hours, while their internal circadian rhythms run out of phase.

**Aim and Objectives:** The consequence of circadian misalignment is a higher risk to develop health problems. Both night workers and extreme chronotypes are at a higher risk for developing cardiovascular problems, metabolic problems and diabetes, sleep problems, mood disorders and maybe even cancer. In this lecture the evidence will be discussed, in addition to practical issues such as how to determine somebody's chronotype and possible interventions to diminish circadian misalignment and reduce detrimental health effects.

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## A18

### **The Chronotherapeutic Treatment of Bipolar Disorders: A Critical Review and Practice Recommendations**

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**Background:** Bipolar disorders (BD) are a prevalent mood illness characterized by fluctuating manic and depressive symptoms. While pharmacotherapy is the mainstay of treatment, it has

multiple shortcomings. Over the past 50 years, several chronotherapeutic treatments have been developed, including bright light therapy (BLT), treatments utilizing sleep deprivation (SD), dark therapy (DT), melatonergic agonists (MA's) and two behavioral strategies, cognitive behavioral therapy for insomnia, adopted for BD, CBTI-BP; and interpersonal social rhythm therapy, IPSRT.

**Study Aim:** Comprehensive and critical review of the outcome literature on the major chronotherapeutic treatments of BD and generation of evidence-based practice recommendations.

**Methods:** Multiple databases were searched for all English-language studies of adult bipolar subjects treated with each chronotherapy using an objective method of measurement. After preliminary screening, the remaining articles were independently reviewed, the major findings described, and the tolerability, study quality and level of evidence was rated.

**Results:** The acute antidepressant (AD) efficacy of BLT was supported by several open-label studies, 3 placebo-controlled RCT's and one meta-analysis. SD showed rapid, acute AD efficacy in 20 case series and uncontrolled trials, and one RCT. Adjunctive DT obtained significant, rapid anti-manic results in one RCT and a comparative, controlled study. MA's displayed no acute efficacy, inconsistent maintenance efficacy, and some evidence of improved sleep in both acute and euthymic states. 4 RCT's and 3 comparative studies demonstrated IPSRT efficacy in both acute and maintenance treatment. Among euthymic BP subjects with insomnia, a single RCT found CBTI-BP effective in delaying manic relapse and improving sleep. Chronotherapies were generally safe and well-tolerated.

**Conclusions:** The outcome literature on the use of chronotherapeutic treatments for BP is variable, with differing evidence bases, non-standardized treatment protocols, heterogeneous study quality and disparate levels of evidence. The heterogeneity of this literature is explored and evidence-based practice recommendations are offered.

gain, under both low-fat diet (LFD) and HFD. Energy balance is most likely tightly regulated under near-*tau* T-cycles. However, this hypothesis has never been tested.

**Methods:** We tested this in a controlled setup in which T-cycles were adjusted for dietary and age-dependent changes in *tau*, and (or) adjusted to deviate from *tau* by 0.3–0.5-h – a deviation that better describes the mismatch in humans and wild-type mice under the 'regular' 24-h T-cycle.

**Results:** By employing these adjustments we showed that energy homeostasis under LFD was unaffected by holding new-born FVB/N mice under a *tau*-resembling T-cycle of 23.7-h, compared with 24-h T-cycle. That was the same for C57BL/6 (B6) mice weaned into a T-cycle adjusted to match the average *tau* of same-age LFD-fed B6 controls weaned into constant darkness (DD) condition (*tau*~23.7-h). HFD under the 24-h T-cycle resulted in DIO that was abolished in FVB/N mice held under a 23.7-h T-cycle, and its onset in B6 mice was postponed under the *tau*-matching, age-adjusted, T-cycle. DIO onset was similarly delayed in B6 mice weaned into a T-cycle with a period length shorter than *tau* by the deviation of *tau* from 24-h (T~23.4-h). DIO under DD conditions resembled the 24-h T-cycle conditions. Its onset was preceded by attenuation of the age-related shortening in *tau*. DIO was always underlined by higher energy intake and reduced locomotor activity, compared with LFD, while the attenuations in DIO were related mainly with preservation of LFD-resembling level of locomotor activity.

**Conclusions:** We showed a pivotal role of HFD in the interconnection between circadian regulation and energy homeostasis. HFD-induced disruption in circadian regulation precedes DIO onset. HFD is essential for predisposing to obesity under circadian desynchrony. They also suggest that the absence of an environmental time-giver predispose to DIO, while long-term energy balance is more tightly regulated under a T-cycle that resonance with *tau* or is slightly faster than *tau*. Better understanding these processes may help to identify a novel risk factor for obesity and inform development of a clock-related pharmaceutical interventions aimed at reducing the prevalence of obesity.

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## A19

### Extent and Onset of High-Fat-Diet-Induced Obesity in Mice is Attenuated Under an Environmental Photic Cycle That Resembles their Endogenous Circadian Rhythm Period Length

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**Background:** Circadian regulation and energy homeostasis are interconnected. A high-fat diet (HFD) is accompanied by disrupted rhythmicity that precedes HFD-induced obesity (DIO) onset. Most physiological parameters oscillate with period lengths (*tau*) deviating slightly from 24-h, obligating daily entrainment to the environmental light-dark cycle (T-cycle). Cumulative data show that deviation of T-cycle from *tau* is correlated with weight

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## A20

### Light Before Bed and Melatonin Suppression in Preschool-Age Children

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**Background:** Although a robust literature has established that exposure to light at night suppresses melatonin production and delays circadian timing in adults, little is known about the light sensitivity of young children. The present study aim is to establish preschool age children's sensitivity to light of varying intensities in the hour before bedtime.

**Methods:** Healthy children (n = 23, ages 3.0–4.9 years, 43% males), participated in a 10-day protocol. For 7 days, children followed a strict sleep schedule. On days 8–10, an in-home assess-

ment was performed under dim-light conditions. On day 8, saliva samples were collected in the evening until 1 hour past habitual bedtime. On day 9, children were exposed to a white light stimulus (ranging from 10 lx to 5000 lx) for 1 hour prior to habitual bedtime, and salivary melatonin was measured before, during, and after the exposure period. On day 10, children provided saliva samples in the evening for 2.5 hours past habitual bedtime. Phase angle of entrainment (habitual bedtime – time of melatonin onset on day 8) and percent melatonin suppression were computed. If melatonin onset on day 8 occurred after the clock time of light exposure on day 9, participants were excluded from analysis (n = 4).

**Results:** During the 1-hour light exposure, salivary melatonin was suppressed between 69% and 94% in all participants, compared to the same period on day 8. Raw percent melatonin suppression did not demonstrate a dose-dependent relationship with light intensity.

**Conclusions:** These preliminary results suggest preschoolers have greater melatonin suppression in response to lower light intensities than previously measured in adults. With young children's increased exposure to light-emitting devices before bed and the prevalence of nighttime settling difficulties, these findings may inform recommendations for parents on limiting evening light exposure.

