Society for Light Treatment and Biological Rhythms

Program and Abstracts: Volume 24

24th Annual Meeting
June 24th – 27th, 2012
Geneva, Switzerland

Marc Hébert, SLTBR President

Scientific Committee: Marc Hébert (chair), Éric Lainey, Anna Wirz-Justice, Farhad Hafezi, and Matthaeus Willet.

Local arrangements are made courtesy of:
Center for Environmental Therapeutics Europe
and the University of Geneva.

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MESSAGE FROM OUR HOSTS

Dear Colleagues,

We are delighted to welcome you in Geneva!

This SLTBR meeting is in the light of an open interdisciplinary exchange between psychiatrists, sleep researchers, biologists as well as ophthalmologists.

We wish all of you a very fruitful congress and unforgettable moments in Geneva.

Sincerely,

Farhad Hafezi, MD PhD    Panteleimon Giannakopoulos, MD
Professor and Chair of Ophthalmology  Professor and Chair - Department of Psychiatry
University of Geneva    University of Geneva
We thank you to the following companies and foundation that generously supported the 24th Annual Meeting of the Society for Light Treatment and Biological Rhythms:

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SLTBR 24th annual meeting program

Sunday, June 24, 2012
16:00 - 18:00  SLTBR Board meeting

19:00 - 21:00 Welcome reception – Top Floor, Auditorium

Monday, June 25, 2012
8:00 - 16:00  Registration

8:45 - 9:00 Welcome
Panteleimon Giannakopoulos, University of Geneva, Switzerland
Farhad Hafezi, University of Geneva, Switzerland - Chair of local Organizing Committee
Marc Hébert, Laval University, Quebec, Canada, President SLTBR

9:00 - 11:30 Symposium I: Light and chronotherapeutic approaches
Chair: Gilles Vandewalle, University of Liège, Belgium
Co-chair: Eric Lainey, CENAS-Sleep Center, Geneva, Switzerland

9:00 - 09:30 Light as a modulator of executive and emotional brain functions
Gilles Vandewalle, University of Liège, Belgium

9:30 - 10:00 Effects of morning light on cognitive performance, mood and melatonin during sleep restriction
Antoine Viola, University of Basel, Switzerland

10:00 - 10:30 Coffee Break

10:30 - 11:00 Blue light compared to standard light therapy in SAD treatment
Ybe Meesters, University Medical Center Groningen, The Netherlands

11:00 - 11:30 Synchronizing circadian clocks for cancer chronotherapeutics
Francis Lévi, Inserm U776, Villejuif, France

11:30 - 13:00 Lunch Break

13:00 - 14:00 Oral Presentations I
Chair: Anna Wirz-Justice, University of Basel, Switzerland
13:00 - 13:15  **Age-related effect of bright light exposure on circadian rhythms and cognitive performance**
Virginie Gabel, University of Basel, Switzerland

13:15 - 13:30  **Effects of bright light treatment on psychomotor speed in top-level athletes: randomized, double-blind, placebo controlled Study**
Mikko P. Tulppo, University of Oulu, Finland

13:30 - 13:45  **Lighting countermeasures for the international space station**
George Brainard, Thomas Jefferson University, Philadelphia, USA

13:45 - 14:00  **Enhancing sleep in hospitals with patient room lighting**
Marina C. Giménez, Philips Research, Eindhoven, The Netherlands

14:00 - 15:30  **Poster Session & Coffee break**
*Presenters are asked to remain in front of their poster. (Posters will stay up on Monday and Tuesday)*

15:30 - 17:00  **Roundtable exchange among clinicians experienced with light therapy: problems, prospects, insights.**
*Chair: Michael Terman, Columbia University, New York, USA*  
*Co-Chair: Panteleimon Giannakopoulos, University of Geneva, Switzerland*

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**Tuesday, June 26, 2012**

8:00 - 16:00  Registration and morning coffee break

9:00 - 11:30  **Symposium II: Genetic Influence on biological rhythms**
*Chair: Kathryn A. Roecklein, University of Pittsburgh, USA*  
*Co-chair: Christian Cajochen, University of Basel, Switzerland*

9:00 - 9:30  **Genetics of biological rhythms in healthy populations--what are the implications for mood disorders?**
Namni Goel, University of Pennsylvania, Philadelphia, USA

9:30 - 10:00  **Melanopsin gene variations in the pupil light reflex in seasonal affective disorder**
Kathryn A. Roecklein, University of Pittsburgh, USA

10:00 - 10:30  **Association between melanopsin gene polymorphism and non-visual response to light**
Shigekazu Higuchi, Kyushu University, Fukuoka, Japan
10:30 - 11:00  Human melatonin and alerting response to light depend on a polymorphism in the clock gene PER3
Sarah L. Chellappa, University of Basel, Switzerland

11:00 - 11:30  Shining light on the circadian clocks
Urs Albrecht, University of Fribourg, Switzerland

11:30 - 13:00 Lunch

13:00 - 14:00  Keynote Speaker: The daily rhythms of genes, cells, and organs.
Ueli Schibler, University of Geneva, Switzerland

14:00 - 15:00  Oral Presentations II
Chair: Dan Oren, Yale University, New Haven, USA

14:00 - 14:15  The gaseous messenger carbon monoxide is released from the eye into the ophthalmic venous blood depending on the intensity of sunlight
Marek Koziorowski, University of Rzeszow, Poland

14:15 - 14:30  Acute effect of wake therapy
Klaus Martiny, University Hospital of Copenhagen, Denmark

14:30 - 14:45  Effective connectivity between amygdala and anterior cingulate cortex predicts antidepressant response to sleep deprivation
Francesco Benedetti, University Vita-Salute San Raffaele, Milan, Italy

14:45 - 15:00  A non-clinical night setting for a treatment of major depression with chronotherapy in a small primary care psychology practice – an exploration
Astrid L.G. van Jaarsveld, PHHaastrecht, Oudewater, The Netherlands

15:00 - 15:30 Coffee break

15:30 - 17:00  SLTBR Annual Business Meeting, Auditorium

19:00  Annual Banquet (Villa - Fondation Louis Jeantet)
Wednesday, June 27th, 2012

8:00 - 9:00  Registration and morning coffee

9:00 - 11:00  Symposium III: Impact of lighting environment on health and work safety  
Chair: Mirjam Münch, Swiss Federal Institute of Technology Lausanne (EPFL), Switzerland  
Co-chair: Claude Gronfier, Inserm U846, Lyon, France

9:00 - 9:30  Sleepiness and work (or other activities) during the night - severity, awareness and risk  
Torbjörn Akerstedt, Stockholm University, Sweden

9:30 - 10:00  Indoor lighting conditions and the impact on visual and non-visual functions  
Mirjam Münch, EPFL, Switzerland

10:00 - 10:30  Optimising the light environment for sleep, performance and circadian phase  
Josephine Arendt, University of Surrey, United Kingdom

10:30 - 11:00  Exploration of 5 theses regarding effects of light and rhythm hygiene on health, sleepiness at work and sleep disorders at home  
Thomas C. Erren, University of Cologne, Germany

11:00 - 11:30  Coffee break

11:30 - 12:45  Oral Presentations III  
Chair: Robert D. Levitan, University of Toronto, Canada  
Co-chair: George Brainard, Thomas Jefferson University, Philadelphia, USA

11:30 - 11:45  Short-term changes in EEG brain states in response to different wavelengths of light during daytime  
Mirjam Münch, Swiss Federal Institute of Technology, Lausanne, Switzerland

11:45 - 12:00  The relationship between sleep quality and preference for morning/evening, seasonality and activity levels in depressed patients with bipolar disorder  
Dorothy Sit, University of Pittsburgh, USA

12:00 - 12:15  High maternal seasonality scores predict high body mass index in newborns  
Robert D. Levitan, University of Toronto, Canada
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<td>Namni Goel, University of Pennsylvania, Philadelphia, USA</td>
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<td>12:30 - 12:45</td>
<td><strong>Molecular clock biomarkers predict light-dependent melatonin signaling in human subjects</strong></td>
<td>Steven A. Brown, University of Zurich, Switzerland</td>
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<td>12:45 - 13:00</td>
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SLEEPINESS AND WORK (OR OTHER ACTIVITIES) DURING THE NIGHT - SEVERITY, AWARENESS AND RISK

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There is a fair amount of reports on sleepiness during night work (or night activity) and there are similar reports on increased accident risk. The two seem to fit nicely together although they have rarely been directly linked in real life. Laboratory studies abound, but may not reflect accurately. Another issue concerns the severity of sleepiness during night work. Lab simulations suggest profound effects, while real life studies (few as they are) show more modest levels. Awareness of sleepiness is another controversial issue. Laboratory simulations suggest impaired awareness, with performance indicators being more sensitive. On the other hand field studies show high sensitivity of awareness while performance indicators seldom make their way into real life studies. In our own studies we find awareness being quite sensitive and closely related to, for example, EEG and EOG indicators of sleepiness. In recent studies we have been able to follow night drivers up to the point of not being able to drive any longer for safety reasons. This occurs in about 40% of drivers around 4-5 a.m. and is accompanied by profound awareness and EEG and EOG changes of sleep intrusions. Our studies indicate that night time activity reach unacceptably high levels of sleepiness in a large proportion of individuals.
SHINING LIGHT ON THE CIRCADIAN CLOCK

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Objectives: The circadian timing system provides a temporal structure across an organism to modulate and synchronize biological function. Individual cells contain the molecular set up to drive a circadian clock. Cellular clocks are directly or indirectly synchronized by a light sensitive pacemaker, which is located in the suprachiasmatic nuclei (SCN). How does light affect the circadian clock in the SCN and other brain clocks and what are the molecular mechanisms involved?

Methods: Wild type and mice mutant in clock genes were used to study the behavioral response to a nocturnal light pulse. In situ hybridization revealed changes in gene expression in response to such a light pulse in brain regions including the SCN. In cell cultures the promoters of clock genes were studied to delineate signaling pathways involved in light mediated clock resetting.

Results: Various signaling pathways including the protein kinase A (PKA), the protein kinase C (PKC) and cGMP pathways were identified to be involved in light mediated signaling in the SCN. Other brain regions such as the habenula showed induction of cFos in response to a nocturnal light pulse.

Conclusions: Multiple signaling pathways converge on the promoters of clock genes regulating in an intricate manner the cellular response to light. In the brain the SCN displays induction of clock genes but other brain areas such as the habenula may also be influenced by light.

Keywords: signal transduction, neurotransmitters

Funding Support: Swiss National Science Foundation, State of Fribourg, Swiss International Cooperative Program, Velux Foundation
DARK INTERFERENCE AND ITS IMPACT ON DAILY RHYTHMS OF A DIURNAL RODENT THE FAT SAND RAT \textit{PSAMMOMYS OBESUS}

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\textbf{Objective:} Modern life style brings humans, as diurnal organisms, to be active during the dark part of the 24h cycle. The results of different studies revealed the negative impact of light at night (LAN) and light interference (LI) on various daily rhythms in particular the suppression of pineal melatonin (MLT) secretion. A question to be asked in regards to MLT produced in the dark is: will dark interference (DI) at day time, have an impact on daily rhythms of a diurnal rodent? We aimed to assess the impact of DI on body temperature ($T_b$) daily rhythms, on MLT and corticosterone secretion of the fat sand rat \textit{Psamommys obesus}

\textbf{Materials:} Fat sand rats $n=10$ were acclimated to 12L:12D at 25$^\circ$C (control) for two weeks. After measuring the various variables they were acclimated for another two weeks to 12L:12D with two hours of DI five hours after lights came on and all variables were measured once again.

\textbf{Results:} Exposure of \textit{P. obesus} to two hours of DI caused a significant change in $T_b$ daily rhythms where such individuals lost rhythmicity, while under 12L:12D a clear $T_b$ daily rhythm was noted. DI also abolished the daily rhythm of MLT secretion and affected the corticosterone rhythm where after exposure values were higher relatively to the control group.

\textbf{Conclusions:} The results of our study suggest that DI during photophase is not anticipated by the fat sand rat. The response in regards to $T_b$ and MLT daily rhythms is, to become arrhythmic, such a result was also obtained when feeding time was changed and restricted to scotophase. DI can be considered a stressor as corticosterone levels increased after the exposure. As humans are also diurnal organisms an interesting question can be asked: will our $T_b$ and MLT daily rhythms be affected in the same way upon sleeping at day time in a complete dark room? Further research is carried out in our center in order to inquire if \textit{P. obesus} can adapt to such conditions.

\textbf{Keywords:} Illumination manipulations, daily rhythm disruption, diurnal, melatonin
PERINATAL PHOTOPERIOD AND LATITUDE AND SEASON AT BIRTH: PREDICTORS OF LATER ADJUSTMENT TO CHRONOBIOLOGICAL STRESS

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Objectives: Studies with rodents have demonstrated the differential effects of short (LD 8:16), equinox(LD 12:12) and long (LD 16:8) perinatal photoperiods on SCN development, SCN response to subsequent light cycle change, and free-running behavior (Ciarleglio et al., Neurosci. 197: 8-16, 2011). In rodents, the specialized ganglion cells connecting the retina to the SCN are understood to be functional from the day of birth. In humans these cells are postulated to become functional during the third trimester. This early functionality of ganglion cells suggests a potential “imprinting effect” of perinatal photoperiod on the circadian clock in humans (Ciarleglio et al., Neurosci. 197: 8-16, 2011). There are 3 potential effects on susceptibility to circadian stress related to time and place of birth: latitude, season of birth, and perinatal photoperiod. However, as noted by Erren et al. (Chronobio. Int. 28: 471-473, 2011) perinatal photoperiod can account for the effects of latitude of birth and season of birth since it is a simple function of both, i.e., the length of the day on which you were born depends only on where and when it occurred. The purpose of this study was to compare latitude of birth, season of birth, and perinatal photoperiod as predictors of seasonal symptoms in a diverse sample of young adults undergoing the circadian stress of winter in Chicago.

Methods: Participants were recruited from new graduate and undergraduate students at a primarily technological university in Chicago. Participants came primarily from North America and East and South Asia (several students born south of the equator were omitted.) Latitude and date of birth were collected as part of an online survey regarding student adjustment. From these values, photoperiod at birth was computed. Seasons were defined as winter (Dec – Feb), spring (Mar – May), summer (Jun – Aug) and fall (Sep – Nov). Outcomes were the Vegetative and Cognitive/affective scales of the Comprehensive Seasonal Assessment Form. Depending on the analysis, sample sizes varied from 67 to 91. 58% of the sample was male and ages ranged from 18 to 38 years (Mean = 22.5, SD = 4.5). Birthplace latitude ranged from 3.1 to 61.1 degree north. (Mean = 37.3, SD = 10.6). Birthdate photoperiod ranged from 8.0 to 18.1 hours (Mean = 12.3, SD = 1.6).

Results: Multiple regression and correlation analyses indicated that latitude (r = .32, p < .005, N = 76), but not perinatal photoperiod or season of birth, predicted vegetative winter symptoms. None of the three variables predicted winter cognitive/affective symptoms.