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#### A21

### The Psychological and Physiological Effects of Fluctuated Lighting on Healthy Participant

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**Background:** For a better quality of life, sleep plays an important role. Many studies have shown that the light exposure at night influences negatively to our sleep. According to the previous research, the important lighting factor for a better sleep at nighttime consists of a lower lighting color temperature and a lower illuminance. Many studies have been conducted about these factors, however there is not enough research how affect the dynamic lighting on our sleep state. Thus, the purpose of this study is to investigate the effects of new fluctuated lighting on human sleep state.

**Methods:** A counterbalanced study was performed on totally two days, one of which was a control day (No FL: No Fluctuated Light as a control), and another one was experimental day (FL: Fluctuated Light). 35 healthy young men and women volunteers in Chinese with the informed consent, took part in a laboratory protocol. In the FL condition, the device which generates the fluctuated lighting is located 50 cm next to their faces. The device repeated a gradual increasing and decreasing of the light intensity during 15 min. The experiment was conducted in daytime after lunch time. EEG and ECG was recorded during the experiment. Subjective sleepiness was examined by using VAS methods.

**Results:** There was a significant decrease of LF/HF in FL condition compared to control condition ( $p < 0.05$ ). 82% participants (29/35) showed the decrease of LF/HF in FL compared control. 88% participants (22/25) showed the higher delta wave power density in FL condition compared to control. 77% participants

(27/35) showed the higher subjective score of easiness to sleep in FL condition.

**Conclusions:** These results suggest that fluctuated light make us calmness which is better for sleep onset. Therefore, fluctuated lighting is an effective way to better sleep onset. Further research is needed to clarify the mechanism of these results.

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#### A22

### Changes in Clock Repression and Circadian Disruption in Response to Inflammation

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**Background:** The mammalian circadian clock is encoded by a transcriptional feedback loop that synchronizes neurobehavioral and gene regulatory processes with the 24-hour rotation of the Earth. Disruption of intrinsic circadian cycles from the light-dark cycle due to genetic or environmental perturbation has been implicated in the development of obesity and metabolic disorders through mechanisms that remain incompletely defined.

**Methods:** Here, we demonstrate how inflammatory response impacts the core circadian clock through inducible transcription factor NF- $\kappa$ B.

**Results:** Specifically, acute induction of NF- $\kappa$ B by lipopolysaccharide (LPS) leads to marked inhibition of clock repressors, including the *Period*, *Cryptochrome*, and *Rev-erb* genes, within the negative limb. Further, activation of NF- $\kappa$ B re-localizes the clock components CLOCK/BMAL1 genome-wide to sites convergent with those bound by NF- $\kappa$ B, marked by acetylated H3K27, and enriched in RNA polymerase II. Similarly, a state of chronic, low-grade inflammation induced by high fat diet (HFD) feeding also re-localized CLOCK/BMAL1 to sites proximate to NF- $\kappa$ B that were enriched in sites induced by LPS. Finally, genetic ablation of NF- $\kappa$ B during adulthood alters the expression of clock repressors, disrupts clock-controlled gene cycles, and impairs rhythmic activity behavior, revealing a role for NF- $\kappa$ B in both unstimulated and activated conditions.

**Conclusion:** Together, these results highlight molecular coupling of metabolic inflammation and circadian pathways.

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#### A23

### Adjunctive Triple Chronotherapy in the Accelerated Treatment of Acute Depression in the Adolescent Population

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**Background:** The objective of this pilot study was to explore the feasibility and proof of concept of triple chronotherapy (TCT) as an adjunctive intervention in the treatment of acute depression in the adolescent population.

**Methods:** The study enrolled thirty-one adolescents with moderate to severe depression. Each participant received a 4-day intervention (TCT) which consisted of one night of sleep deprivation followed by three days of sleep phase advancement and daily bright light therapy. Primary outcomes were feasibility and depression, as measured by the Hamilton Depression Scale-17 (HAMD-17). Secondary outcomes were severity of illness, anxiety, self-harm, insomnia, and suicidality.

**Results:** Twenty-nine (94%) adolescents completed the 4-day intervention. Twenty-six (84%) of the 31 participants experienced a reduction in depressive symptoms of at least 50% from baseline; 24 (77%) achieved remission, defined as a HAMD-17 score of less than 8. The mean depression score was severe prior to the start of the intervention ( $\bar{X} = 21.8 + 3.8$ ) and was below the threshold for remission by day 4 ( $\bar{X} = 4.4 + 5.1$ ;  $p < 0.001$ ); the mean depression score was mild at 1-week ( $n = 17$ ;  $\bar{X} = 9.3 + 5.2$ ;  $p < 0.001$ ) and 1-month ( $n = 10$ ,  $\bar{X} = 7.8 + 5.2$ ;  $p < 0.001$ ). Severity of illness scores according to the Clinical Global Impression showed improvement from a mean of 5.3 at baseline to 3.1 following the TCT intervention ( $p < 0.0001$ ); the effect was sustained through the 1-week post-discharge and the 1-month follow-ups. Secondary outcomes showed significant improvement following the 4-day TCT intervention; improvement was sustained through the 1-week and 1-month follow-up periods.

**Conclusions:** This pilot indicates that TCT may be a feasible, safe, rapid, and potentially effective adjunctive treatment for depression in the adolescent population.

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## A24

### Association between the Evening Use of Electronic Media, Sleep, and Chronotypes of Employees in Japan

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**Background:** Light is known to entrain the circadian rhythm and regulate sleep/wake cycles. Night time exposure to light leads to circadian misalignment in addition to various consequences on our health. Study aim. This study investigated the association between evening exposure to electronic devices and individual's midpoint of sleep and chronotypes among employees in Japan.

**Methods:** A representative sample of 623 non-shift working employees (21–68 years old,  $43.5 \pm 11.1$  years; 54% female) were included in the analysis. Participants completed a series of lifestyle related questionnaires including the use of smartphones and TV before sleep, and Morningness-Eveningness Questionnaire (MEQ) in addition to the one-week assessment of sleep using actigraphy and sleep log. This study was approved by the Ethics Committee of the University of Tsukuba.

**Results:** Smartphone usage before sleep in the sample population was 417 (61.1%) while the TV was 191 (28.0%). Smartphone usage was significantly associated with the average mid-sleep time, defined by the halfway point between sleep onset and wake up time, among individuals under 39 years old ( $3:28 \pm 1:11$  for non-smartphone users;  $3:56 \pm 1:03$  for smartphone users;  $p < 0.001$ ), while there was no association in individuals who were 40 years and older. Smartphone usage was significantly associated with evening types (smartphone users 12.2% vs non-users 3.0%;  $p < 0.001$ ). The average mid-sleep time was not significantly different with TV viewing before sleep.

**Conclusions:** Although the causal effect of light on the phase shift is unclear from this study, the exposure to light before sleep may be associated with the delay in mid-sleep time, especially in the younger generation. Further studies are necessary to understand the effects of electronic devices on health and sleep.