Conclusions: This preliminary investigation appears to be the first to examine the relationship between perinatal photoperiod and later adjustment in a sample of adults with a wide range of birth location. However, the results did not support the role of perinatal photoperiod. Rather, simple latitude at birth was related to later winter vegetative symptoms. This suggests the relevant factor may be the experience of variation of photoperiod across the seasons rather than the light-dark balance in the months after birth. In addition, although seasonal affective disorder is considered a depressive disorder, it is changes in sleep, appetite, and energy that are considered the core of the syndrome that is related to environmental variables (Young, et al., 1991). The findings here are consistent with this formulation. Limitations of this study include the relatively small sample size, not accounting for where else participants may have lived after birth, and the use of an outcome variable that is influenced by many factors in addition to those related to chronobiology. Implications and suggestions for future research will be discussed.

Keywords: Perinatal photoperiod, latitude, circadian rhythms, seasonality,
OPTIMISING THE LIGHT ENVIRONMENT FOR SLEEP, PERFORMANCE AND CIRCADIAN PHASE

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Objectives: The final objective of the studies reported here is to optimise artificial light environments with respect to circadian phase, sleep and performance in regions with low natural light levels in winter. At high latitudes, with no sunlight in winter, delayed sleep and circadian phase has frequently been reported with overt free-running in some circumstances.

Methods: Participants were recruited from over-wintering base personnel at Halley base, Antarctica (75°S). Light environment studies have been carried out on this base since 1985 and the overall results will be summarised. Circadian phase was assessed by the rhythm of plasma melatonin or 6-sulphatoxymelatonin (aMT6s) in sequential urine samples. Sleep characteristics were derived from actigraphy (ActiwatchL, AWL, Cambridge Neurotechnology Ltd) and/or sleep diaries. Cognitive performance was assessed by three validated tests at different times of day. Light exposure was recorded continuously using AWLs. Light treatment was carried out, both by short (1 h) pulses of bright white light (2000 lux) in the morning (between 08:00 and 09:30 h), or in the morning and the evening (skeleton photoperiod, 08:00-09:00 and 19:30-20:30 h) and also by imposing a full circa 10 h photoperiod of extra light, either blue enriched (10,000 or 17000 K) or standard white light (4000 - 5300 K) from 08:00 h. Comparable control periods or control subjects with no extra light were used in all studies.

Results: A substantial delay of the melatonin rhythm has consistently been observed on this base and in other high latitude environments in winter. A similar delay in sleep timing, which may become free-running after a period of night shift, is also seen. We have not compared performance between winter and summer however the circadian delay would predict decrements in performance. A skeleton photoperiod applied for 6 weeks in winter restored the summer phase position of the melatonin rhythm. A full 10 h photoperiod of either standard white or blue-enriched (Activiva Active) light alternating for 4-5 week intervals from March to October greatly reduced the delay in circadian phase and sleep timing, blue enriched light (notably 17000 K) being slightly more effective than standard white light. The maximum light intensity experienced during the working day was the most important factor maintaining sleep timing irrespective of spectral composition. The most effective treatments gave a personal light exposure of up to 2000 lux or more. Most recently, a single 1 h pulse of standard bright white light (4500-5000 lux) given for two weeks from 08:30h on either side of the winter solstice, was able to maintain circadian phase and also to improve performance compared to equivalent control periods with no extra light. In two small studies, light treatment also had significant benefits in hastening adaptation to day work after night shift.

Conclusions: To maintain phase, sleep timing and performance in the absence of natural sunlight the light environment ideally needs to provide circa 2000 lux during at least part of the day. It is possible that 30 min to 1 h of this light intensity in the morning will be sufficient, although further studies in larger numbers are needed. Data from Polar regions are likely to have applicability in urban environments with winter day lengths shorter than the working day.

Key Words: Light, Phase Shift, Circadian, Sleep, Melatonin, Latitude


EFFECTIVE CONNECTIVITY BETWEEN AMYGDALA AND ANTERIOR CINGULATE CORTEX PREDICTS ANTIDEPRESSANT RESPONSE TO SLEEP DEPRIVATION

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Objectives: Despite confirmed evidences about some neurochemical effects of antidepressant treatments, there is still an high level of uncertainty about which biological changes are needed to recover from a major depressive episode. Functional connectivity has been demonstrated to be a good predictor of response to treatment, but only few studies investigated the effect of treatment using functional connectivity with no study evaluating the impact of response to treatment.

Methods: BOLD fMRI with an emotional task was performed in 40 patients affected by a major depressive episode in course of bipolar disorder type I, and in 28 healthy subjects. Choosing the appropriate regions based on the significant changes in activation before and after treatment (combined sleep deprivation and light therapy), we tested competing dynamic causal models of effective connectivity between the left amygdala (Amy) and the anterior cingulate cortex (ACC). Model 1 (M1)=driving inputs via ACC and forward only intrinsic connection. Model 2=model 1 with bi-directional intrinsic connections. Model 3=driving inputs via Amygdala and forward only intrinsic connection. Model 4=model 3 with bi-directional intrinsic connections.

Results: Both responders to treatment and healthy subjects showed significant evidence of effective connectivity between ACC and Amy according to Model 1, while non-responders did not. This was true both at baseline and after treatment.

Conclusions: Effective connectivity between cortico-limbic regions predicts antidepressant response to repeated sleep deprivation and light therapy. The functional status of the brain before treatment could be a major factor affecting response to chronotherapeutics.
ALTERED SUBJECTIVE ALERTNESS AND VISUAL COMFORT IN EXTREME CHRONOTYPES IN RESPONSE TO DIFFERENT OFFICE LIGHTING CONDITIONS: PRELIMINARY RESULTS

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Introduction: The quality and quantity of daily light through the eyes influences our visual perception but also non-visual functions such as alertness and work performance. Since a large part of the adult population worldwide spends more than eight hours at working places inside of office buildings, it becomes crucial to determine not only more optimal lighting conditions but also to take into account inter-individual differences. Our study aims to test the effects of light on alertness and visual comfort in extreme chronotypes in order to learn more on inter-individual light responses in this healthy population with known diurnal sleep-wake preferences.

Methods: Based on diurnal sleep-wake preferences and as assessed by two questionnaires, we only considered healthy young extreme chronotypes for the study. So far, four young morning types (MT) and four evening types (ET) completed the study. They came three times to the laboratory and spent sixteen hours under different lighting conditions. The three lighting conditions were 1) dim light (DIM; <5lux) condition, 2) bright light condition (BL; target vertical illuminance ≈ 1000 lux), and 3) a self-selected lighting (SSL) condition. The BL and SSL condition comprised both day- and artificial light. Each study session started approximately one hour after habitual wake time. Participants were asked to regularly rate their subjective alertness and visual comfort on different questionnaires.

Results: Preliminary results suggest a decrease of subjective alertness over time (2-way rANOVA; main effect of time; p<0.05; n=8), and greater visual comfort under SSL than under both, DIM and BL conditions (2-way rANOVA; main effect of condition; p<0.05). To assess differences between chronotypes, we aligned subjective alertness and visual comfort ratings during SSL and BL conditions relative to habitual wake times and expressed them relative to DIM. We found that MT rated themselves on average 24.5% more alert in the BL and 11.8 % more alert in the SSL than ET. Within MT there was almost no difference (1.4%) between the two lighting conditions in the first half of the study session, whereas in the second half, MT were 38.6% more alert in the BL than the SSL condition. For ET, the difference between both lighting conditions did not exceed 6.4 %. During the SSL condition, MT chose on average almost twice the level of illuminance, compared to ET (MT: 1307±912lx; ET 689±220lx; mean ± SD). In the first eight hours of the SSL condition, ET selected 64.1% of the average illuminance measured in MT. This portion decreased to 24.4% in the second half of the study session, such that ET were on average exposed to 184±32 lux during the last eight hours of the SSL condition. Visual comfort ratings were similar for both chronotypes in the first half of the BL condition (<1% difference) but became worse for ET in the second half of the study session, compared to MT (with a difference of 58.8%). For SSL we found that MT rated greater visual comfort for both, the first (18.8%) and the second half (21%) of the study session, than ET.

Conclusions: Continuous BL exposure had on average the greatest alerting response in MT during the second part of the study, at the cost of lower visual comfort. On the other hand, the rather large illuminance differences in ET between BL and SSL (>800 lux) in the second part of the study had only little effects on their subjective alertness, but decreased their visual comfort in BL. Our preliminary results suggest potentially different light responses between extreme chronotypes, which need to be verified with more subjects and also objective variables.

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Keywords: Alerting Effects, Inter-Individual Differences, Self-Selected Lighting, Morning-Evening Types
LIGHTING COUNTERMEASURES FOR THE INTERNATIONAL SPACE STATION

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Objectives: Onboard lighting for the International Space Station (ISS) is currently provided by fluorescent lamps but these will be replaced in 2015-2016. Arrays of solid-state light emitting diodes (LEDs) are attractive candidates for a new ISS lighting system. The advantages of LEDs over conventional fluorescent light sources include lower up-mass, power consumption and heat generation, as well as fewer toxic materials, greater resistance to damage, and long lamp life. A prototype Solid-State Lighting Assembly (SSLA) was developed at Kennedy Space Center and successfully installed on the ISS. The broad goal of this work is to meet NASA’s requirements for development, testing and installation of SSLAs on the ISS that will support astronaut vision as well as provide optimum circadian, neuroendocrine, neurobehavioral and sleep regulation.

Methods: A four-day, ground-based pilot study was conducted using 9 healthy, astronaut-aged males (27-53 years). The volunteers were studied under different light exposure conditions produced by prototypes of the SSLAs to be installed on ISS (broad bandwidth, polychromatic light of 2300 K at 20 lux, 3500 K at 238 lux and 6500 K at 1270 lux). The experiments were conducted, in part, inside a high-fidelity replica of the ISS Crew Sleeping Quarters (CQ). Measures were made of visual responses, plasma melatonin, neurobehavioral performance and sleep relative to SSLA lighting exposure conditions.

Results: Data analysis is ongoing, but preliminary assessment with ANOVAs and paired t-tests showed different SSLA light settings had no significant effect on visual performance, but a significant effect on color discrimination (F=26.19, df=3, p<0.0001). Different SSLA light settings also had a significant effect on pre-sleep melatonin levels (t=2.38, df=8, p<0.05) and the Digit Symbol Substitution Task accuracy post-sleep (F=9.69, p<0.003). There were non-significant trends for some of the other neurobehavioral measures and for sleep measures relative to the different light settings. These data will be used to facilitate statistical power analyses for larger, crossover studies.

Conclusions: Risk factors for the health and safety of astronauts include disturbed circadian rhythms and altered sleep-wake patterns (1, 2). The data presented here, along with other emergent data (3, 4) will help determine if SSLA lighting can be used both to support astronaut vision and to serve as an in-flight countermeasure for circadian disruption, sleep disturbances and performance deficits on the ISS.

Keywords: Melatonin, LEDs, Lighting

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References:
BRIGHT LIGHT INTERVENTION IN RENAL TRANSPLANT RECIPIENTS HAVING POOR SLEEP QUALITY AND DAYTIME SLEEPINESS

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Objectives: Renal transplantation (RTx) is a cost effective therapeutic option for patients with end stage renal disease. Sleep-wake disturbances are common in patients with end stage renal disease as well as in RTx patients although evidence shows improvement of sleep parameters after Tx. The cause of sleep-wake disturbances in end stage renal disease and RTx is unknown and seems to be multifaceted. Poor sleep quality (SQ) and daytime sleepiness (DS) are very prevalent in RTx recipients. There are no prevalence data on sleep disorders in this population. Pharmacologic interventions are limited due to interactions with immunosuppressive drugs and the danger to impair the organ function. The aims of our studies were: 1) to assess the prevalence of poor SQ and DS; 2) to diagnose patients with sleep disorders following the ICSD-2 classification; 3) to assess the effect of bright light therapy in home dwelling RTx patients with sleep-wake disturbances.

Methods: Study 1: Using a cross-sectional multicenter design, we included a convenience sample of 927 RTx patients (36.9% female; mean age: 58.0±12.3 y.; years since Tx 10.6±7.6) transplanted at 3 Swiss Transplant centers. We assessed SQ using the Pittsburgh Sleep Quality Index (PSQI) (score >5 indicates poor SQ) and DS by the Epworth Sleepiness Scale (ESS) (score ≥6 for DS). Study 2: We categorized all patients from study 1 in 4 groups [(G1) good SQ & no DS, (G2) good SQ & DS, (G3) poor SQ & no DS, (G4) poor SQ & DS]. Distribution among these subgroups was following: G1:17.8%; G2: 17.0%; G3: 31.3%; G4: 33.9%. All patients belonging to G2, G3 and G4 were asked to participate in a sleep assessment interview following the ICSD-2 classification of sleep disorders. Study 3: We will randomize 15 patients into the intervention group and 15 into the waiting list control group (having the intervention (Philips EnergyLight, 10’000 lux for 30 minutes) at the end of the study period). This feasibility and pilot RCT will randomize patients into an intervention group having bright light from day 21 until day 42 or into a control group (waiting list) having light therapy at the end of the study (day 63 to 84). Actigraphy, diaries, neuropsychological tests [attention, psychomotor speed, cognitive flexibility and executive functions, speed and reaction inhibition/distractibility and semantic verbal fluency] and a depression questionnaire (DASS-21) will be utilised. Circadian and sleep parameters derived from actimetry will be evaluated for 63 days. All patients will collect multiple saliva samples for melatonin assay and will fill in the depression scale at day 1, 42 and 63. Neuropsychological tests will be performed at day 1 and 63.

Results: Study 1: The prevalence of poor SQ was 65.2% and DS 52%. Study 2: Two hundred and fifty four patients were interviewed, 56 had a presumable diagnosis of sleep-wake disturbances. Study 3: The analysis of the trial is in progress; therefore we present only the methodology.

Conclusions: We found a very high prevalence of poor sleep quality and daytime sleepiness in RTx recipients. Sleep-wake disturbances are common, although caused by different predisposing and precipitating factors. Analysis of the data on the effect of bright light intervention is ongoing.

Key words: Renal transplantation, Bright light intervention, Saliva melatonin

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Objectives: This study is based on the hypothesis that the mechanisms of synaptic potentiation are disrupted in bipolar patients (BPD). A recent hypothesis, the synaptic homeostasis hypothesis [1], suggest that sleep is responsible for the regulation of the overall strength of cortical synapses. Specifically the function of sleep is to downscale the weight of cortical synapses, which increases progressively during wakefulness (and sleep deprivation) due to learning and plasticity processes. Here we propose to study the relationships linking depression, cortical plasticity and sleep. It is well known that in some of these patients sleep deprivation brings about clear improvement of depressive symptoms. Specifically, we asked whether the improvement of depressive symptoms occurring after total sleep deprivation (TSD) is related to a compensatory increase of synaptic potentiation induced by prolonged wakefulness. Thus, sleep deprivation would directly acts on neuroplasticity fundamental factors. Understanding the neural correlates of sleep deprivation of bipolar patients could provide useful information for guiding treatment [2].

Methods: To test this hypothesis we plan to employ a combination of transcranial magnetic stimulation (TMS) and high density electroencephalogram (EEG). This technique allows perturbing the spontaneous activity of the brain to measure directly and non-invasively cortical excitability in humans. Electroencephalographic responses to transcranial magnetic stimulation of the prefrontal cortex were recorded in 23 bipolar patients treated with three nights of total sleep deprivation interposed with three nights of sleep (recovery sleep). To monitor cortical excitability in each subject as a function of time awake, we performed 7 TMS/EEG sessions, from morning to evening, namely at the beginning, after the first night of total sleep deprivation, after the recovery night and at the end of whole treatment. Cortical excitability was measured as the immediate (IRS, 0-20ms) EEG response to TMS in the stimulated area (prefrontal cortex).

Results: To investigate the possible relationship between the measurable changes of cortical circuits and changes in the severity of the depressive psychopathology before/after treatment, a repeated measures analysis of variance showed a highly significant main effect of response to treatment ($P < 0.05$), with no significant interaction with time: IRS values were higher in responders than in non responders both at baseline and after the total sleep deprivation treatment. Moreover, changes of IRS before/after treatment followed similar slopes of time course in the two groups: IRS values increased progressively after one night of total sleep deprivation and decreased after one night of recovery sleep suggesting that prolonged wakefulness and repeated sleep deprivation may reactivate the normal processes of synaptic potentiation.

Conclusions: In accordance with the synaptic homeostasis hypothesis, sleep deprivation increases frontal cortex excitability, as measured by TMS/EEG, in patients affected by bipolar disorder, during a severe depressive episode. In association with the severity of the depressive psychopathology, cortical excitability predicts antidepressant response to repeated sleep deprivation suggesting that, in non responder depressed patients, the process underlying the build-up of synaptic strength may be even more impaired than in responder. Thus, the efficacy of sleep deprivation in activating the normal mechanisms of cortical plasticity in bipolar depressed patients may be related to the functional status of the cortical circuits before the treatment.

Keywords: Bipolar Disorder, Sleep Deprivation, Cortical excitability, TMS\EEG.
DAYLIGHT EXPOSURE DELAY REDUCES HOSPITALIZATION LENGTH AND SELF REPORTED SYMPTOMATOLOGY IN MANIC PATIENTS

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Objectives: Several studies linked wake–sleep and light–dark rhythms and psychopathological status in patients affected by Bipolar Disorder (BD). Patients affected by BD are more sensitive to the biological effects of light: the exposure to light can exert antidepressant effects and trigger rapid mood swings. A relationships were detected between mood, hours of sunlight, and solar exposure in affective patients, with admissions rates for mania correlating with length of day and levels of sunshine. A strict control of the wake–sleep and light–dark rhythms could act as a mood stabilizer. Some studies showed that extended bed rest and darkness could stabilize timing and duration of sleep, and rapidly improve mood swings in rapid cycling patients. The orientation of rooms in a Canadian ward provided a ‘natural experiment’ on the relationship between sunlight and length of hospitalization for depression (Beauchemin, 1996). In a first study carried out in 1999 and in a second study over a 3-year period (2008-2010) at San Raffaele-Turro Hospital in Milan this result was replicated. In a corridor with rooms on either side, windows are oriented towards the East (E) or the West (W). Ambient light intensity in the two conditions showed wide differences. Inpatients in E rooms had a shorter hospital stay than patients in W rooms. The aim of the present work was to investigate if inpatients affected by BD during Manic Episode show a similar sensibility to light exposure and therefore a therapeutic effect due to an extended dark period in terms of reduction of manic symptomatology, with an inverse relationship with respect to depressed patients.

Methods: We reviewed charts for all admissions for Manic Episode (DSM IV criteria), with a diagnosis of Bipolar Disorder, over a 9-month period (July 2011-March 2012) at San Raffaele-Turro Hospital of Milan, Italy (14 subjects) and at Santa Croce Clinic of Locarno, Switzerland (19 subjects), with the same rooms orientation. Rooms (E or W) had been randomly assigned based on first available free space. Young Mania Rating Scale (YMRS) was repeatedly administered to assess the basal level and the disease course. In addition sleep diaries and Self-Report Mania Inventory (SRMI) were administered to the Milan sub-sample (14 subjects). SRMI is a subjective, self-administered questionnaire which evaluates symptom perception and the levels of insight of a manic episode in bipolar patients. Medications were administered upon clinical need. According to daytime clinical activities, patients stayed in rooms in morning and evening hours. No exact recording of time spent in rooms is available. Length of hospitalization, based on room orientation, was calculated and compared for the whole sample of 33 (14 males, 19 females) Bipolar Manic inpatients.

Results: Patients hospitalized in E rooms and in W rooms didn’t show differences for clinic and demographic characteristics for both the locations: two groups were overlapped for gender distribution, age, diagnosis and YMRS basal scores. In addition the sleep diary administered in the Italian sample rooms showed no significant differences in amount of hours slept per night for patients in E rooms and W. Hospitalization was significantly shorter for W rooms, with a concordance of both the locations, than E rooms. Taking into account both the Milan sample and the Locarno sample (N° 33) we observed a length of hospitalization of 43.43 days for patients in E rooms (N° 23) and of 30.80 days for those (N° 10) in W rooms (T-test: 2.15; p=0.04). In addition SRMI administered in the Italian sample, showed differences between W and E rooms: specifically, subscale mean scores are higher in E rooms than W rooms, and this differences last throughout the entire hospitalization length.

Conclusions: Bipolar patients showed an increased sensitivity to the biological effects of light. Our results support the hypothesis that reduction of light exposure and the dark period expansion can have a therapeutic effect during Manic Episodes, and are consistent with studies stressing the role of photoperiodic mechanisms in the course of BD. In addition, the fact that no differences resulted in the average of hours slept for patients in E and W rooms implicates that the faster episode remission is not affected by amount of hours slept. Difference observed in some subscales of SRMI could suggest that manic patients in W rooms not only benefit of a faster symptom remission and therefore a shorter hospitalization length than those in E rooms, but also that their subjective perception of the manic episode and the level of insight seems to improve accordingly. These results, obtained with a prospective study, confirm our previous results that we had acquired with a retrospective ‘natural experiment’ presented in the SLTBR 2011. This confirms that it is important to control also environmental stimuli in the treatment of acute mania.

Bibliography:

Keywords: Circadian Rhythm, Bipolar Disorder, Manic Episode, Light Exposure, Dark Therapy
HUMAN MELATONIN AND ALERTING RESPONSE TO LIGHT DEPEND ON A POLYMORPHISM IN THE CLOCK GENE PER3

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Objectives: Nonvisual responses to light show maximal sensitivity to light at short-wavelengths [460–480 nm (blue) light] (Hattar et al., 2002). Novel evidence suggests that the PERIOD3 (PER3) variable-number, tandem-repeat polymorphism has a differential impact on cognitive brain responses to light, and to circadian phase and sleep pressure (Vandewalle et al., 2011). However, it is unknown whether the effects of this polymorphism are mediated by a different response to light or by an altered interaction of the sleep-wake homeostatic and circadian system. Here we investigated if interindividual differences in melatonin suppression, cortisol secretion and the alerting effect of light are driven by a clock gene polymorphism that is also involved in the regulation of human sleep-wake cycles.

Methods: Eighteen healthy young men homozygous for the PER3 polymorphism (9 PER3 5/5 and 9 PER3 4/4), matched by age, body mass index, and ethnicity, underwent three types of evening light exposure in a balanced crossover design during the winter season. During each protocol, participants spent 1.5 h under dim light, 2 h under complete darkness, 2 h of light exposure (compact fluorescent lamps at 40 lux with 6500 or 2500K or incandescent light bulbs at 40 lux with 3000 K), and a post-light episode of approximately 45 min under dim light until habitual sleep time. Salivary melatonin and cortisol were sampled every 40 minutes during scheduled wakefulness. EEG activity was recorded continuously during 6 h of scheduled wakefulness. The Karolinska Drowsiness Test (KDT) was performed hourly during scheduled wakefulness. The 3-min EEGs during the KDTs were manually scored for artifacts, and absolute EEG activity was calculated for artifact-free, 2-sec epochs in the frequency range of 0.5–20 Hz.

Results: We observed a wavelength-dependent attenuation of the evening increase in melatonin secretion, which was modulated by the PER3 polymorphism, such that melatonin significantly decreased in PER3 5/5 but not in PER3 4/4 individuals only after 90 min of blue light (p<0.05). Absolute levels of salivary cortisol tended to be higher in PER3 5/5 in comparison to PER3 4/4 individuals, but did not significantly differ with respect to the light conditions. Blue-enriched light significantly reduced subjective sleepiness in a genotype-dependent manner, such that PER3 5/5 were less sleepy in comparison to PER3 4/4 individuals. The subjective perception of sleepiness was mirrored by changes in waking EEG activity in the theta range (5–7 Hz), a correlate of sleepiness. These differences were such that theta EEG activity was significantly reduced during blue-light exposure in PER3 5/5 individuals as compared with PER3 4/4. Correlations between melatonin suppression and the alerting response to light, as indexed by subjective sleepiness, revealed that, only during blue-enriched light, PER3 5/5 had a strong correlation of the degree of melatonin suppression and the alerting response to light (r =0.77; p< 0.05), which was not observed in PER3 4/4 carriers.

Conclusions: Our data indicate that humans homozygous for the PER3 5/5 allele are particularly sensitive to blue-enriched light, as indexed by the suppression of endogenous nocturnal melatonin, subjective sleepiness and waking theta activity. Thus, light sensitivity may be modulated by a clock gene polymorphism also implicated in sleep-wake regulation. These findings may help to better understand the inter-individual variability of the nonvisual responses to light.

Keywords: Light, Melatonin, Waking EEG activity, PER3 polymorphism
Molecular Clock Biomarkers Predict Light-Dependent Melatonin Signaling in Human Subjects

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Circadian rhythms in human physiology and behavior are generated and synchronized to the environment by a master clock located in the suprachiasmatic nucleus of the brain hypothalamus. Neurons within the SCN, as well as most other cells in the body, contain intracellular molecular clocks driven by conserved autoregulatory transcriptional and translational feedback loops. Previously, our laboratory has conducted multiple studies to show that the clocks in SCN and peripheral tissues are highly similar. Therefore, variations in SCN-controlled circadian behavior among different individuals were mirrored by changes in fibroblast clocks measured in vitro.

However, beyond the core circadian clockwork, many other conserved signaling pathways influence both circadian clock function and its effects upon human physiology and behavior. These include universally used pathways like cAMP/CREB and MAP kinases, which have been implicated not only in clock signaling, but also in growth, metabolism, and cognitive function. We hypothesized that the same inter-individual differences that we observed in molecular clock function would also exist in these signaling pathways, and that variations would correlate with physiological differences in human neuroendocrine response, both circadian and otherwise.

Therefore, we developed a lentivirus–based reporter system that allowed us to measure expression profiles for chosen cellular pathways directly in human primary fibroblast cells. Using this system, we examined the activation profiles of three principal signaling pathways in fibroblasts from ten healthy human subjects. Surprisingly wide inter-individual variations in activation profiles were observed in all pathways, with fivefold to twentyfold differences in amplitude between the most extreme cases for each pathway. Moreover, these differences were matched by genome-wide alterations in transcription from promoters known to be activated by these pathways, as well as by differences in cellular sensitivity to toxins and efficacy of pathway-specific drugs.

To test the applicability of cellular pathway profiling to elucidate circadian neuroendocrine responses, we chose to examine the CREB pathway, which has been established to control melatonin synthesis and suppression in rodents. Ultimately, fibroblast profiling of CREB signaling was used to predict the degree of suppression of the hormone melatonin by light in human volunteers, demonstrating the applicability of cellular pathway profiling to complex responses in otherwise non-accessible tissues. Therefore, the resulting information can be a potent predictor both of simple drug efficacy and of more complex responses. Altogether, individual fibroblast profiling could be useful both clinically to determine optimal pharmacological treatments for different individuals, and genetically to map human modifier loci underlying human individuality in circadian and other signal transduction pathways.
PER2 PROTEIN RHYTHMS IN PERIPHERY ARE NOT SELF-SUSTAINED

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The SCN is both necessary and sufficient to drive circadian rhythms in overt behaviors in mammals. In contrast, at the cellular/tissue level, circadian rhythms depend on interlocking transcription-translation feedback loops involving clock genes. In vitro and ex vivo studies have convincingly shown that this molecular machinery generates self-sustained circadian rhythms independent of the SCN. We have previously reported that the expression of the core clock gene Period-2 (Per2) increases and that the DNA-binding of CLOCK, NPAS2, and BMAL1 decreases in the cerebral cortex after sleep deprivation (SD). Moreover, the homeostatic regulation of sleep is altered in mice carrying targeted deletions of clock genes. Together, these findings suggest that in the whole animal, clock gene rhythms in extra-SCN tissues do not reflect self-sustained oscillation but are, to some extent, sleep-wake driven. Using Per2::luciferase mice, we quantified, in the whole living mouse, the sleep-wake dependent and circadian contributions to the changes in PER2 protein under LD and DD conditions, after 6h SD, and after lesioning the SCN (SCNx). Under LD conditions large amplitude changes in PER2 were observed in brain, liver, and kidney (n=24). SD increased PER2 levels not only in the brain but also in liver and kidney. Immunohistofluorescence analyses demonstrated that SD affects PER2 mainly in the cerebral cortex leaving the SCN unaffected (n=6). In SCNx, arrhythmic mice (n=11) kept under DD conditions, PER2 expression in the brain, liver and kidney did not vary with time-of-day, consistent with the lack of a circadian sleep-wake distribution. These results demonstrate that despite an intact molecular circadian clock, PER2 does not oscillate in peripheral tissues in the whole animal when overt rhythms in sleep-wake behavior are lacking.
HOCKEY-STICK METHOD TO ESTIMATE EVENING DIM LIGHT MELATONIN ONSET (DLMO)

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Objectives: Melatonin is the best and most widely useful index of circadian timing in humans. In practice, sampling saliva in half-hourly to hourly intervals in the evening (when melatonin levels begin to rise) is sufficient to estimate circadian phase. The estimation so far is based on either a fixed threshold method (time of attaining a 1- or 3-pg/ml level) or dynamic threshold method (so-called "3k" or "5k": 2 SDs above the mean of three or five baseline values). However, the fixed method is problematic for inter-individual (and sometimes for intra-individual) comparison (e.g., low- vs. high-secretors). The dynamic method is hardly applicable when too few (less than 3) or inconsistent values form the baseline part of the curve. We developed an algorithm ("hockey-stick" method) to estimate the most probable time of turning from no-rise to rise in the evening melatonin profiles, a task long proposed but so far unsolved.

Methods: In total, 235 evening salivary melatonin profiles obtained from 85 participants in Novosibirsk and Basel studies were available for the analysis. The profiles were composed of 4 to 12 half-hourly melatonin values (rarely with gaps) forming the baseline and curves of the evening rise (to greater than 2.3 pg/ml). Approximately 75% of the melatonin profiles had a linear-like evening rise, while ~20% had accelerating or decelerating parabolic-like increase, in ~5% it was difficult to visually judge the inflection point. We tested different approaches to approximate the melatonin turning point on the profile, in the MATLAB software.

Results: A piecewise continuous linear-parabolic curve was chosen and its single equation was defined to fit the melatonin profiles. The curve was fitted using least-squares distance method. Several constraints and conditions were applied to the algorithm. The curve's inflection point indicated melatonin turning time, DLMO. Preliminary testing of the method, by visual inspection, yielded satisfactory results.

Conclusions: We developed a satisfactory programmed basis for the new hockey-stick method to approximate a turning point on the evening melatonin profiles. The algorithm is being currently transferred to an interactive executable module (.exe file) to be widely available.