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## A25

### Shining Light on Glucose Metabolism

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**Background:** All mammalian species possess a circadian timing system consisting of a central brain clock and peripheral tissue clocks. The central clock in the brain is synchronized to the 24 hr light/dark rhythm of the environment via retinal input, and synchronizes the peripheral clock rhythms via hormones, the autonomic nervous system and the regulation of (feeding) behaviour. The increased incidence of metabolic disorders, such as obesity and diabetes mellitus, in our current 24/7 society may be caused (at least partly) by eating, sleeping and exposure to artificial light at the wrong time of day. Recently we showed in rats that 2 h of light-at-night (LAN) acutely decreased glucose tolerance. This effect was dependent on time-of-day, light intensity and wavelength. It is unknown how these light effects are transmitted to the periphery, but they probably involve changes in hepatic glucose production, systemic glucose uptake and/or pancreatic insulin release. Study Aim and Objective. To test the possible involvement of hormonal and nervous pathways in the effects of LAN on liver metabolism.

**Methods:** We studied the effects of a denervation of the autonomic nervous input to the liver on the liver transcriptome after exposure of rats LAN.

**Results:** Hepatic denervation modulated the liver transcriptome, with removal of the parasympathetic nerve and total denervation resulting in more significantly enriched pathways than sympathectomy. In particular, pathways related to intracellular and insulin signalling and circadian rhythms were affected. Expression levels of individual genes were not markedly affected by LAN, nevertheless pathway analysis revealed clustered changes in many endocrine pathways. Removal of the sympathetic and parasympathetic hepatic nerves combined with LAN exposure clearly modu-

lated the effects of LAN on the liver transcriptome, but left most endocrine pathways unaffected.

**Conclusions:** Our most recent studies provided the first evidence for similar deleterious effects of LAN in a diurnal rodent.

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## A26

### Effects of Light Transitions on Subjective and Objective Measures of Alertness, Comfort and Affective State

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**Background:** Light researchers often study effects of static lighting conditions. With the advent of intelligent, personalized lighting systems, the question of how people respond to light *transitions* becomes more relevant. Some argue that dynamic indoor lighting could be beneficial for humans, as natural light also varies throughout the day. However, very few studies actually tested light transitions' effects on alertness, visual comfort or mood, although knowledge on the direction and persistence of these effects may additionally shed light on the dominance of underlying mechanisms (IF or NIF).

**Study Aim:** We examined temporal trajectories in subjective and objective indicators of alertness, comfort and mood in constant light or after an abrupt transition. We contrasted bright, cool light ( $E_v = 1000 \text{ lx}/E_{v,\text{mel}} = 850 \text{ lx}$  at the eye, at 5800 K) with dim, warm light ( $E_v = 100 \text{ lx}/E_{v,\text{mel}} = 40 \text{ lx}$ , at 2700 K).

**Methods:** In this controlled 2 (begin state: bright/cool vs. dim/warm) by 2 (end state: bright/cool vs. dim/warm) randomized, within-subject experiment, thirty-eight healthy subjects (19 female;  $M_{\text{age}} = 24$ ,  $SD_{\text{age}} = 2.9$ ) participated in four separate sessions. In every session, both begin and end state lasted 45 minutes (1.5 hrs in total). Subjective experiences (alertness, visual comfort and mood) and objective measures of alertness and arousal (PVT performance; HR, HRV, and skin conductance) were studied. Physiology was tracked continuously; subjective and performance measures were taken every 15 minutes during the last hour. We employ mixed linear model analysis. The study was approved by the local Ethical Committee.

**Results:** Preliminary results revealed both acute and gradual effects of a transition. Acute effects were sometimes transient (e.g. acceptance, comfort, KSS), but persistent for other indicators (sensation, skin conductance). Furthermore, effects of upward vs. downward transitions were not always symmetrical.

**Conclusions:** Temporal trajectories point at independent effects of both states and transitions and different underlying pathways.

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## A27

### Can Disease "Start" with Perinatal Light? – PLICCS Results in 190,000 Live Births from the International Childhood Cancer Cohort Consortium [I4C]

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**Background:** At the SLTBR meeting in Montreal in 2011, evidence from an animal model published in Nature Neuroscience (Ciarleglio et al., 14: 25–7, 2010) was translated into epidemiological predictions (Erren et al., Neuro Endocrinol Lett, 33: 314–7, 2012). In 2017, experimental and epidemiological evidence was systematically reviewed (Lewis & Erren, Chronobiol Int, 34: 782–801, 2017) and synthesized in the PLICCS and cancer hypothesis (Lewis & Erren, Front Oncol, 7: 44, 2017): Perinatal Light (duration of daylight) may Imprint developing Circadian Clocks and Systems, with longer or shorter photoperiods predisposing to lower or higher risks of disease, including cancer. We explore this hypothesis using pooled cohort data regarding some 190,000 live births on four continents prospectively collected by the International Childhood Cancer Cohort Consortium (I4C).

**Methods:** Latitude and time of year of birth (determining perinatal daily photoperiods) were combined to develop photoperiod metrics and Cox proportional hazards regression was used to investigate whether these metrics associate with cancer risks. Gestational age, sex, birthweight, mother/father levels of education, adjoining perinatal window mean daily photoperiod, and direction of photoperiod change were assessed as potential covariates.

**Results:** We are analysing data from six geographically diverse cohorts with temporally diverse recruitment years (CPP – USA, 1959–65; JPS – Israel, 1964–76; THIS – Tasmania, 1987–95; ALSPAC – UK, 1991–92; DNBC – Denmark, 1996–2002; MoBa – Norway 1999–2009). Preliminary data from the first four cohorts suggest a protective trend of increasing 3rd trimester mean daily photoperiod across cohorts with point estimates all below 1. Analyses of all six cohorts will be completed shortly.

**Conclusions:** Increased daily photoperiod in the 3rd trimester of pregnancy may be associated with reduced childhood cancer risk in offspring, at least in the four cohorts explored so far. Further studies are warranted and planned.

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## A28

### Effects of Bright Light Exposure on Alertness Under Forced Desynchrony Conditions

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**Background:** Light effects on alertness are more prominent during nighttime compared to daytime, which might be caused by differences in homeostatic sleep pressure levels or circadian clock time. These factors can be disentangled in a forced desynchrony (FD) design, which have only been performed in dim light (<10 lux). Light is known to phase shift the SCN which interferes with disentangling homeostatic and circadian components. The aim of this experiment was to investigate whether it is possible to unravel circadian and homeostatic influences on alertness in a FD protocol under relatively high light conditions.