Keywords: Dim Light Melatonin Onset, Algorithm

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CARE AND CHRONOBIOLOGICAL TREATMENT: THE ITALIAN EXPERIENCE AT SAN RAFFAELE-TURRO HOSPITAL, MOOD DISORDER UNIT


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Objectives: The Mood Disorder Unit is located in Milan at the San Raffaele-Turro Hospital within the Department of Clinical Neurosciences. It is a comprehensive multi-disciplinary structure, with psychiatric, neurological and psychological teams. It is organized with inpatients wards, outpatient services and day-hospital services. Specifically for psychiatry there are four different wards divided according to pathology, with more than 120 beds. The Mood Disorder Unit consists of 48 beds. There is an equipe of psychiatrists, residents, psychologists and students. The main fields of interest, in terms of research and therapies is chronobiology. Chronobiological applications are Light Therapy (LT) and Total Sleep Deprivation (TSD). Particular attention is focused on Bipolar Disorder (BD) and its stabilization, with lithium salts. The aim of this study is to provide a description of the main epidemiological features of our patients within a period of 21 months (from July 2010 to March 2012). We assess different diagnosis and therapies, such as mood stabilizers and antipsychotics, but also all antidepressants and non-pharmacological treatment such as chronobiological ones.

Methods: For this study we took into consideration all the patients consecutively admitted to our Mood Disorder Unit from July 2010 to March 2012, for a global observation that lasted 21 months. We checked the discharging papers of all the patients and also the outpatient documents in order to collect main epidemiological and clinical features of our population. We created a database and carried out statistical analysis with appropriate software.

Results: During the observation period we had 826 hospitalizations and a mean hospitalization length of 21.81 ± 11.75 days. The amount of patients treated was 726, in particular 626 (86.23 %) patients were hospitalized one time, 548 (75.47 %) of these patients regularly carry out check-ups at our out-service. Sex and gender distribution shows: 223 males (30.72 %) and 503 (69.28 %) females with a mean age of 54.18 ± 14.71 for males and 56.95 ± 14.22 for females. 766 cases contributed to a MD diagnosis (92.74 %), while in 60 cases (7.26 %) the diagnosis was not relevant to our Unit. Taking into consideration MD, the diagnosis distribution was: 325 cases (39.35 %) for Major Depression (MD) with a moderate Episode, 31 cases (3.75 %) for MD with a severe or delusional Episode, 221 cases (26.76 %) for BD with a moderate Episode, 20 cases (2.4 %) for BD with a severe or delusional Episode, 77 cases (9.32 %) for BD with a manic Episode, 36 cases (4.36 %) for BD with a mixed Episode, two cases (0.24 %) for Schizoaffective Disorder, 54 cases (6.54 %) for Unspecified MD. Focusing our attention on drug therapies for MD we took into consideration mood stabilizers in the first place. 32 / 356 (8.99 %) patients with MD and 246 / 354 (69.49 %) with BD take lithium salts. The second choice was sodium valproate for 9 patients with MD and 109 patients with BD (for 65 cases was in association with lithium salts). Other mood stabilizers used were gabapentin (N° 68), carbamazepine (N° 26), lamotrigine (N° 12) and topiramate (N° 8). The mean lithium dose for depressed patients was 635.56 ± 218.46 mg/die while for manic ones 816.00 ± 310.77 mg/die (t-value=4.68; p=0.00). Plasmatic lithium levels were 0.54 ± 0.19 mmol/l for depressed patients and 0.63 ± 0.18 mmol/l for manic patients (t-value=2.64; p=0.00). Non-pharmacological compounds were used as augmentation or substitutes of antidepressants. In particular our depressed patients were treated with LT in 65 cases, 99 patients underwent to LT and 27 patients had BP treatment. Taking into consideration TSD and BP, we underline that 95 patients underwent to this treatment and 27 (28.42 %) patients were discharged without any other drug. Antidepressants associated with TSD were fluoxetine in 18 (18.95 %) cases and venlafaxine in 15 (15.79 %) cases. There is a non statistical difference in terms of length of hospitalization between depressed patients treated with TSD and the others with a mean of 24.05 days for TSD groups and 26.07 days for the others (p=0.10). Antipsychotics have a low percentage of use: 63 / 597 cases (10.55 %) for depressed patients.

Conclusions: At the end of our analysis we can conclude that the 92.74 % of the hospitalizations were relevant to a Mood Disorder Unit. In our opinion this fact could give an extra profit to patients mostly in terms of cognitive distortion and psychoeducation. Most of our bipolar patients are stabilized with lithium salts (69.49 %). There is a significant difference in terms of dose and plasmatic levels between depressed patients and manic ones. In particular for patients affected by BD we use chronobiological treatments such as TSD (39.32 %), and about the 30 % of these don’t need antidepressants, with a difference in terms of hospitalization length of about 2 days. We tend to use antipsychotics just to treat delusional Manic Episodes or associated to tricyclics in case of resistant depression.

Keywords: Mood Disorder Unit, Bipolar Disorder, Chronobiology, Lithium
SLEEP-WAKE PROFILES AND LIGHT TREATMENT IN PATIENTS WITH CIRRHOSIS

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Objectives: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome which occurs in patients with cirrhosis, in relation to incomplete liver detoxification of neurotoxic substances of gut origin (i.e. ammonia). Sleep-wake disturbances are also common in these patients (Cordoba et al, 1998; Montagnese et al., 2009). However, their origin and their relationship with HE remain debated. In addition, they are not routinely sought for in clinical practice and therapeutic options are limited, due to impaired hepatic metabolism of common hypnotics and these patients’ sensitivity to psychoactive drugs (Montagnese et al., 2009). The aims of the present studies were to assess: 1) the relationship between excessive daytime sleepiness and HE; 2) the sleep-wake profiles of a group of hospitalised cirrhotic patients; 3) the effect of light therapy in hospitalised cirrhotic patients.

Methods: Study 1: One hundred and six consecutive outpatients with cirrhosis were enrolled. They were asked to answer yes/no to three questions investigating the presence of difficulties falling asleep, frequent night awakenings and excessive daytime sleepiness in daily life. All underwent formal HE assessment, to include wake electroencephalography (EEG) and paper-and-pencil psychometry. The EEG was analyzed spectrally and psychometric tests scored according to age-/education-adjusted Italian norms. Fifty-eight patients were followed up prospectively for 8±6 months, in relation to the occurrence of death/transplantation and HE-related hospitalisations.

Studies 2-3: Twelve consecutive inpatients were enrolled; five were hospitalised in standard single rooms and 7 in a single room with controlled lighting (wall-mounted lamp; automatic timed switching, variable light intensity/spectrum; Derungs-Waldmann Illuminotecina). Actigraphy and validated questionnaires were utilised to assess sleep quality [Pittsburgh Sleep Quality Index (PSQI)], daytime sleepiness [Epworth/Karolinska Sleepiness Scale (E/KSS)], diurnal preference [Horne-Östberg (HÖ)], sleep timing (diaries), circadian rhythms (6-sulphatoxymelatonin), quality of life [SF-36, Chronic Liver Disease Questionnaire (CLDQ)] and mood [Beck Depression Inventory (BDI)].

Study 3: Sleep timing and sleep quality were evaluated for 8.4±6.1 days. Four/12 patients underwent a second urine collection for 6-sulphatoxymelatonin (at 7 days from admission) and two/12 a further one (at 14 days).

Results: Study 1: No association was observed between increased sleep latency/night awakenings and indices of HE. In contrast, patients complaining of excessive daytime sleepiness had slower EEGs than their counterparts with no difficulties staying awake (p=0.05). Excessive daytime sleepiness was also associated with a history of HE (72 vs. 28%; p<0.01) and with a higher likelihood of developing HE during the follow-up period (p=0.07). Study 2: These patients had severely impaired night sleep quality (PSQI: 16.3±2.1), significant daytime sleepiness (ESS: 8.3±3.2) and an intermediate/moderately morning chronotype. Sleep diaries and actigraphy were consistent with subjectively reported sleep disturbances. Quality of life was also impaired (SF-36-physical: 22±9; SF-36-mental: 39±13; CLDQ: 4.3±0.2) and mood moderately depressed (BDI: 19±8). Study 3: The analysis of the full cohort is in progress. An obvious effect of hospitalisation in the room with controlled light was observed in an 82-year old cirrhotic patient who had been admitted for chest infection. Both at home and in hospital she had a tendency to sleep-wake inversion, with extreme morning sleepiness and restless nights. On discharge, after 15 days, she showed significant improvement in sleep-wake rhythms, with reduced daytime sleepiness (KSS: 6 vs. 8.5) and fewer night awakenings (3 vs. 7.5); she remained well at four weeks (De Rui et al., 2011).

Conclusions: A significant association was observed between HE and excessive daytime sleepiness, but not between HE and night-time sleep disturbance. Sleep-wake rhythms, quality of life and mood were severely compromised in hospitalised patients with cirrhosis. Analysis of the data on the effect of hospital-based light therapy is underway, but the presented case report is encouraging.

Key words: Cirrhosis, Light, 6-sulphatoxymelatonin

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RESEARCH INTO SLEEP AND RISKS OF CHRONIC DISEASE: TIME TO USE A ‘SLEEP-YEARS’ INDEX?

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Objectives: In the course of the Cologne Symposium 2002 “Light, Endocrine Systems and Cancer”, it was predicted (Erren TC, Neuro Endocrinol Lett 23 Suppl 2:61-70, 2002; Stevens RG, Neuro Endocrinol Lett 23 Suppl 2:57-60, 2002) that sleep duration can be causally linked to the development of internal cancers. In 2012, the sixth study on the issues concerned was published, reporting mixed results. With regard to how long one sleeps, initial (the first five studies) – but not all (one study) – epidemiological evidence supports the idea that there may be increased cancer risks in those who sleep less than others. Rather than assigning study individuals to fixed or average “baseline sleep categories”, such as ≤5, 6, 7, 8, ≥9 hours of habitual sleep as done in past studies, the accumulated amount of sleep over decades should be constructed in both retrospective and prospective studies. To achieve this end, this presentation explains why and how future epidemiological studies that investigate the links between “sleep” and health and disease may want to use a sleep-years index [SYI].

Methods: This presentation examines the roots of the SYI, explains why and how it should be used, and how it could be interpreted in rigorous studies of biologically plausible links between sleep, on the one hand, and the development of chronic diseases, such as internal cancers, on the other. Four key premises will be examined: An exposure parameter to assess “sleep” should (i) be simple, valid, feasible and affordable for studying populations, be they small or large; (ii) take note of, and be sensitive to, the fact that the habitual duration of sleep in individuals – certainly more often than not – changes over time; (iii) allow to capture sleep length characteristics over many years and decades – which should be of interest provided that the hypothesized causal links between sleep and the development of chronic disease were there; (iv) allow to capture sleep facets beyond its sheer duration and accumulated amount, such as sleep quality.

Results: Roots of the SYI go back to landmark smoking research in the 1940s. In retrospect, two “favourable facts facilitated” the landmark work (Wynder, EL, Am J Epidemiol 143:747-749, 1996). One, there was a strong association between smoking and lung cancer. Two, the information about relevant exposure was easily obtained. Exposure assessment was quite simple: researchers asked smokers how often and how much they smoked, and for how long they had been smokers. This information allowed researchers to obtain relevant exposure gradients in a straightforward way. Indeed, exposure information that was critical to unmask smoking as the cancer culprit was simply based on the number of cigarettes smoked per day and the number of years which study individuals had smoked (“pack-years” concept thereafter). Remarkably, the situation around smoking and lung cancer may have similarities with sleep and chronic disease. The facts that everyone is “exposed to sleep” over years and decades, on the one hand, and our inability to work with sensible gradients, on the other, may have hitherto masked a strong effect of sleep on the development of chronic disease. How would we obtain the relevant information on sleep? We could do so via interviews of study individuals, which seek information on the average length of sleep throughout the relevant period of time (many years and sometimes decades) preceding the development of cancer. To exemplify, 6 or 9 hours of sleep/day for a given year could correspond with 1 or 1.5 SYs, respectively. How would we interpret the lack of an association between SYs and the development of cancer? Not detecting associations would not necessarily exonerate the notion that there may be a link between facets of sleep and carcinogenesis. After all, the SYI may not be sensitive enough to the critical aspects of sleep, such as sleep quality. How would we interpret an association between SYs and the development of cancer? Detection of a significant correlation between SYs and cancer could imply that the quantity of sleep one gets has real effects, which may have a significant impact on public health.

Conclusions: The simple SY exposure parameter promises to be a sensible, feasible and affordable way to approximate cumulative time spent asleep in critical time windows over many years which we should expect to be relevant for the development of chronic disease, including cancer. The SYI could be tested and used in observational studies which promise to be comparable and may be merged. Interestingly, the proposed approach may prove useful beyond sleep studies per se. Research into suggested causal links between disrupted natural sleep-wakefulness cycles and increased cancer risks in shift-workers could also benefit. Finally, the suggested SYI is also a sustainable approach (Dyson F, Oxford University Press, 1999); indeed, while more complex scenarios such as looking into circadian genes may be academically tempting, their very interpretation within highly complex circadian system circuits will be very difficult and conceivably impossible. In addition, employing circadian gene analyses are – in view of associated costs – unlikely to become a part of routine methodology in observational studies that investigate possible links between sleep and chronic disease.

Keywords: Sleep, Sleep-Years, Sleep Duration, Sleep Quality, Sleep Accumulation, Light, Melatonin, Chronic Disease, Cancer, shift-work
CHRONOMEDICINE: AN OLD CONCEPT’S FLEDGING? A SELECTIVE LITERATURE SEARCH

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Objectives: Chronomedicine has been used as a term and somewhat pursued as a discipline for decades. However, it appears chronomedicine has captured a broader interest as a promising specialty only more recently. Chronomedicine can be conceptualized as dealing with the prevention, causation, diagnosis, and treatment of diseases in humans with a particular focus on the role “time” [Greek: χρόνος] plays in our physiology, endocrinology, metabolism and behavior at many organizational levels. This poster presentation has two objectives: (i) to examine roots of chronomedicine, and (ii) to possibly identify perspectives for chronomedicine. Researching the origins of chronomedicine should enable the appropriate recognition of groundwork and should help to avoid “re-inventing the wheel” pitfalls (Sanderson K, *Nature News* doi:10.1038/news.2007.341).

Methods: A selective literature search was conducted with regard to roots of chronobiology and chronomedicine in the 20th century via MEDLINE and the ISI WEB OF KNOWLEDGE.

Results: Classical terms of chronobiology, e.g., *Zeitgeber*, *melatonin* and *circadian* may be traced back to Aschoff, Lerner and Halberg, respectively. But roots of the terms chronobiology, chronopharmacology and chronomedicine are less clear. A key defining event of chronobiology as a scientific discipline was the Cold Spring Harbor Symposia on Quantitative Biology in 1960 (XXV: Biological Clocks). In retrospect, Halberg envisaged the direction of the field rather to be chronomedicine with a focus on humans and medical applications. To Pittendrigh, however, it was pivotal to determine the inter-species evolutionary and ecological pathways of chronobiology. The very term “chronomedicine” was used, and the discipline of chronomedicine as a whole was referred to, in publications decades ago. But identifying the specific roots and nestor(s) proves to be difficult. PUBMED and ISI WEB OF KNOWLEDGE searches of the word produced merely n=39 different hits between 1981 and 2011 in English (19), Russian (14), Chinese (3) and German (3). Examination of Russian texts suggested that the term appears to originate in the late 1960s to early 1970 in the former USSR.