**Methods:** The study was approved by the medical ethics committee of the University Medical Center Groningen. The FD experiment was performed in dim (DL, 6 lux) and bright white light (BL, 1500 lux) in 8 men in a semi-randomized within subject design. Within each light condition, baseline Dim Light Melatonin Onset (DLMO) measurement was followed by 4 x 18 hours FD protocol (5 h sleep, 13 h wake; total 72 hours), and another DLMO assessment. Subjects gave hourly saliva samples (melatonin and cortisol assessment) and performed 2-hourly test-sessions to assess subjective sleepiness (Karolinska Sleepiness Scale) and objective sleepiness (Karolinska Drowsiness Test, Psychomotor vigilance and Go-NoGo task).

**Results:** Melatonin rhythms were suppressed in BL, but cortisol rhythms were unaffected, with strong similarities between successive circa 24 h cycles, indicating that the clock was free running in both light conditions. Light effects on subjective sleepiness depended both on elapsed time awake and circadian phase. Homeostatic sleep pressure did not affect performance and EEG measures, although performance was better and alpha/theta power density was lower throughout BL exposure.

**Conclusions:** This experiment shows for the first time that (1) FD paradigms can be performed in high intensity light without disturbing circadian rhythms (cortisol), and (2) Light affects melatonin, subjective and objective measures of sleepiness via different pathways.

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## A29

### Optimized Indoor Daylight Exposure Through 2-Layered versus 3-Layered Window Glass in Residential Housing: Sleep, Visual Comfort and Energy Consumption

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**Background:** In recent years, research has provided new knowledge about the importance of daylight for human health. People spend approximately 90% of their time in the indoor environment, exposed to low light intensity levels. This may impact overall health of the population by affecting circadian rhythms, sleep, and vitamin D levels.

**Method:** The project is the first of its kind to investigate the health effects and energy performance of two different glass types: 2-layered low-iron glass with high light transmittance, and 3-layered low energy glass with a lower light transmittance index. The project renovated 36 apartments using 2-layered low-iron glass and 36 apartments using 3-layered low energy glass.

**Results:** The daylight intensity in apartments with 2-layered iron-low glass was statistically significant higher (>15%) compared to apartments with 3-layered low energy glass. The 3-layered glass completely blocked the UVB light whereas 2-layered low-iron windows transmitted 5% of the UVB light and 20% more light in the blue spectral range (460–480 nm). A statistically significant deterioration in sleep quality of the residents in the housing with 3-layered low energy glass was found compared to the housing with 2-layered glass. Overall satisfaction with the daylight increased statistically significantly in the housing with 3-layered low energy windows. Lastly, 3-layered low energy windows did not provide any reduction in registered energy consumption for heating when compared to 2-layered low-iron windows.

**Conclusions:** Low-iron 2-layered windows performed better than 3-layered low energy windows on sleep and life cycle assessment.

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A30

### **Room-Light: Dynamic LED-Light as Treatment for Depressed Inpatients – A Feasibility Trial**

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**Introduction:** Despite the development of pharmacological and psychotherapeutic treatments for depressed patients, a considerable proportion only recover partially during hospitalization. A previous study showed that depressed inpatients, admitted to southeast-facing bright rooms had a shorter length of hospitalization compared to patients admitted to northwest-facing dim rooms, which suggests that the intensity and timing of daylight in inpatient wards might be important for improvement. Traditional light therapy has shown a good antidepressant effect and helps to stabilize the circadian rhythms. Objectives. In the ROOM-LIGHT feasibility trial we developed and tested the tolerability, side effects, and visual comfort of a new form of dynamic LED-lighting in the treatment of patients with unipolar or bipolar depression.

**Methods:** A total of 15 depressed patients was included at an inpatient psychiatric ward in a 2:1 randomized 4-week trial with two parallel groups: a) using dynamic LED-light with change in intensity and color during the 24-hour day to mimic daylight and, b) a static LED-light with constant illumination.

**Results:** No patients developed manic symptoms. Side-effect was low without any differences between groups. Patients preferred the dynamic lighting but the evening light, in both groups, was evaluated to be too dim. Dropout was high, primarily due to patients being discharged before the end of the trial period. Suicidal scores from the SIDAS scale was equal between groups.

**Conclusions:** The results from this trial have contributed to alterations in the lighting system incorporated in the upcoming randomized efficacy study (N = 150) starting in April 2019 with dynamic lighting built into 10 single bedrooms.

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A31

### **Circadian Rhythm Regulation of Reward Processes through Metabolic Signaling in the Brain**

Colleen McClung

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**Background:** The regulation of midbrain dopamine levels is important in a variety of diseases including addiction and mood disorders. Nearly every aspect of dopaminergic transmission has a diurnal rhythm. This includes expression of the rate limiting enzyme in dopamine synthesis, tyrosine hydroxylase (TH).

**Methods:** We and others examined TH expression and dopamine synthesis that are directly regulated by proteins that make up the circadian clock.

**Results:** TH transcription is modulated by the redox state of neurons and daily rhythms in cellular redox balance, providing a mechanism by which dopaminergic transmission is dependent upon proper daily rhythms in energy balance. Furthermore, diurnal rhythms in TH transcription is largely disrupted following chronic cocaine administration, and interactions between circadian proteins and metabolic factors are important in the regulation of the reward value of cocaine. Taken together, we find that rhythms in cellular metabolism and circadian gene expression work together to regulate dopamine synthesis and the reward value for drugs of abuse.

**Conclusions:** This work has important implications in the prevention and treatment of disorders that involve disruptions in reward value and anhedonia.

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A32

### **Loss of Circadian Rhythmicity of Renin-Angiotensin-Aldosterone System and Sodium and Potassium Balance in Lupus Nephritis Mice**

Rakesh Mishra

The Feinstein Institute for Medical Research, USA

**Background:** The mammalian circadian system regulates numerous physiological processes including immune responses. Several core clock genes, including *Bmal1*, *Per*, *CLOCK*, and *Cry* encode transcription factors that regulate gene expression in the kidney and other organs. We found a disturbance of expression of key clock transcriptional regulators in the kidneys of mice with SLE nephritis. The purpose of this study was to determine how this abnormality affected transcriptional regulation of renally expressed genes and immune cell mediated homeostasis.

**Methods:** We studied NZB/W mice at the age of 12 weeks (without proteinuria) and >30 weeks (with proteinuria). Kidneys, urine and blood were harvested at 4 hour intervals. Kidneys were perfused with PBS and used to generate RNA, protein lysates and single cells for flow cytometry. Blood pressure was measured in conscious animals by the tail-cuff method (CODA). Urine Na and K were measured by Charles River Laboratories. Blood and urine aldosterone was measured by ELISA.