Conclusions: This selective literature review can not conclusively answer the questions “who” first suggested the term chronomedicine and “how” it should be pursued. Insights from others to these open questions are welcome. That chronomedicine has been used merely 39 times over three decades in peer-reviewed literature abstracts may contradict the expectation that chronomedicine has prospect as an emerging discipline. However, in the field of chronobiology, animal-models for understanding human health and disease have been increasingly developed. Thus, it could be(come) rather straightforward to transfer abundant insights gained from chronobiology to strategies in chronomedicine. In addition, there are practical indications of chronomedicine’s fledging: dedicated meetings have been held in recent years, including this year’s Leopoldina symposium “The Circadian System: from Chronobiology to Chronomedicine” in Frankfurt, Germany. Moreover, the European Biological Rhythms Society’s mission statement starts out with “EBRS aims to promote chronobiology and chronomedicine”. At present, publications regarding insights of interest for chronomedicine (e.g., the discovery of pRGCs; suggestions for a light-associated perinatal imprinting of circadian system stability) can be found in core interdisciplinary journals such as Nature and Science. Other facets of chronomedical relevance are published in specialized journals which cover many links in the chains of causation that may be broken to promote health and prevent disease. To exemplify, causes of circadian disruption or chronodisruption are presented and discussed in occupational (shift-work) and environmental (light at unusual times) medicine and epidemiology journals; possible key intermediates such as melatonin are covered in neuroendocrinology and chronobiology journals; and endpoints such as cancer, sleep or mental disorders et cetera are published in cancer, oncology, sleep and psychiatry journals. Overall, due to the “maturing” of chronomedicine as a field, one might think about a section dedicated to chronomedicine in existing journals, or even a ‘journal of chronomedicine’ as vectors of ideas and research. There appear to be good reasons that the near future could bring precisely that.

Keywords: Chronomedicine, Chronobiology, Zeitgeber, Melatonin, Aschoff, Lerner, Halberg, Pittendrigh
A PERINATAL SIGNATURE OF LIGHT ON BIOLOGICAL RHYTHM STABILITY: IMPLICATIONS FOR EXPERIMENTAL RESEARCH

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Objectives: First tantalizing evidence from experiments suggests that perinatal photoperiods may imprint the stability of circadian clocks and systems and may determine their very stability with regard to exposures to light and other Zeitgeber cues later in – and possibly throughout – life. At the 2011 SLTBR meeting, we translated suggestions by Ciarleglio et al. and Ohta et al. into a hypothesis, corollary and associated predictions that can be systematically investigated in epidemiological research. Our objective at the 2012 SLTBR meeting is to identify possible questions and consequences of the – yet unreplicated – findings for experimental research. To illustrate possible implications of an unrecognized and unappreciated perinatal imprinting on circadian system stability, a case study of a long-time experimental conundrum is presented.

Methods: We explore three theses via a selective literature review: (i) Experimental animal research should record and publish details of the perinatal season/perinatal light:dark [L:D] conditions animals were kept under. (ii) Experimental research should provide answers as to how perinatal experimental conditions compare with animals that are bred and raised under wildlife conditions. (iii) Melatonin will likely have a key role in perinatal light-associated imprinting of circadian clocks and circadian system stability.

Results: Regarding (i): As long as rigorous research has not falsified the hypothesis of a perinatal signature of light on circadian system stability, conclusions of experiments that investigate determinants of health and disease may be regarded as incomplete without the perinatal L:D information. Such information can be relevant in understanding individual experiments independently as well as in comparisons with others. Regarding (ii): Perinatal experimental conditions chosen for convenience and comparability of animals may have introduced biases that need to be investigated. For instance, how does the reproductive system of hamsters respond to short day exposure when they are born in the laboratory (under a light dark cycle of, for example, 14:10) compared to responses of hamsters born in the wild (where they are born in underground burrows and remain in constant darkness until they are weaned)? Regarding (iii): It is reasonable to expect that melatonin will play an important role in the suggested imprinting of circadian systems, for instance as a messenger of environmental time in whatever time window – early or late – of developmental stages. Initial empirical evidence suggests that melatonin is implicated by relating the developing perinatal circadian time-keeping system to environmental signals which the mother receives and communicates.

Case study: In 2004, Fedrowitz et al. (Cancer Res 64:243-251, 2004) resolved “Why different labs doing what appear to be identical experiments, produce conflicting results” (Slesin, http://www.microwavenews.com/geneticsstupid.html, 2004) through systematic work. After diligent analyses, the authors concluded that “Probably the most important difference between our and the Battelle studies was the use of different substrains of SD [Sprague-Dawley] rats” (Fedrowitz et al., 2004) when investigating whether power-line frequency (50-Hz) magnetic fields have co-carcinogenic or tumor-promoting effects or not. Slesin summarized the long-lasting controversy of conflicting replication studies in EMF research between 1993 and 2004, albeit in a somewhat provocative way, as “It’s genetics, stupid” (Slesin, 2004).

In a similar vein, we may postulate today “It’s when and how they were raised” when trying to explain results in animal experimentation regarding biomedical results. Indeed, unless proven otherwise, ignoring the biological plausibility of perinatal imprinting of circadian clocks and systems, and thus differential susceptibility to a host of exposures, may leave us with animal experiments that are not interpretable.

Conclusions: The quoted experiments will clearly have to be replicated and extended. And, equally clearly, our above advice to publish perinatal season or perinatal light:dark [L-D] conditions experimental animals are/were kept under may have to be considered by journals that publish experimental animal studies. After all most, if not all, animal responses to experimental conditions – until proven otherwise – show some circadian rhythmicity and/or are affected by biological rhythms. Authors who gathered this relevant information in the past may want to revisit their work in the light of the possible impact of a perinatal imprinting of circadian system stability on study results and their interpretation.

Keywords: Light, perinatal, circadian clocks, circadian systems, imprinting, experimental research, wildlife conditions
EXPLORATION OF 5 THESES REGARDING EFFECTS OF LIGHT HYGIENE AND RHYTHM HYGIENE ON HEALTH, SLEEPINESS AT WORK AND SLEEP DISORDERS AT HOME

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Objectives: (A) To provide current evidence for effects of lighting environments on health, sleepiness at work and sleep disorders at home. (B) To identify insights – new and old – that could be used to contribute to lighting environments which are improved in terms of light hygiene and rhythm hygiene. Our focus on light is based on 4 premises: 1. While there are many Zeitgeber (Aschoff J, Naturwissenschaften 38:506-507, 1951; Naturwissenschaften 41:49–56, 1954) cues which concur and compete, light and the absence of light can be considered as key time cues for circadian rhythmicity, health and performance; 2. Lighting environments can be specifically designed; 3. Individuals can be selected for specific lighting environments; 4. Endpoints with regard to facets of “sleep” were chosen in view of its pivotal role for health and disease in many species, including man.

Methods: We explore the validity of 5 interrelated theses with available data: (i) Treatment with light of differential intensity and composition at work and/or at home can decrease sleepiness and sleep disorders. (ii) Lighting environments can be designed to maximize short-term alertness and performance at the cost of circadian disruption or chronodisruption (CD; Erren et al., J Pineal Res. 46:245-247, 2009). (iii) Lighting environments can be designed to minimize/eliminate CD. (iv) Individuals who are more robust to defined lighting environments than others can be identified. (v) Individuals who are more susceptible to defined lighting environments than others can be identified. With regard to (i), we instigated a systematic COCHRANE review of Randomized Clinical Trials (RCTs) in 2012. With regard to (ii) – (v), we conduct a selective literature review.

Expectations: Regarding (i): The rigorous COCHRANE search strategy aims to identify all RCTs and epidemiological studies that have been published with regard to the issues concerned. The COCHRANE review of RCTs will be completed in 2013. Moreover, our international consortium will conduct meta-analyses of the identified cohort and case-control studies. Regarding (ii) – (v): The selective literature review promises identification, or the lack, of relevant information on differential lighting environments, on the one hand, and on individuals’ differential susceptibility to lighting environments, on the other. From an a priori viewpoint, we expect that the individual chronotype (Erren TC, Epidemiol Perspect Innov. 30;7:11, 2010) could be a valid explanatory variable (“predictor”) to be tested with regard to all 5 theses.

Tentative conclusions: The 5 theses above need to be systematically explored. The envisaged COCHRANE review and meta-analyses promise a synthesis of what we “know” and “what we don’t know”. Both identifying insights and patterns across studies and lacks of knowledge with regard to (i) through (v) must be considered when planning future studies. As a general strategy, we need sustainable approaches, i.e., measures which are feasible and come at costs that make them candidates for follow-up projects rather than limiting them to one- or two-time enterprises. With considerable likelihood, employing the individual chronotype to theses (i) through (v) could be a candidate approach to base both research and preventative measures on and would meet the sustainability criteria suggested by Dyson (Dyson F, Oxford University Press, 1999).

Keywords: Light, Light Hygiene, Rhythm Hygiene, Sleep, Sleepiness, Sleep Disorders, Cochrane Review, Meta-Analyses, Randomized Clinical Trial (RCT), Cohort Study, Case-Control Study, Chronotype, Susceptibility, Sustainability
AGE-RELATED EFFECT OF BRIGHT LIGHT EXPOSURE ON CIRCADIAN RHYTHMS AND COGNITIVE PERFORMANCES

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Objectives: Light exposure elicits numerous effects on human physiology and behavior. However, it remains inconclusive whether daytime light exposure has beneficial effects on cognitive performance and circadian physiology during sleep deprivation (SD) and even less whether this light affects young and older people in the same way. Here we investigated the role of light exposure as a countermeasure for impaired cognitive performance and sleepiness during SD.

Methods: Currently, 16 participants (11 young (23.4±0.5) and 5 old (65.6±2.4)) have completed the in-lab part of the study, which consists of a balanced cross-over design with light exposure during 40h of sleep deprivation. Participants underwent two sessions where they were subject to either a bright light (BL: 250 lux) exposure or a dim light (DL: 8lux) exposure. Cognitive tests were performed every 2.5h and questionnaires were administered hourly to assess subjective sleepiness. Salivary melatonin was collected at regular intervals.

Results: Analysis of cognitive performance yielded a significant main effect of "light condition" (p<0.0001) in both age groups. Cognitive performance remains stable across time but with a significantly higher level in BL compared to DL. Analysis of subjective sleepiness revealed no significant differences in the aged. However, a main effect of "time" (p<0.0001) and "light" (p<0.0001) condition were observed in the young, such that bright light exposure led to a lower level of sleepiness until the end of the biological night. On the second day, these differences did not further reveal significances between BL and DL. Concerning the melatonin, no significant differences were observed in the aged, whereas in the young, we observed a significant main effect of the condition "light" (p= 0.0006), "time" (p<0.0001) and the interaction between this 2 conditions (p= 0.0038). Bright light exposure led to a phase delay of melatonin onset.

Conclusion: Our preliminary data indicate that light exposure during a SD protocol improves subjective sleepiness and affects circadian phase markers in young participants. However, these differences are not emerging in the older people, but these results should be confirmed with largest effectives. On the other side, BL improves cognitive performance in both age groups. In a broader context, these light conditions may provide an effective rationale for enhancing performance and sleepiness in individuals who experience prolonged wakefulness.

Keywords: Age, Extended light exposure, Circadian rhythms, Cognitive performances

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ENHANCING SLEEP IN HOSPITALS WITH PATIENT ROOM LIGHTING

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Impaired sleep has negative consequences for health. Sleep within most hospitals is less optimal than in the home situation. Light strongly influences the 24 h sleep-wake pattern and has a broad impact on health and well-being, also within healthcare settings. Lighting standards for hospitals prescribe a horizontal illuminance of at least 300 lux. This is relatively modest as compared to the natural daytime illuminance outdoors. Objectives: To investigate the effects of a dynamic, ambience providing, electrical hospital patient room lighting system on total sleep duration (TSD), sleep onset latency (SOL), depression-, anxiety-, and satisfaction-scores.

Methods: Cardiovascular patients (n=171) of the Maastricht University Medical Center were assigned to a control room with standard lighting, or to an intervention room equipped with a prototype of the Philips HealWell lighting system. This system provides general lighting with automated gradual changes in correlated color temperature and illuminance across the day. The maximum vertical illuminance at eye level exceeds 750 lux. Moreover, the system comprises (multicolor) lighting elements for a pleasant ambience with bedside control for the patients. Sleep was measured by means of Actiwatch-Spectrum® devices. Questionnaires were used to probe depression & anxiety (HADS) and satisfaction.

Results: Mixed-effect linear regression analysis revealed a significant intervention by time interaction. After 7 days in the intervention room TSD increased by 8% and SOL was reduced by 32% as compared to the first night, whereas both parameters hardly changed in the control room. Satisfaction scores of patients and staff for the intervention lighting system were significantly higher as compared to the standard lighting of the control condition.

Conclusions: The present lighting intervention achieves modest benefits on various sleep parameters of cardiovascular patients. Patients and nursing staff positively appreciate the intervention lighting system.

Keywords: Artificial lighting, hospitals, wrist actigraphy, sleep, satisfaction.

Funding support: Application Solutions, Philips Lighting, Eindhoven, Netherlands.
RELATIONSHIP OF MELATONIN CIRCADIAN PHASE TO NEUROBEHAVIORAL VULNERABILITY TO SLEEP LOSS

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Objectives: Subjects undergoing sleep restriction show differential neurobehavioral vulnerability to sleep loss, but reliable markers for predicting such inter-individual differences remain elusive. This study determined whether circadian phase, as measured by dim light melatonin onset (DLMO), is a predictor of neurobehavioral vulnerability responses to chronic sleep restriction.

Methods: 17 healthy adults (30.2 ± 8.9 y; 7 females) completed 2 baseline (10h time in bed) nights followed by 5 consecutive sleep restriction nights (4h time in bed) in a laboratory experiment. Neurobehavioral testing, including the Psychomotor Vigilance Test (PVT), Digit Symbol Substitution Task (DSST) and Karolinska Sleepiness Scale (KSS), occurred every 2h during wakefulness. Modified Maintenance of Wakefulness Tests (MWTs) were conducted between 1445h-1600h during the 1st and 5th sleep restriction days. Sleep onset latency was defined as time to the first microsleep (10-sec EEG theta) or 30 minutes if no sleep occurred. Subjects provided 13 saliva samples at 30-minute intervals, under <50 lux, from 1930h-0130h after the 2nd baseline night and the 4th sleep restriction night. DLMO was defined as the first interpolated point at 3.0 pg/ml on the rising curve of melatonin concentration.

Results: As a result of dim light conditions, DLMO significantly phase delayed from baseline to the 4th sleep restriction night (paired t-test, p<0.0001). Baseline DLMO did not predict PVT performance (lapses or 1/RT), DSST performance, MWT sleep onset latency, or KSS scores during the 1st day after sleep restriction (Spearman rank-order correlation coefficients; p’s>0.05). DLMO on the 4th sleep restriction night failed to predict PVT or DSST performance, or KSS scores during the 5th day after sleep restriction (Spearman rank-order correlation coefficients; p’s>0.05), but was significantly related to MWT sleep onset latency (rho=-0.64; p=0.006), whereby earlier circadian phase predicted a greater ability to resist sleep.

Conclusions: Melatonin circadian phase after several nights of sleep restriction predicts the ability to resist sleep during the next afternoon, but does not relate to diurnal neurobehavioral performance. Melatonin circadian phase may be a biomarker for predicting individual differences in physiological alertness in response to sleep restriction, though more data are needed to confirm this finding.

Keywords: DLMO, Individual Differences, Sleep Deprivation, Cognitive Functioning, Alertness

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GENETICS OF BIOLOGICAL RHYTHMS IN HEALTHY POPULATIONS - WHAT ARE THE IMPLICATIONS FOR MOOD DISORDERS?

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Objectives: Healthy adults show large, highly reliable (trait-like) individual differences in the magnitude of cognitive performance, fatigue and sleepiness, and sleep homeostatic vulnerability to acute total sleep deprivation and chronic sleep restriction. The factors underlying these stable phenotypic differential vulnerabilities are unknown, but are not accounted for by demographic factors, chronotype, IQ or sleep need. The stable, trait-like (phenotypic) inter-individual differences observed in response to sleep loss—with intraclass correlation coefficients accounting for 58%-92% of the variance in neurobehavioral measures—point to an underlying genetic component. To this end, laboratory studies were used to investigate the role of three common candidate gene variants [PERIOD3 (PER3), Circadian Locomotor Output Cycles Kaput (CLOCK), and catechol-O-Methyltransferase (COMT)]—each independently—in relation to cumulative neurobehavioral and sleep homeostatic responses to chronic partial sleep deprivation. Notably, chronic partial sleep deprivation is similar to the sleep-wake patterns found in bipolar disorder and other mood disorders whereby patients experience repeatedly curtailed or fragmented sleep rather than loss of an entire night of sleep.

Methods: 129 healthy adults (29.9 ± 6.9y; 63 females) completed 2 baseline nights of 10 hours time in bed per night, followed by 5 consecutive sleep restriction nights of 4 hours time in bed per night in controlled laboratory experiments assessing physiological sleep responses and neurobehavioral measures. Genotypes were determined via standard, previously published extraction and genotyping techniques. Comparisons were made across groups defined by genotype; statistical analyses were corrected for ethnicity differences as appropriate.

Results: The variable number tandem repeat polymorphism in the circadian gene, PER3, related to individual differences in sleep homeostatic responses, but not performance responses to chronic partial sleep deprivation. The T3111C polymorphism of CLOCK, a core circadian gene, predicted individual differences in executive functioning performance on the Tower of London, and sleepiness and mood differences during sleep loss. The COMT Val158Met polymorphism, involved in cognitive performance, predicted individual differences in sleep homeostasis and physiology—but not in cognitive and executive functioning—resulting from chronic partial sleep deprivation.

Conclusions: These data collectively indicate that common genetic polymorphisms involved in circadian, sleep-wake, and cognitive regulation may serve as markers for prediction of inter-individual differences in sleep homeostatic and neurobehavioral vulnerability to chronic partial sleep deprivation in healthy adults. Beyond healthy sleepers, these results may provide insight into predicting sleep, alertness and cognitive responses to sleep loss in patients with mood disorders, since these groups repeatedly experience chronically-curtailed sleep and also demonstrate PER3-, COMT-, and/or CLOCK-related treatment responses, as well as risk factors for symptom development, exacerbation or recurrence.

Keywords: DLMO, Individual Differences, Sleep Deprivation, Cognitive Functioning, Alertness

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BLUE LIGHT IN THE MORNING PHASE ADVANCES THE RHYTHM OF MELATONIN AND REDUCES SLEEPINESS AT WAKING UP

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Objectives: It is known that light in the morning is able to induce phase advances of the endogenous clock, but optimal treatment parameters have not been identified. In theory, a high intensity short morning-light pulse in the short-wavelengths-range (blue light) should be capable of inducing phase advances. If true, this could be a highly applicable basis for light treatment in late chronotypes who suffer from a late sleep phase.

Methods: In our home-study carried out in summer, 13 relatively late chronotypes (aged 23-27y, 6f/7m) participated in three conditions: (1) 3 consecutive days of 30 min blue morning-light exposure, (2) 3 consecutive days of 60 min blue light exposure and (3) a control week. The blue light pulse was applied by use of the Philips GoLite BLU (HF3320, blue leds, intensity at the cornea ~3.6E+14 photons/cm²/s between 460-480 nm).

Results: DLMO (dim light melatonin onset) significantly advanced to an amount of 50 min (SD 63) after three days with 30-min blue light pulses (p<0.01), which was statistically not different (F(1,12)=0.01, ns) from the average phase advance of 48 min (SD 31) after three days with 60 min light pulses (p<0.01). During the control week with no light pulses, a non-significant delay of 30 min (SD 79) was observed over three days, which was significantly different from both light conditions (F(2,11)=5.0, p<0.05). In addition to the blue light pulses, we calculated the total amount of environmental blue light that subjects received at eye level during different parts of the day. Our preliminary data (n=6) suggest that day to day differences in the phase of DLMO are related to the morning/evening environmental blue light ratio; the higher the ratio the earlier DLMO. There was a reduction in sleepiness (Karolinska Sleepiness Scale, KSS) immediately after waking up on days with light (compared to the baseline day) in both light conditions which was significantly different from the course of sleepiness after waking up in the control week (30 min. & control F(2,11)=8.5, p<0.05), 60 min. & control F(2,11) = 7.5, p<0.05). Sleepiness ratings in the 30 min. light pulse week were not significantly different from those in the 60 min. light pulse week (F(2,11) = 2.7, N.S.).

Conclusions: Both 30 min. and 60 min. pulses of high intensity blue light at home in the morning are capable of inducing a phase advance of the melatonin rhythm of almost 1 hour within three days. This is accompanied by a rapid reduction of sleepiness after waking up.

Keywords: Circadian rhythm sleep disturbance, Late chronotype, Blue light therapy, Melatonin, Sleep inertia

Funding Support: The work was financially supported by an unrestricted research grant of Philips Consumer Lifestyle B.V, Drachten, The Netherlands and by the 6th European Framework project EUCLOCK (018741).
A COLOR TEMPERATURE COMPARISON ON MELATONIN REGULATION IN HEALTHY HUMANS FROM A SOLID-STATE LIGHTING ASSEMBLY IN A REPLICA OF THE INTERNATIONAL SPACE STATION CREW QUARTERS

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Objectives: In the near future the current fluorescent lighting system aboard the International Space Station (ISS) will be replaced by Solid-State Lighting Assemblies (SSLAs) utilizing arrays of light emitting diodes (LEDs). The SSLAs will provide an opportunity to control light illuminance as well as the blends of wavelength and its resultant correlated color temperature (CCT) aboard the ISS. This unprecedented control of onboard lighting may allow for improving astronauts’ circadian, neuroendocrine, sleep and neurobehavioral regulation. To test the SSLA’s capacity to suppress nighttime melatonin secretion, a replica of the ISS crew quarters (CQ) with similar interior dimensions, volume, and luminaire placement was constructed. The CQs on ISS provide astronauts private space for waking activities and sleeping. Our aim was to test the hypothesis that arrays of LED light which include more wavelengths in the blue-appearing portion of the spectrum with a CCT of 6,500 K will have increased efficacy for melatonin suppression when compared to low CCT light of 2,700 K.

Methods: Acute plasma melatonin regulation is being assessed in two separate cohorts of healthy males and females (mean age 26.8 ± 0.6 years, N=8 per group) with normal color vision (mean FM-100 score 104.8 ± 15.0) in two ongoing protocols. Subjects in both studies are being exposed to nine irradiances of light at a long-wavelength shifted CCT of 2,700 K or light at a short-wavelength shifted CCT of 6,500 K. Each experiment includes a dark control exposure and experimental nights have at least one week between each exposure. After being blindfolded for two hours, volunteers sit quietly inside the CQ replica and are allowed to gaze in any direction during light exposure while doing various tasks not involving any additional light sources. The volunteers’ pupils remain freely reactive during the light exposure between 2:00 and 3:30 AM. Blood samples are collected before and after light exposure and are quantified for melatonin by radioimmunoassay.

Results: Preliminary repeated measures ANOVA for the melatonin suppression show that there is a significant difference across control-adjusted percent difference plasma melatonin levels (2,700 K, F=10.66, p < 0.0001; 6,500 K, F=14.22, p < 0.0005) with Fisher’s PLSD post-hoc testing showing significant differences between multiple intensities. With additional data after completion of the studies, dose-response functions of melatonin suppression versus intensity will be calculated and the half-saturation constants will be compared.

Conclusions: The data provided support the hypothesis that light which includes more wavelengths in the blue-appearing portion of the spectrum with a higher CCT has an increased efficacy for melatonin suppression when compared to low CCT light. These studies will help determine if SSLA lighting can be used to serve as an in-flight countermeasure for circadian disruption and sleep during long duration space exploration.

Keywords: Light, Melatonin, Circadian Rhythms, Correlated Color Temperature

Funding Support: National Space Biomedical Research Institute through NASA NCC 9-58 and NASA #NNX09AM68G.
ASSOCIATIONS BETWEEN MELANOPSIN GENE POLYMORPHISM AND NON-VISUAL RESPONSES TO LIGHT

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Objectives: Melanopsin-containing retinal ganglion cells (mRGCs) play an important role in non-visual responses to light, such as circadian phototentrainment, light-induced melatonin suppression and pupillary light reflex. There are some single nucleotide polymorphisms (SNPs) in the melanopsin gene in humans (NCBI dbSNP). However, the associations between melanopsin gene polymorphism and non-visual responses to light remain unclear. We examined the associations of melanopsin gene polymorphism with pupillary light response and light-induced melatonin suppression.

Methods: One hundred ninety-three healthy Japanese university students (mean age: 21.1 ± 1.8 years) with normal color vision participated in our study. All participants gave written informed consent and the study was approved by the local research ethics committee. Genomic DNA was extracted from hair follicle cells. Target regions of the melanopsin gene were rs2675703 (P10L) and rs1079610 (I394T), which are the SNPs in coding regions. Pupil diameter was measured under six lighting conditions (<1 lx, 10 lx, 1000 lx, 3000 lx, 6000 lx). To measure light-induced melatonin suppression, the subjects were exposed to bright light (1000 lx and 4000 lx) for three hours at night, and salivary samples were collected every hour.

Results: Significant interaction between the genotype of rs1079610 and luminance levels was found in pupil diameter. Pupil diameter in the C/C + C/T genotype group (n=38) under low illuminance light (< 1 lx) was significantly larger than that in the T/T genotype group (n=58). On the other hand, pupil diameters in the C/C + C/T genotype group under high illuminance light (3000 lx and 6000 lx) were significantly smaller than those in the T/T genotype group. Light-induced melatonin suppression was compared between different genotypes at rs1079610. Although salivary melatonin concentration was significantly decreased by exposure to both lighting conditions, no significant differences were found between the percentages of melatonin suppression in the two genotype groups.

Conclusions: We found a significant association between SNP at rs1079610 of the melanopsin gene and pupillary light response, suggesting a functional connection between melanopsin gene polymorphism and non-visual response to light. However, we failed to find a significant association between this SNP and light-induced melatonin suppression. Other environmental and/or genetic factors may affect individual variation in light-induced melatonin suppression.

Keywords: Melanopsin gene polymorphism, melatonin suppression, Pupillary light response

Funding support: This study was supported by Grant-in-Aid for Scientific Research (No. 22657063 and No. 24370102) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.
THE EFFECT OF TRANSCRANIAL BRIGHT LIGHT TREATMENT VIA EAR CANALS ON HUMAN PSYCHOPHYSIOLOGY – A RANDOMIZED CONTROLLED STUDY

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Objectives: Conventional bright light therapy has commonly recognized to improve cognitive performance and mood. Recently, transcranially administered bright light via ear canals (TBL) has found to alleviate symptoms of SAD. In addition, TBL stimulation has proved to modulate the neural networks of the human brain inducing a gradual increase in functional connectivity of lateral visual and sensomotor networks (Starck et al., WJNS, in press). The aim of the present study was to investigate whether the TBL has effects on cognitive performance and depressive symptoms in young healthy adults.

Methods: Forty one healthy university students (age: 24±4 years) participated in this study. Subjects were randomly divided into the TBL and control (C) groups. During three week study period, subjects in TBL group received 12 min daily doses of TBL via both ear canals. TBL was administered at morning after awakening at home. TBL was produced using blue based light emitting diodes (LEDs). Scientifically validated CogniSpeed© software was utilized for measuring attentional performance by Recognition Task (RT), which measures temporal threshold for the recognition of masked character presented to subject. The depressive symptoms were evaluated using Beck depression inventory® (BDI-II).

Results: At baseline TBL and C groups did not differ significantly regarding age, gender and depressive symptoms. After study period significant difference (p=0.018) was found between TBL and C groups in improvement of attentional performance (RT). Recognition time decreased in TBL group 20ms. Corresponding value for C group was 3ms. Furthermore, depressive symptoms decreased significantly in TBL group compared to C groups (p<0.044). The mean BDI total score decreased in TBL group from 4.39 to 2.69. Corresponding decrease in C group was from 4.76 to 4.52.

Conclusions: TBL treatment improves attention performance measured by recognition task in young healthy adults. A plausible mechanism for the faster recognition of characters in TBL group could be linked to the earlier findings of increased power of low frequency fluctuations and functional connectivity increase in healthy controls during single bout of TBL (Starck et al., WJNS, in press). Based on this TBL might be altering phase-locking fluctuations in neuronal networks by affecting stochastic resonance and thus increase in recognition capability in the TBL subjects (Velasquez et al., J. Biol. Phys. 33: 49-59, 2007). Furthermore, significant decrease in depressive symptoms in healthy subjects is worth noticing.

Keywords: Transcranial Bright Light, Attentional Performance, Recognition Time, Depressive Symptoms

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THE GASEOUS MESSENGER CARBON MONOXIDE IS RELEASED FROM THE EYE INTO THE OPHTALMIC VENOUS BLOOD DEPENDING ON THE INTENSITY OF SUNLIGHT

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Objectives: The study was designed to determine whether the concentration of carbon monoxide (CO) in the ophthalmic venous blood changed depending on the phase of the day and differing extremely light intensity seasons: summer and winter. Circadian and seasonal rhythms in the daylight affect many physiological processes. In the eye, energy of intense visible light not only initiates a well-studied neural reaction in the retina, that modulates the secretory function of the hypothalamus and pineal gland but also activates the heme oxygenase (HO) to produce carbon monoxide (CO).

Methods: All the procedures were carried out in compliance with Polish legal regulations (act of January 21, 2005), which determine the terms and conditions for performing experiments on animals, and were in accordance with the protocol of the Local Ethics Commission for Animal Experiments in Lublin No. 8/2007. Mature males of a wild boar and pig crossbreed (12 months of age, body mass ~100-120 kg, n=16) were used for the study. The animals were housed in an experimental farm in Kolbuszowa (50°N) near Rzeszów (Physiology and Reproduction of Animals Department, Rzeszów University). They were kept under natural illumination and had ad libitum access to water and food. Under general anesthesia two silastic catheters (o.d., 2.4 mm; i.d., 1.8 mm) were inserted into the dorsal nasal vein. The first catheter was directed into the proximal part of the nasal vein to collect nasal venous blood. The second catheter was inserted in the opposite direction such that it passed through the angularis oculi vein and ended near the venous ophthalmic sinus. This catheter placement allowed for the collection of venous blood flowing out of the eye. Two additional catheters were inserted into the carotid artery and jugular vein to collect systemic arterial and venous blood. For two consecutive days, blood samples (10 ml) were collected from the nasal vein and the venous ophthalmic sinus every four hours during the day (4:00, 8:00 and 12:00 a.m. and 4:00, 8:00 and 10:00 p.m.) and every two hours during the night (12:00 p.m., 2:00 a.m.). Systemic arterial blood samples were simultaneously collected every eight hours during the day, and systemic venous blood samples were collected every eight hours during the day and night from each animal.