**Results:** Kidneys of young mice displayed a normal circadian pattern of expression of the master transcriptional regulators of circadian rhythm including *Bmal1*, *Clock*, *Per* and *Cry*. By contrast, the nephritic mice had attenuated rhythm of these genes with dampened *BMAL* expression and inversion of the normal pattern. We examined protein levels of clock proteins (*BMAL1* & *PER2*) in the kidneys of young and nephritic mice at different ZT times and confirmed a significant reduction in *BMAL-1* protein expression in nephritic mice compared to young mice with inversion of the normal expression pattern. Expression of multiple genes involved in physiologic renal functions such as solute transport, fluid balance and cell metabolism were also dysregulated. To investigate whether timed regulation of renal function was disrupted

SLE nephritis mice we compared urinary sodium and potassium excretion during the night versus the day. Consistent with previous reports, young mice exhibited significant day/night differences in urinary [Na] and [K]. In contrast, SLE mice did not exhibit a day/night difference in urinary [Na] and [K]. In parallel, these mice lost the normal circadian rhythm of plasma aldosterone levels and blood pressure with a spike in blood pressure during the day instead of at night.

**Conclusions:** Collectively, these data show that the circadian clock mechanism is disrupted in the setting of renal inflammation resulting in dysregulation of normal renal physiologic functions. This may have important implications for renal disease progression as well as for the delivery and metabolism of therapeutic interventions.

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### A33

#### Inputs and Outputs of the Diurnal Primate Clock

Ludovic Mure

SALK Institute, USA

**Background:** All organisms have developed an endogenous circadian clock (*circa diem*, about 24 h) allowing anticipating changes in environmental conditions. Circadian rhythms control the timing of a wide range of functions across different organs and brain regions leading to optimal adaptation of physiology, metabolism, and behavior to the day-night cycle.

**Methods:** I will give an overview of the mechanisms behind the unique response properties of ipRGCs and present new data on primate ipRGCs. I will present our recently published diurnal transcriptome atlas of *Papio anubis* (baboon) that revealed the extent and the unique features of the rhythmic gene expression in the primate. We found that more than 80% of protein-coding genes display daily rhythms in expression.

**Results:** Our results also unveil a different temporal organization of central and peripheral tissues between diurnal and nocturnal animals. Light is the primary time cue for the mammalian circadian system. Changes in the illumination are detected not only by rods and cones that mediate image-forming vision but also by a subset of intrinsically photosensitive retinal ganglion cells (ipRGCs).

**Conclusions:** ipRGCs express the light-sensing protein melanopsin and play a critical role in non-visual responses to light such as synchronizing the circadian clock to the day-night cycle, regulating sleep and the pupillary light reflex.

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### A34

#### Critically-Timed Wake and Light Therapy: Mood Effects on Premenstrual, Peripartum and Menopausal Depression Depend on Melatonin-Sleep Timing

Barbara Parry, Charles Meliska, Diane Sorenson, L. Fernando Martinez, Ana Lopez, Sharron Dawes, Richard Hauger, Daniel Kripke

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**Background:** We tested the hypothesis that wake/light treatment improves mood in premenstrual, peripartum and menopausal depression by differentially altering melatonin-sleep timing.

**Methods:** After IRB approval, 144 premenstrual, peripartum and menopausal depressed (DSM-5) participants-DP (N = 73) or normal controls-NC (N = 71) randomized to a parallel trial of 1) phase-delay intervention (PDI): 1-night early-wake therapy-EWT (sleep 3–7 am) + 1 (Premenstrual Dysphoric Disorder-PMDD), 6 (peripartum) or 8 (perimenopause) weeks of evening (PM) bright white light-BWL (Litebook Advantage) for 60 min starting 90 min before habitual sleep time, vs. 2) phase-advance intervention (PAI): 1-night late-wake therapy-LWT (sleep 9 pm–1 am) + 1–8 weeks of morning (AM) BWL for 60 min starting within 30 min of wake time. Primary outcome measures included mood (Structured Interview Guide Hamilton Rating Scale for Depression-Atypical Depression Supplement-SIGH-ADS), Morningness-Eveningness questionnaire (MEQ), melatonin (2 overnight urine samples for 6-sulphatoxy melatonin-6-SMT) and sleep (actigraphy). We calculated (cosinor analyses) 6-SMT Onset/Offset, Acrophase; sleep Onset/Offset times (SOT/SET); phase-angle differences (PADs) by MANCOVA/ANOVA.

**Results:** In PMDD, baseline 6-SMT Offset phase-delay correlated with atypical depressed mood ( $p=.038$ ), PAI improved mood more than PDI ( $p = 0.002$ ), and correlated with phase-advanced 6-SMT Offset ( $p = 0.004$ ) and reduced 6-SMT Offset\_SOT PAD ( $p = 0.003$ ). Pregnant DP mood improved more after PDI ( $p = 0.016$  MEQ covariate); in Postpartum DP mood improved more after PAI ( $p = 0.019$ ), and correlated with phase-advanced 6-SMT Offset ( $p = 0.003$ ) and Acrophase ( $p < 0.05$ ). In menopausal DP, PAI, but not PDI, improved mood, phase-advanced 6-SMT Offset ( $p = 0.043$ ) and Acrophase, correlated with mood improvement ( $p = 0.002$ ). Equal efficacy of mood improvement (+70%,  $p = 0.007$ ) occurred after 1, 2 and 8 weeks.

**Conclusions:** Mood improved differentially in PMDD, peripartum and menopausal DP dependent on distinct melatonin/sleep timing disturbances characterizing each reproductive epoch, which determined responsiveness to critically-timed wake and light interventions. Combined wake/light therapy has antidepressant effects within 1–2 weeks.

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A35

### **NIF and IF Effects of Different Light Scenarios in a Real-Life Office Setting**

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Eindhoven University of Technology, The Netherlands.

**Background:** Effects of light on well-being and performance are often studied in the controlled confines of a laboratory. In real-life, we need to optimally balance circadian and acute effects on the one hand and visual comfort on the other, as both impact human daytime functioning and wellbeing. Our aim was to investigate concurrent image-forming (IF) and non-image-forming (NIF) effects of three contrasting light scenarios on alertness, mood and comfort in a real-life office context.

**Methods:** Two field studies were performed (summer vs. winter) in an office in The Netherlands. The study received approval of the local ethical committee. In summer 12 office workers (1 female,  $M_{\text{age}} = 45$ ) participated, in winter 11 (1 female,  $M_{\text{age}} = 43$ ). Each study lasted 3 weeks – one for each scenario. In contrast to a constant neutral electric light scenario (300 lx on desk, 100 lx at the eye, 4000 K), we tested a scenario with morning bright light (900 lx on desk, 300 lux at the eye) and a scenario with afternoon bright light. On top of these electric scenarios, the daylight added substantially to illuminances at desk and eye. We employed experience sampling (alertness (KSS), vitality, mood and light and temperature appraisals, 10 times per day) in combination with continuous person-worn and office-bound sensors (objective light exposure, skin temperature and actigraphy).

**Results:** Preliminary results indicate that bright electric light was perceived as less pleasant in summer. Moreover, alertness and vitality scores were lower throughout days with bright morning light. In contrast, pleasantness was not affected by the conditions in winter, and vitality and mood significantly dropped after morning bright light in the first week.

**Conclusions:** When designing light interventions it is important to take both NIF and IF effects into account. Brighter light is not always better, particularly in real-life environments.