Results: During the longest days of the summer the concentration of CO in ophthalmic venous blood averaged 3.32 ± 0.71 and 3.43 ± 0.8 nmol/ml in the morning and afternoon, respectively, and was significantly higher than in the night averaging 0.89 ± 0.12 nmol/ml (p<0.001). During the shortest day of the winter CO concentration in ophthalmic venous blood was 1.11 ± 0.10 and 1.13 ± 0.14 nmol/ml during the light and nocturnal phase, respectively, and did not differ between phases, but was lower than in light phase of the summer (p<0.01). The CO concentration in the control nasal venous blood did not differ between seasons and day phases and was lower than in ophthalmic venous blood during the summer (p<0.01) and winter (p<0.05).

Conclusion: The results indicate that the gaseous messenger carbon monoxide is released from the eye into the ophthalmic venous blood depending on the intensity of sunlight. In the periophthalmic vascular complex (ophthalmic venous sinus and rete mirabile of external ophthalmic artery) the arterial and venous blood stream are closely located to each other making it possible for counter current exchange of particles with the tendency to balance concentrations. We suggest, that under these conditions, after COHb dissociation, CO (size of 28.01 Da) may permeate from venous to arterial blood and be retrograde transferred with ophthalmic arterial blood. It may affect the function of ophthalmic vessels (as exogenous molecule) by influencing the synthesis of cGMP and increasing retinal and choroidal blood flow as it was found after inhaling CO in healthy humans. Venous blood from the ophthalmic sinus with high concentration of CO flows to the cavernous sinus. It is probable that CO, according to Oren’s concept, may be transferred from venous blood of the cavernous sinus to the arterial blood of rete mirabile of the carotic artery supplying the pituitary and the brain, similarly as it was discovered for numerous neuropeptides and steroid hormones. We suggest that the increased amount of CO in the blood circulating in the area of the brain during the summer acts as a factor of vasodilatation preventing the symptoms of depression, in contrast to the period of autumn and winter.

Key words: carbon monoxide, eye physiology, gaseous messenger
SYNCHRONIZING CIRCADIAN CLOCKS FOR CANCER CHRONOTHERAPEUTICS.

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Chronotherapeutics aims at improving treatment outcomes through the delivery of medicines according to circadian rhythms. Indeed, xenobiotic metabolism and detoxification, as well as cell cycle events, DNA repair, apoptosis and angiogenesis are rhythmically controlled by the Circadian Timing System (CTS). The CTS is a hierarchical network of molecular clocks in each cell. The cellular circadian clocks are coordinated by the suprachiasmatic nuclei (SCN), the main circadian pacemaker in the hypothalamus, which directly or indirectly generates an array of physiological rhythms. The CTS then makes the molecular clocks tick in synchrony in the host tissues that can otherwise be damaged by anticancer agents. As a result, circadian timing can modify 2- to 10-fold the tolerability of anticancer medications in experimental models and in cancer patients (Lévi et al. Annu Rev Pharm Toxicol 2010). Improved efficacy is also seen when drugs are given near their respective times of best tolerability. Both experimental and clinical data thus support a unique paradigm for cancer therapy: “the lesser the toxicity, the better the efficacy” (Innominato et al. 2011). Stochastic and deterministic mathematical models are addressing the three-way interactions between circadian clocks, cell cycle and drug pharmacodynamics at single cell or cell population levels, while integrative models address the issues of therapeutic optimization at whole body level. Several data-based chronotherapeutic models not only confirm experimental and clinical chronopharmacology data, but also allow the exploration of many sources of variability, that would otherwise remain hidden (Altinok et al. ADDR 2007, Eur J Pharm Sci 2009; Clairambault 2010; Bernard et al. Plos Comput Biol 2010; Ballesta et al. Plos Comput Biol 2011). Such “systems chronopharmacology” reveal that optimal cancer chronotherapeutics require circadian entrainment to be robust in healthy cells and weak or disrupted in cancer cells. Indeed host clocks are disrupted whenever anticancer drugs are wrongly dosed or timed (Ahowesso et al. Chronobiology Int 2011). Circadian disruption is deleterious for cancer control, since it accelerates experimental and clinical cancer progression (Filipski et al. JNCI 2002; 2005; Innominato et al Cancer Res 2009). Experimental and clinical evidence further show that female patients display more toxicities than males, and may be more prone to treatment-induced circadian disruption (Giacchetti et al. JCO 2006, Lévi et al. ADDR 2007). Therefore, non invasive circadian biomarkers (Scully et al. Interface Focus 2011) are critical for the modeling of CTS dynamics and the personalization of cancer chronotherapeutics. Indeed biomarker-guided enhancement of CTS synchronization could involve light therapy and both help the personalization of circadian chemotherapy delivery schedules and improve fatigue, anorexia, and sleep disorders, a symptom cluster associated with circadian disruption.

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HIGH MATERNAL SEASONALITY SCORES PREDICT HIGH BODY MASS INDEX IN NEWBORNS

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Objectives: It has been suggested that the weight gain and female preponderance characteristic of seasonal affective disorder reflect a vestigial evolutionary mechanism to ensure survival of mothers and their offspring in harsh winter conditions. If so, maternal seasonality should be associated with higher neonatal BMIs.

Methods: Basic weight and length measures at birth were collected in consecutive children taking part in a longitudinal study of maternal adversity, vulnerability and neurodevelopment (MAVAN). Mothers completed the SPAQ several years later during a study visit. We examined whether maternal seasonality scores were associated with infant BMI at birth and/or the trajectory of BMI over the first three years of life.

Results: As hypothesized, there was a significant correlation between maternal SPAQ scores and infant BMI at birth (r=.254, p=.038). Further analysis confirmed that mothers who reported seasonality as being a problem had infants with a higher BMI at birth than did other mothers (13.4 +/- 1.7 kg/m² vs 12.4 +/- 1.3 kg/m² respectively; t=2.52; p=.014). BMI changes from birth to age three also differed in children born to mothers who reported seasonality as a problem vs. others (F=2.78, df=4,31, p=.044).

Conclusions: In the MAVAN cohort, maternal seasonality predicts higher infant BMIs at birth, and a different trajectory of weight gain in the first three years of life. If replicated in the full sample, these results support evolutionary models of seasonality as it relates to reproduction.


Keyword: seasonality, seasonal thrifty hypothesis, obesity risk

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CHRONOTYPE AND SLEEP IN RAPIDLY ROTATING SHIFT WORK: PRELIMINARY RESULTS

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Objectives: The chronotype (or circadian preference) has been suggested to have an impact on the level of adaptation to shift work. There is debate about whether being an evening chronotype is a facilitating factor in shift work. Low level of morningness has been related to higher levels of shift work tolerance. Moreover, eveningness has been related to better sleep during the night shifts. However, in a nurse sample, eveningness was associated with more sleep complaints during day shifts. To our knowledge, no study has compared night shift vs day shift sleep between chronotype using objective sleep data in rapidly rotating shift work. The objective of this study was then to compare actigraphic sleep parameters of chronotypes in night schedules and day schedules.

Methods: Fourteen patrol police officers on rapidly rotating schedules (9 males), aged 25-32 years (mean ± SD = 28.4 ± 2.5) completed a morningness-eveningness questionnaire (MEQ). Police officers’ sleep was monitored with an actigraph (Actiwatch-L, Mini-Mitter) for four consecutive night shifts and four consecutive day shifts in Quebec City (latitude 46°48′ N) between June and September. Night work schedule was 23h00-07h00 and day work schedule was 07h00-15h00. Sleep parameters such as sleep latency, wake after sleep onset and sleep efficiency were calculated using Actiware-R software version 5.0. Mixed models with compound symmetry were used for statistical analysis.

Results: None of the subjects were categorized as Morning-types. Mixed models showed that overall subjects had similar sleep parameters during the night shifts and the day shifts. However, a chronotype effect was found, with Evening-types (E-types, n=6) having lower levels of sleep efficiency than Intermediate-types (I-types, n=8) during day shifts (77.8% vs 85.8%, p<0.05), but not during night shifts. In addition, E-types spent more minutes awake after sleep onset during the day shifts, as compared to I-types (57.0 min vs 34.1 min, p<0.01), but not during night shifts. E-types and I-types had similar sleep durations and sleep latencies during night and day schedules.

Conclusions: Preliminary analysis indicate that during day schedules, eveningness in shift workers is related to higher rate of wake episode after their sleep onset, yielding to lower sleep efficiency. This suggests that E-types may have more problems to adapt to day shifts than I-types in a rotating shift schedule context. Melatonin secretion and environmental light exposure analysis shall provide more information regarding the underlying mechanisms.

Keywords: Chronotype, sleep, shift work
ACUTE EFFECT OF WAKE THERAPY


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Objectives: To investigate the stability of improvement in patients with major depression when treated with a wake therapy regime including daily light therapy and sleep time stabilisation.

Methods: In all, 75 patients were included in a nine weeks trial. Patients were randomised to an exercise or a wake therapy group. After a one-week run-in phase, all patients were admitted to an in-patient ward for a one-weeks stay. Patients randomised to the wake group did three wake therapies with a recovery night between, and started daily morning light therapy and stabilisation of the sleep wake cycle by psycho-education. An algorithm from the Morningness Eveningness Questionnaire was used to time light therapy. All patients were treated with 60mg duloxetine daily. During wake nights patients filled in the Stanford Sleepiness Scale for each hour. Patients were assessed daily during the in-patient stay with the Hamilton depression subscale (HAM-D6). This subscale does not contain sleep items and is thus ideal to follow depression severity during wake therapy. We used last observation carried forward and intention to treat. Thus, all randomized patients were included in the analysis.

Results: Patients in the wake group had a very powerful and instant antidepressant response to treatment compared to patients in the exercise group. Very few patients experienced relapse to pre-intervention severity or above, during the intervention week. In the wake group response was 78.4 % on day five and 21.1 % percent in the exercise group. Remission, at day five, was 54.1 % in the wake group and 7.9 % in the exercise group. During the subsequent days, response and remission was somewhat reduced in both groups ending up with a response rate of 37.8 % and 10.5 % in the wake and exercise groups and correspondingly, remission rates of 18.9 % versus 5.3 %. During the subsequent weeks both the response and remission rates increased substantially but the difference between groups were maintained. No patients dropped out during the intervention week. The Stanford Sleepiness Scale showed moderate sleepiness and exhibited a circadian influence in the late hours.

Conclusions: Wake therapy induced a powerful antidepressant effect. During the intervention there were few relapses to pre-intervention severity or above. The immediate antidepressant effect diminished somewhat in the days after the end of the in-patient stay, especially in the wake group, but patients in the wake groups still had a statistically and clinically meaningful better outcome compared to the exercise group. Even though the results show that wake therapy is safe and effective, we need to invent methods to better sustain the powerful antidepressant effect of wake therapy.

Keywords: Wake therapy, Sleep deprivation, Major depression, Light therapy, Sleep time stabilization.

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Melanopsin-expressing ganglion cells in the retina (i-RGC), which are intrinsically sensitive to blue light, are directly connected to many central brain areas. Beside the suprachiasmatic nucleus (SCN) the intrageniculate leaflet (IGL) and olivary pretectal nucleus (OPN) are responsible for regulation of circadian rhythms, light pupillary reflexes, and projections to lateral habenula (LHb), medial amygdaloid nucleus (MA), and ventrolateral preoptic area (VLPO). These are involved in the regulation of mood, emotions, and sleep had been reported in rodents (Hattar et al. 2006). In human research it has been reported that patients suffering from Seasonal Affective Disorder (SAD) process emotions differently than healthy controls. SAD patients under blue light and emotional stimuli showed increased activation of the hypothalamic region, with the same region being less active under green light (Vanderwalle et al., 2011). In four studies in the most recent winter seasons, we compared the Seasonal Affective Disorder (SAD) treatment by standard 10 000 lux full spectrum light treatment (SLT) with a treatment that used short-wavelength blue-enriched white light in different intensities or narrow-band blue light.

The first study where the effects of blue enriched light (17 000 °K) were compared with the effects of SLT (5000 °K) did not show any differences in therapeutic outcomes. Because this might have been caused by saturation effects of the blue-enriched light condition, the second study compared the effects of low-intensity blue-enriched light (750 lux, 17 000 °K) with SLT. In this study no difference in treatment outcome was found either. Both light conditions were highly effective. In these two studies, participants were exposed to light for two weeks on workdays.

In the third study, a comparison was made between the effects of narrow-band blue light (100 lux) and those of SLT. In this study, no differences in treatment outcome were found on the main parameters. Participants were exposed to light during 5 days. In these three studies sessions lasted 30 minutes a day in the early morning and treatment was administered at the clinic.

In the fourth study, a comparison was made between the effects of narrow-band blue light compared and those of SLT in the treatment of patients suffering from sub-SAD (winter blues). Participants were exposed to the light during 5 days in 20-minute sessions in the morning. This treatment was administered at home. In this study, the effects of the two treatment conditions did not differ either.

Key Words: SAD, Light treatment, narrow banded blue light

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CIRCADIAN RHYTHMICITY AND LIGHT RESPONSIVENESS OF THE ZEBRAFISH BRAIN

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Objectives: Light is the most effective time-cue to synchronise the internal body clock with the daily environmental cycle. Zebrafish have circadian clocks throughout their body and furthermore these tissues are directly light responsive. The role of the brain in synchronizing these body clocks is unknown, but it itself is also thought to be globally rhythmic and light sensitive. To investigate this idea further, we examined the endogenous expression of core clock genes, cryptochrome1a (cry1a), period2 (per2) and period3 (per3) in the zebrafish brain. These genes are known to be important in the zebrafish circadian pacemaker in cells and embryos, with cry1a and per2 being directly light inducible. We also used a per3-luc transgenic zebrafish (Kaneko et al. PLoS Biology, 3, 313, 2005) to show the effect of light on rhythms from central and peripheral tissues during entrainment and in constant darkness.

Methods: For the rhythmic experiments fish were kept on a 14:10LD or DD and killed at 6-hour intervals over 4 days. For the light responsive experiments adult wild type zebrafish were dark adapted for 3 days and then either exposed to light for 3 hours, or kept in the dark, and killed at CT3. For the culture experiment whole brains were dissected and cultured for 5 days in L-15 media with antibiotics, and collected at 6-hour intervals. Standard qPCR and in situ hybridization techniques were used. For the bioluminescent recordings, per3-luc fish were killed and the tissues promptly placed into L-15 media with antibiotics in a 96-well plate, and monitored using a Topcount Scintillation Counter for up to two weeks.

Results: Per3 was highly rhythmic in acutely dissected brains (p<0.0001, Two way ANOVA of peak trough ZT3/15, n=3-9), and also rhythmic, though dampened, in whole brain cultures (p<0.01 in LD, p<0.05 in DD, Two way ANOVA of peak trough ZT3/15, n=3-4). qPCR analysis showed a 4-6 fold increase in the mRNA expression of both per2 and cry1a in the brains of the light pulsed fish (p<0.001, unpaired two-tailed t-test, n=4). In situ hybridization on fixed, sectioned brain slices reveals discrete areas of cry1a (n=3), per2 (n=4), and per3 (n=3) expression. These regions include the granular layer of the valvula cerebelli, the periventricular gray zone of the optic tectum, and the hypothalamus. Other regions that did not express the clock genes include the molecular layer of the valvula cerebelli, the optic chiasm, and the optic tract. All the per3-luc organs tested were able to entrain to a light dark regime with similar phase timing, and would free run in constant darkness.