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A36

### **Non-Image Forming Responses to Light: New Light Metrics and Insights**

*Luc Schlangen*

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**Background:** Photometric units like lx and lumen are insufficient to characterize light when considering its various non-image forming effects, such as regulating sleep, circadian rhythms, alertness, mood and hormone secretion. These effects originate with a photoreceptor within the eye that was discovered less than 20 years ago: the intrinsically-photosensitive retinal ganglion cell (ipRGC). Next to receiving input from rods and cones, this photoreceptor senses light via its blue-light-sensitive photopigment melanopsin. Light exposures, light treatments and lighting designs

need to be described in terms of all five photoreceptor inputs (rods, RGB-cones, ipRGCs) that can contribute to eye-mediated non-image forming responses.

**Methods:** The International Commission on Illumination (CIE), the worldwide body responsible for developing international reports and standards on light and lighting, has published a new standard (CIE S 026/E:2018) with new metrology, quantities and spectral sensitivity functions that can characterize light in relation to its important ipRGC-mediated, non-visual function in human health.

**Results:** The new standard is applied to explore and quantify the role of a single photoreceptor type (or any photoreceptor combination) in driving a particular non-visual effect and its dose-response relationship/curve. The relative contribution of each individual photoreceptor type to a non-visual effect can vary depending on the non-visual response and light exposure properties such as duration, intensity, spectrum, timing (external and internal/circadian), prior light history and sleep deprivation.

**Conclusions:** New light metrics enable researchers, lighting designers and light therapy practitioners to characterize and quantify light in a unified framework that is based on rod, cone and ipRGC photoreception within the human retina. Adoption of these metrics is an important step towards a formal and quantitative specification of light treatments, light exposures and lighting conditions that are beneficial, or counter-productive, for health and well-being.

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A37

### **Sad Rats: Effects of Short Photoperiod on Sleep and Carbohydrate Consumption in Grass Rats**

*Anusha Shankar, Cory Williams*

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**Background:** 3% of all Americans, and up to 9% of Alaskan women, are affected by seasonal affective disorder (SAD), a form of recurrent depression triggered by exposure to short photoperiods. Apart from being a significant mental health issue, SAD has been linked to circadian dysfunction and weight gain, both of which have important implications for susceptibility to cardiovascular disease, type II diabetes, and metabolic syndrome. We are using a diurnal rodent model species, the Nile grass rat (*Arvicanthis niloticus*), to study SAD. Aim and objectives. Though grass rats are known to exhibit depressive-like behaviors under short photoperiods, we are testing whether other prominent symptoms of SAD, including disrupted sleep patterns, increased carbohydrate consumption, and body mass gain, occur in this diurnal rodent model.

**Methods:** We are using a piezoelectric sheet below the cage floor, with custom software, to track sleep-wake behaviors in 24 grass rats (12 in short 4:20 LD photoperiods and 12 in neutral 12:12 LD photoperiods). To assess affective-like behaviors, we are conducting forced swim tests after four weeks of exposure short photoperiods. To assess anhedonia, we are measuring their consumption of low-concentration (2%) sucrose (LCS) solution. We are then assessing their reward-seeking behavior by measuring

their consumption of high-concentration (8%) sucrose (HCS) solution over three weeks. We will then euthanize animals and assess their fat content. All experiments are IACUC-approved.

**Results:** We are mid-way through the short photoperiod treatment at time of submission. Preliminary results show that animals in short photoperiod exhibit similar subjective day lengths, but disrupted sleep patterns.

**Conclusions:** We predict that individuals exposed to short-photoperiods will consume less LCS, but more HCS, and will gain more body and fat mass compared to neutral-photoperiod controls. We expect short-photoperiod individuals to maintain strong diurnal rhythms, but display fragmented sleep patterns, relative to neutral-photoperiod controls.

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### A38

#### 'Hands-On Clinical Workshop' on Light Therapy For sleep and Mood Problems

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USA

**Background:** Given the limitations of existing drug therapies, bright light and chronotherapeutic protocols are appealing non-drug somatic options which can effectively target symptoms and enhance treatment outcomes in patients with major mood disorders.

**Methods:** In this work-shop, I will explain the diagnostic criteria of the major mood disorders. I will provide a brief review of the research study methods and design in clinical trials of light therapy. I will highlight the key findings from recent clinical trials reports on the efficacy of bright light therapy for seasonal and non-seasonal major depression, perinatal depression and bipolar depression. I will provide a more detailed discussion on the implementation of light therapy in clinical practice. I will explain how to select the appropriate light emitting device, clinical assessments of response, side effects and safety, and the proper management of adverse effects from light therapy.

**Results:** Advances in the therapeutics for bipolar disorders (BD) have improved the management of bipolar mania. But, the responses for bipolar depression are fairly limited. For this reason, we conducted a clinical study to investigate the efficacy of midday bright light treatment for depressed adults with BD. After 4–6 weeks, 68.2% of patients who were treated with bright white light experienced full remission (none or only low levels of depression and significantly better functioning) compared to only 22.2% of the patients assigned to the placebo unit. The findings confirmed that adjunctive midday bright LT is efficacious for bipolar depression.

**Conclusions:** In the treatment of bipolar depression, the innovative use of a dose-titration protocol, implementation of bright light at midday, and the requirement for prophylactic antimanic treatment likely mitigated the risks for emergent bipolar mania. This approach is conservative and reasonable for indicated patients.

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### A39

#### A Behavior-Based Assessment of Attitude Toward Sleep Hygiene and Chronotype-Dependent Differences in the Engagement in Sleep-Promoting Behaviors

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**Background:** Sleep hygiene refers to the set of behaviors that promote good sleep quantity and quality. While several scales for sleep hygiene exist, they lack the inclusion of items probing light exposure and social media technology use. Moreover, these instruments typically ignore the behavioral costs of the sleep-promoting behaviors.

**Objectives:** First, we aimed to test the efficacy of the Campbell Paradigm (CP) for measuring individual differences in attitude/commitment toward sleep hygiene, which in CP is demonstrated in the amount of effort and costs a person is willing to invest in promoting or maintaining good sleep (including behaviors related to light exposure and social media technology use). Second, we tested whether early chronotypes have a more positive attitude to sleep hygiene, and thus take more, and more demanding actions to improve their sleep.

**Methods:** Forty-nine behavioral self-report items were developed based on literature and sleep experts, and administered online with the Munich Chronotype questionnaire and Pittsburgh Sleep Quality Index (N = 202; 76 male; M<sub>age</sub> = 37.7; SD = 10.9). We employed Rasch modelling and correlational analyses. The study was approved by the local Ethical Committee.

**Results:** Preliminary results showed that the items fitted the Rasch model sufficiently, with all except six items having mean-square outfit values of MS < 1.30. This indicates that the sleep hygiene behaviors form a one-dimensional scale. Reliability of attitude estimates was good with 0.75. Relatively early compared to late chronotypes had a higher likelihood to engage in sleep-promoting behaviors (such as minimizing light exposure in the evening).

**Conclusions:** The CP can be used to reliably compare individuals on their attitude toward sleep hygiene based on specific self-reported behaviors. By assessing individual attitude levels and the costs of sleep-promoting actions simultaneously, the instrument can support different types of interventions, such as personalized or chronotype-dependent behavioral recommendations on how to improve sleep.

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**A40****Effects of Lighting with Continuously Changing Color Temperature and Illuminance on Melatonin Profile, Skin Temperature and Sleep**

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**Background:** Current understanding of the term Human Centric Lighting (HCL) is the change of correlated color temperature and illuminance across the day. Here we tested the repercussions of a HCL solution on melatonin secretion, thermophysiology and sleep during two 16:8 hour (hr) light:dark cycles in men.

**Methods:** Fourteen male healthy sleepers spent two 49 hr sessions in the laboratory once under a static light condition (sLED) and once under dynamically changing light (dynLED) in a balanced crossover design. After a 13-hr baseline phase (5 hr preparation under 2,800 K/ 100 lux followed by 8 hr sleep), a 35-hr phase followed (16 hr of scheduled wakefulness – 8 hr of scheduled sleep – 11 hr scheduled wakefulness). During wakefulness light exposure in the fixed condition was set to 4,000 K and 90 lux (vertical at eye level). The dynamic condition was defined as a light change starting in the morning with 3,500 K/<1 lux incrementally increasing until reaching a 5,000 K/100 lux during the day until 5 p.m. Correlated color temperature and illuminance continuously decreased afterwards finally reaching 2,700 K/<1 lux at bedtime.

**Results:** The diurnal melatonin profile yielded an almost significant interaction between “light condition” and “time of day”. Post-hoc comparisons revealed significantly higher melatonin values under dynLED compared to sLED 1.5 hr prior bedtime ( $p = 0.035$ ). Skin temperatures in proximal and distal skin regions were significantly higher under a dynLED compared to sLED. These offsets of around 0.17°C ( $p < 0.01$ ) in both distal and proximal skin regions did not change the distal-proximal gradient. A phase shift, as hypothesized and reported in the literature for other light-exposure protocols could not be observed. Sleep was quantified for sleep stages based on electroencephalography (EEG). There was a significant effect of the factor light on sleep latency to N2 ( $p = 0.049$ ). On average it takes 3.7 minutes longer to fall asleep under sLED (17.4 minutes) than under dynLED (13.7 minutes).

**Conclusion:** We examined whether continuously changing color temperatures and illuminances during 16 h of wakefulness influences melatonin profile, skin temperature and sleep as it is often promoted by HCL concepts. According to these concepts and the general recommendation of using low illuminances and less blue components in the spectrum in the evening and at night, we compared a static lighting condition with a dynamically changing light. The light conditions did neither influence sleep structure nor sleep quality. Our findings are consistent with previous work showing that melatonin suppression was significantly greater at colder color temperatures and higher illuminances in the evening (static condition).

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**A41****Decoding the ‘Spectral Diet’**

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**Background:** Entrainment of the circadian pacemaker depends on both the intensity and spectral distribution of light reaching the retina, in addition to other contextual modulators. Daily ocular exposure to light is mediated by materials in our environment, whose reflectance properties manipulate incident light spectra in ways which are not easily predictable. We refer to the set of seen spectra as the ‘spectral diet’ which is a subset of all possible spectra. The spectral diet contains useful information about how an individual’s circadian system will respond to new stimuli over time.

**Methods:** Here we outline some approaches to decode spectral information in a way which maximizes insights about the biological response to changes in spectral distribution, while reducing the dimensionality of our dataset. For our preliminary analysis we chose to generate a set of possible spectra from existing illuminant and reflectance datasets, quantified their effect on the five human photoreceptor classes (CIE S 026), and looked at both relative and absolute quantities.

**Results:** Toward this end, we present a dimension-reduced framework with five photoreceptors. The next step will be to assemble a database of actual spectra from subjects in the built environment using novel, small-footprint wearable spectrometers.

**Conclusion:** We hope to use our method to identify a set of ‘basis spectra’ which are observed with high frequency in real life to illustrate how statistical regularities in real world material properties and illuminant spectra further reduce the dimensionality of the problem.

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**A42****The Association Between Assignment to Dim or Bright Hospital Room and Symptom Burden During Stem Cell Transplantation: A Longitudinal Pilot Study**

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**Background:** Patients undergoing autologous stem cell transplantation (SCT) may experience significant symptom burden. Evidence suggests that circadian rhythm disruption may be an underlying mechanism of numerous cancer- and cancer treatment-related symptoms. Given that light is the strongest entrainer of circadian rhythms, symptom burden may be modulated by light

exposure during hospitalization. The aim of this pilot study was to investigate associations between assignment to “dim” or “bright” inpatient rooms and symptom burden during SCT. We hypothesized that patients assigned to dim rooms would experience greater symptom severity and interference with daily life functioning over time than patients assigned to bright rooms.

**Methods:** Patients about to undergo SCT for a hematological malignancy who were assigned (based on availability) to “bright” East facing or “dim” West facing rooms were approached to participate. Eligible and consenting participants completed the MD Anderson Symptom Inventory daily from Day 0 (immediately prior to SCT) to Day 12 after SCT. Linear mixed models (LMMs) were undertaken to investigate between-group differences in symptom severity and symptom interference over time.

**Results:** Fifteen participants were included in the final analyses (9 in dim rooms, 6 in bright rooms). After controlling for a between-group baseline difference in symptom severity, a LMM revealed a significant time × room assignment interaction effect for symptom severity over time with dim room participants’ symptom severity increasing over time, but not in bright room participants ( $[F_{11}, 52] = 2.07; p = 0.04$ ), with a large effect size (partial eta squared = 0.30). A marginally significant interaction effect was found for symptom interference over time ( $[F_{12}, 65] = 1.67; p = 0.09$ ), with a large effect size (partial eta squared = 0.24) and following a similar trajectory.

**Conclusions:** Preliminary findings suggest that assignment to hospital rooms with greater bright light exposure may have beneficial effects on the trajectory of symptom burden in SCT patients. Larger scale studies are warranted.

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#### A43

### The Scotopic Electretinogram of C57Bl/6 Mice Display Circadian Rhythmicity

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**Background:** The vertebrate retina is unique in exhibiting circadian rhythms. While the retina receives and relays light inputs that entrain the central clock, it has its own circadian clock which is entrained directly by the light. The retinal function is assessed by electroretinogram (ERG), which is a sensitive and noninvasive method. Although the diurnal variations in the ERG response in mice is known, evidence is still lacking that define a time point for maximum ERG response in terms of ‘a’ and ‘b’ wave amplitudes and their implicit times.

**Methods:** To address this, we performed scotopic ERG in dark-adapted C57Bl/6 mice at different time intervals.

**Results:** Our data demonstrate that scotopic ERG amplitude for ‘a’ and ‘b’ wave displays circadian rhythmicity in response to different intensities of light stimulus. The ‘a’ and ‘b’ wave amplitudes were observed to peak just before the ‘lights off’ time. The implicit times for ‘a’ and ‘b’ wave also exhibited circadian rhythmicity depending on the intensity of light stimulus. The amplitude of oscillatory potential also showed circadian rhythmicity.

**Conclusions:** Our results point to the need for adjusting the reference values with respect to timing while interpreting ERG results. The data have broader implications in defining the timing for light therapy.

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#### A44

### A Network Model of Seasonal Depression: Implications for Etiology and Treatment

Michael Young

Illinois Institute of Technology, USA

**Background:** Network models are used in a wide variety of fields and more recently have been applied to personality and psychopathology. A network model conceptualizes a disorder as a mutually interacting set of symptoms rather than as an underlying entity that generates the symptoms. The idea of symptoms “causing” other symptoms is not rare in our informal clinical thinking; however, it is not a formal part of our usual definitions of a disorder.

**Methods:** One formal example is the Dual Vulnerability Model (DVM) of Seasonal Affective Disorder (SAD; Young et al., 1991, 2008), which proposes that psychological depressive symptoms are responses to seasonal vegetative symptoms. A network analysis of SAD symptoms was conducted to explore the possible network structure of SAD and whether the DVM is consistent with the obtained network.

**Results:** Findings support the idea that the etiology of SAD symptomatology is not unitary. Effective etiological research should account for this multi-faceted etiology when searching for correlates of the disorder, whether biological or psychological.

**Conclusion:** Network model results suggest multiple entry points for single or combined treatments.

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#### A45

### Human Circadian Rhythm Studies: Practical Guidelines for Inclusion/Exclusion Criteria and Protocol

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**Background:** Circadian dysfunction has been implicated in diseases as distinct as cancer, obesity, and depression. For this reason, interest in circadian rhythms on the cellular and organism-wide level has significantly expanded in the past few decades and there is an increasing need to perform circadian studies in humans. Here, consensus recommendations from previous circadian studies are provided for investigators designing similar studies. The guidelines listed are intended to reduce confounding variables from affecting circadian rhythm studies. The scientific rationale behind each recommendation is provided when available. Otherwise, recommendations are based on empirical decisions made in previous

studies in order to provide consistency. While not all recommendations listed may be practical in all research settings and with limited potential participants, the goal is to allow investigators to make well-informed decisions about their screening procedures and protocol techniques.

**Methods:** We examined 43 studies for their inclusion criteria and protocol if available. When possible, references providing justification for study choices were also examined.

**Results:** Psychopathology, drug use, shift work, and menstrual cycle are addressed as screening considerations. For example, abstinence from caffeine, nicotine, and cannabis, is recommended to be two, four and six weeks prior to the study based on their effective half-lives, the duration of their effects on sleep quality parameters or the most popular practice. Best practices for measuring serum melatonin, based on the effects of posture and the light intensity-melatonin response curve, are also provided.

**Conclusions:** The suggested guidelines in this review may provide a practical tool for human circadian rhythm studies.

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#### A46

### Novel Approaches to Diagnose Circadian Rhythm Disorders

Phyllis Zee

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**Background:** The concept of circadian health captures the necessity of proper function of internal body clocks and their synchronization with external influences such as the light/dark cycle, lifestyle choice and work/school schedules. Circadian disorders have been classically characterized by disorders of abnormal timing of the sleep-wake cycle. The discovery that circadian clocks are found in nearly all cells and tissues, and in addition to timing, regulate cellular bioenergetics, inflammation and cell division, has broadened our view of the impact of circadian disorders beyond sleep. It is now evident that circadian dysfunction can play a role in a wide range of pathology, from the increased risk for cardiometabolic disease and malignancy in shift workers, to the changes in circadian amplitude that often precede the clinical symptoms of neurodegenerative disorders.

**Methods:** As our understanding of the importance of circadian dysfunction in sleep and other disorders grow, we need to develop clinically practical tools and biomarkers for assessing biological timing in central, as well as peripheral tissues. For research and in the clinic, the most common measures used to assess circadian rhythm phase and amplitude include melatonin levels, core body temperature, and rest-activity cycles. The circadian rhythm of melatonin has been considered to be a gold standard for assessing endogenous circadian timing in humans, but requires frequent sampling across 24 hours or more, rendering it less practical in most clinical settings.

**Results:** Gene expression analyses, proteomics and metabolomics offer new opportunities to examine circadian timing by using computational quantification of temporal organization. A novel algorithm for inferring circadian rhythmicity from gene expression in blood (TimeSignature) has been shown to produce highly accurate results in a healthy population (predictions of circadian

phase to within 1.5 h on average using 2 samples), but it remains to be applied to patient populations. In addition, diagnostic tests such as pupillometry can help distinguish patients with delayed sleep-wake phase disorder who are “circadian” vs. “behaviorally” delayed.

**Conclusions:** Determining the state of an individual’s internal physiological clock has important implications for precision medicine, from diagnosing circadian disorders, to optimizing timing of diagnostics and therapeutics.

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#### A47

### Less is More: Ultrashort Light Flashes for Resetting the Human Circadian Clock

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**Background:** It is unknown whether the magnitude of light-induced circadian phase shifts in humans is limited by ocular physiology or the clock itself. We have engaged in a multi-year series of studies to examine whether we could drive larger phase shifts by using a series of light flashes that optimize the light input to the clock. Study aim. To determine the optimal sequences of light flashes for inducing rapid resetting of the human circadian clock.

**Methods:** Participants (n = 110) engaged in series of parallel group 16-day studies. Days 1–14 were an at-home circadian phase stabilization protocol. The final two days were spent in a time isolation laboratory. On night 15, after a modified constant routine, participants were exposed to a one-hour sequence of light that varied by interflash interval length, individual flash duration, flash intensity, or whether flashes were delivered while participants were awake or asleep. The one-hour flash sequence started two hours after habitual bedtime. Phase shifting and melatonin suppression were examined *post hoc* through analysis of salivary melatonin concentrations.

**Results:** Optimal interflash interval length is approximately 10 seconds, which generates more than 3-fold greater phase shifts than those observed after continuous, equiluminant light. Flashes as brief as 10 microseconds induce phase shifts similar to those observed after exposure to flashes 100,000 times longer. Flashes as dim as 30 lux produce 80% of the phase shift observed after exposure to flashes 100-times brighter. A flash sequence during sleep shifts the circadian system similarly to the same flash sequence during wake, and does so without interfering with sleep.

**Conclusions:** Flash sequences can generate larger phase shifts than continuous light and can be delivered during sleep when the pacemaker is typically more sensitive to light. This opens new therapeutic avenues for the treatment of circadian-based sleep disorders.

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