Conclusions: This is the first finding to show that the zebrafish brain is not ubiquitously light responsive, but in fact has specific regions expressing the light responsive genes, cry1a, and per2, and the rhythmic gene per3. All the light responsive regions overlapped with the rhythmic area, suggesting these brain regions are important for the circadian clock. This is also the first study to show rhythmicity from a whole zebrafish brain in culture over 5 days; these results confirm that the tissue is directly light sensitive in multiple regions. The next step will be to resolve which photoreceptive opsins are being expressed in the brain cells expressing core clock genes.

Keywords: Light, Circadian Rhythms, Neuroscience, Bioluminescence, Zebrafish,

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BRIGHT LIGHT TREATMENT, TOTAL SLEEP DEPRIVATION AND PINDOLOL AS AN AUGMENTATION STRATEGY IN THERAPY RESISTANT BIPOLAR DEPRESSION: FIRST RESULTS FROM THE SALZBURG BIPOLAR COHORT

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Objectives: Bipolar disorders are characterized by a comparably high frequency and long duration of depressive episodes as well as considerable rates of therapy resistance. In these cases, most treatment algorithms focus on psychopharmacological combinations of various drugs or electroconvulsive therapy (ECT). Total sleep deprivation (TSD) and bright light therapy (BLT) have previously been shown to be effective chronobiological approaches in various depressive disorders. In addition, the combination of pindolol with TSD has been shown to prolong the antidepressant effects. For that reason, since 2008, these therapeutic interventions have been included in the regularly proposed treatment options for therapy resistant bipolar depressive (TRBD) patients referred to our Bipolar Outpatient Clinic.

Methods: All patients referred to our outpatient clinic with TRBD were offered the therapeutic option of BLT, TSD and pindolol. They were included in our ongoing cohort study if they met DSM-IV criteria for Bipolar Disorder (Type 1) and gave informed consent. Patient assessment included the Mini-International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM disorders (SCID) I and II, Global Assessment of Functioning (GAF), Hamilton Depression Rating Scale 17 (HDRS-17), Young Mania Rating Scale (YMRS), various other rating scales pertaining to cognitive functioning, seasonality and a variety of clinical symptoms, as well as blood sampling for laboratory analysis and future genotyping. We present the basic clinical data of our first twenty patients who received a single night sleep deprivation followed by BLT of 30 minutes via a light box (10,000 lux) the next five mornings.

Results: Eight patients had previously been treated with ECT and twelve had received at least two pharmacological combination therapies commonly approved for TRBD. Ten patients were additionally treated with pindolol; the other half either had clinical contraindications against beta blockers or did not wish prescription of any additional drug. The initial average HDRS-17 Score was 34, with a range from 23 to 40. Five patients failed to respond, one of whom worsened considerably on day three, with a rise in HDRS-17 from 28 to 40. The remaining fifteen patients responded well to the treatment, with a drop in the HDRS-17 Score to an average of 11 with nine patients attaining symptomatic remission (HDRS<7). The antidepressant effect was sustained in all fifteen patients at week 1 after treatment, in ten patients at week two and five patients after one month. There were no cases of treatment-emergent mania or other serious adverse events.

Conclusions: The combination of BLT, TSD and pindolol can be an effective, well tolerated and valuable therapeutic option for TRBD patients in a naturalistic clinical setting. Larger studies are needed to identify predictors of response and tolerability.
Objective: A series of neuroimaging studies demonstrated various cortical and subcortical activity changes in response to light of different wavelengths, starting within the first minute after light onset. These acute light effects selectively impact non-visual functions such as alertness, mood, and cognitive performance in humans. By using electroencephalography we aimed at demonstrating that the spectral quality of light during daytime determines changes in brain activity at very short latencies after stimulus onset (<100 ms).

Methods: Sixteen young study participants were exposed to four different light conditions in a within subject design. Each condition comprised two exposures to 160 repeated short light stimuli (and random stimulus intervals) for event related potential (ERP) recordings. The two ERP recordings were scheduled 1) after dim light (DL) adaptation and 2) after 60 min of continuous light (CL) exposure. For ERPs and CL exposures we used blue, green and red monochromatic light (at 480nm, 555nm and 620nm) as well as polychromatic white light at equal photon fluxes (2.8 x 10^{13} photons/cm^2/s). High resolution EEG (128 channels) was continuously recorded with a sampling rate of 512 Hz (BioSemi, Amsterdam, The Netherlands). Artifact free epochs were aligned to stimulus onset -100 to 400ms per subject and averaged across stimuli, referenced to the average reference for each ERP by using the software Cartool (by Denis Brunet; brainmapping.unige.ch/cartool). Global field power (GFP) was calculated to assess neuronal response strength throughout the brain. Statistical differences between light conditions and light adaptation effects (i.e. after DL and after CL exposure) were tested with a mixed linear regression analysis. We also applied topographical analysis to examine spatial variations of the EEG scalp potential distributions between light conditions over time. We therefore segmented the continuous grand average into 8 discrete template maps by using a hierarchical clustering algorithm and applied statistics on individually back fitted maps.

Results: Early ERP responses resulted in higher GFP activity for green (52-82ms after stimulus onset) and blue light (58 to 62ms) than for red light. Late ERPs showed greater GFP for blue compared to both white (340 to 360ms) and red light (358 to 364ms; main effect of color; p<0.05). From 160 to 272ms after stimulus onset the GFP was significantly higher for DL adapted ERPs, than for ERPs after CL exposure, indicating a general light adaptation effect (p<0.05). From 226 to 250ms the GFP for DL adapted red light ERPs was significantly higher compared to all light conditions except DL adapted green and white light ERPs (interaction ‘light condition’ x ‘light adaptation’; p<0.05). We also found different temporal contributions in 4 out of 8 eight topographical segmentation maps (p<0.05).

Conclusions: Our results indicate GFP differences as well as temporal changes in EEG topographical segmentation maps. These differences can be attributed to different spectral qualities of light and to light adaptation effects on short term EEG brain states.


Keywords: Evoked Potentials, EEG Microstates, Acute Light Effects, High Resolution EEG, Monochromatic Light

Funding Support: MM is financially supported by the Velux Foundation Switzerland. The software Cartool is programmed by Denis Brunet from the Functional Brain Mapping Laboratory, Geneva, Switzerland, and supported by the Center for Biomedical Imaging (CIBM) of Lausanne and Geneva.
Introduction: Melanopsin-containing photoreceptors in ganglion cells of the inner retina (ipRGC) provide the biological clock with non-visual photic input to entrain mammalian circadian rhythms. In addition, the ipRGC also regulate a number of acute visual functions and acute light responses, being enmeshed in a complex network together with outer retinal photoreceptors, the rods and cones. Remarkably, the ipRGC alone are capable of eliciting specific and essential non-visual light responses in physiology and behavior. Thus they respond to characteristics of light such as the electromagnetic spectrum, exposure duration, prior light exposure, time of day, and light distribution. Among many other biological functions (genetic predisposition, age) and/or pathological factors (retinal diseases, psychiatric disorders), the major impact of light still comes from inter-individual differences in daily light exposure within a dynamic 24-h light-dark cycle. One of the factors biasing the impact of daily outdoor and indoor light exposure on biological functions is individual behavior. It is therefore crucial not only to better understand individual behavior throughout the day in terms of light choices, but, in the case of indoor lighting conditions, also to optimize and tailor them both in terms of biological functions and visual (and thermal) comfort.

Methods: We are currently investigating how light quality and quantity can impact inter-individual behavior in different light settings. Extreme chronotypes such as morning (MT) and evening types (ET) serve as a 'natural model' for inter-individual light preferences, since their habitual sleep-wake cycle times differ relative to external clock time. In extreme chronotypes we are studying visual and thermal comfort, mood and alertness, together with skin temperature, performance, hormonal secretion, and glare calculation from light distribution in the room. Importantly, the different lighting conditions contain both artificial and dynamic natural light.

Results: Preliminary results (N=5) indicate (as expected), an overall earlier dim light melatonin onset (DLMO) in MT than ET, when related to external clock time. However, when DLMO was aligned relative to individual sleep-wake time, ET chose lower lighting conditions in the second half of their waking period than MT, which would counteract any further delay in their endogenous rhythm. On the other hand, in the first three hours after habitual wake time, ET chose higher lighting levels and had lower salivary cortisol concentrations than MT.

Conclusion: As suggested by Begeman\(^1\) and others there is growing evidence for the existence of what he called ‘Mr. Bright and Mr. Dim Light’\(^1\), in that people modulate their own circadian rhythms by changing light exposure. This is known from natural light exposure studies in different chronotypes \(^2,\(^3\). Whether such inter-individual differences have genetic, physiological and behavioral causes and consequences remains to be elucidated.

Funding Support: MM and AB were financially supported by the VELUX Foundation (Switzerland), and LM received a Sciex Fellowship (Switzerland).


Keywords: Inter-Individual Differences, Self-Selected Lighting, Chronotypes, Circadian Phase
THE PLATELET SEROTONIN TRANSPORTER PROTEOME IS REGULATED BY SUNLIGHT

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**Objectives:** Serotonin is involved in the modulation of several physiological functions that vary with the seasons. Brain serotonin transporter (5-HTT) binding shows seasonal variation, and so does the efficiency of 5-HTT mediated in- and outward transport in platelets. Moreover, efficiency of 5-HTT transport is altered in depressed patients with seasonal affective disorder (SAD; (Willeit et al. 2008). Here, we further investigated the molecular background of seasonal variation in 5-HTT function by studying the association between environmental light, 5-HTT function, and two important proteins of the 5-HTT regulome, integrin \(\alpha_{IIb}\) \(\beta_3\) (ITGB3) and the ITGB3 associated adaptor protein HIC-5 (Carneiro et al. 2008).

**Methods:** This study used blood samples of a study on platelet 5-HTT function in patients with SAD (n=73) and healthy low-seasonality control subjects (n=70). Here we report on values derived from blood samples taken between October and January (during depression in SAD). Platelets from subjects below and above the 25\(^{th}\) percentile of maximal 5-HTT transport velocity in both groups where analyzed for 5-HTT, ITGB3, and HIC-5 protein expression using Bradford protein concentration analysis. Meteorological data of local duration of sunshine for the day of blood draws, and averages of daily sunshine from day one up to 30 days before were used for analyzing the correlation between the amount of sunshine and platelet 5-HTT function (tyramine-induced reverse transport; \(E_{\text{TYR}}\)) and platelet 5-HTT, ITGB3, and HIC-5 expression.

**Results:** \(E_{\text{TYR}}\), 5-HTT, ITGB3, and HIC-5 expression showed significant negative correlation with the average duration of sunshine in healthy subjects. Peak correlations were found for the period of approximately ten days before blood draws (p≤.0001). Protein expression showed no (or if anything, non-significant positive) correlation with duration of sunshine in patients with SAD. The figure shows Pearson product moment coefficients (y-axis) between the respective biochemical parameters and duration of sunshine from 1 to 28 days before blood was drawn.

**Conclusion:** Our data suggest that function and expression of platelet 5-HTTs and the 5-HTT associated proteins ITGB3 and HIC-5 are down-regulated by sunlight in healthy, non-seasonal subjects. This possibly adaptive mechanism seems to be absent or dysfunctional in patients with SAD. If replicated, these findings may help to identify and understand some of the key components of serotonin dysregulation in SAD and other psychiatric disorders.

**Key words:** SAD; Serotonin; Integrin beta-3; HIC-5; Serotonin Transporter


EFFECTS OF IMPERFECT LIGHT SENSING ON CIRCADIAN PHASE ESTIMATION

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Objectives: For unobtrusively estimating the phase of the human circadian pacemaker (HCP) using light exposure and activity, typically a wrist-worn device is used that contains motion and light sensors. The signals from this device are input to a mathematical model that describes the dynamics of the HCP and the influence of light on it. This model allows the phase of the HCP to be estimated with certain accuracy, typically within plus or minus one hour from a reference marker. This way of sensing light is not ideal, especially because the device may sometimes be covered, e.g. by a sleeve, which may confound the estimation. In this study, we investigate the effect of occasionally covering a wrist-worn light sensing device on the estimation of the phase of the HCP using the model.

Methods: To this end, we use 9 light traces, each trace covering typically 13 days of light exposure, and distort them by replacing in the traces randomly chosen intervals with intervals of 0 lx, mimicking the covering of the device by a sleeve. We compare the original and distorted traces in terms of the differences in estimated phases. By varying the amount and length of insertions, we investigate the relationship between total coverage time and phase estimation differences.

Results: The results show that (1) the effect depends on the light trace under consideration, (2) in case of a considerable effect, it is grossly linear in the total coverage time, (3) the effect can be in the order of tens of minutes rather than minutes, with an outlier of over one and a half hour, (4) there is no correlation between the average or maximum light exposure and the size of the effect, i.e. the slope of the regression line.

Conclusions: The results endorse the usual requirement in studies involving such devices not to cover the device, e.g., with a sleeve, as this may confound results based on the light traces obtained. We have shown this for the estimation of the phase of the human circadian pacemaker, based on light exposure information. The same approach can be used to investigate another imperfection in light sensing using such devices, i.e., the inability to sense eye closures. The approach allows an analysis of the effect on the human circadian phase of prolonged eye closures, such as during a nap, although the statistical model used to describe coverings should be adapted to mimic eye closures, and the choice of 0 lx should be replaced by more realistic values.

Keywords: Circadian Rhythm Estimation, Light Sensing, Imperfect Sensing
MELANOPSIN GENE (OPN4) VARIATIONS IN THE PUPIL LIGHT REFLEX IN SEASONAL AFFECTIVE DISORDER

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Objectives: Individuals with seasonal affective disorder (SAD) may have decreased retinal sensitivity, impairing entrainment of the circadian clock to the environmental light dark cycle. Retinal subsensitivity may be mediated by individual differences in retinal signaling whereby a decrement in normal increases in retinal sensitivity in response to low light levels in winter occurs, leading the retina to be less sensitive than necessary for healthy functioning (Hebert et al., J Affect Disord 68: 191-202, 2002). We compared individuals with SAD and healthy controls on the pupil light reflex (PLR) during red and blue equal irradiance stimuli, and on the post-illumination pupil response (PIPR), as this measure is driven by melanopsin cells, the main photocceptors entraining the circadian clock. In addition, we will compare individuals with and without a variation in the melanopsin gene (OPN4) on the PLR and PIPR, as our previous studies indicate that OPN4 variations are associated with SAD.

Methods: Participants were measured in the fall/winter when individuals in the SAD group were symptomatic. The Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version was used to confirm episode status, along with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders. Infrared pupillometry was used to measure pupil diameter during and after high irradiance LED light stimuli of two wavelengths, red and blue. PIPR was calculated based on previous reports (Kankipati et al., IOVS, 52: 2287-92, 2011).

Results: Participants were 21 SAD and 19 controls matched on age and gender (80% women, mean age 35.0 years, SD = 12.9 years). Net PIPR change (%) was calculated as Blue PIPR change (%) minus Red PIPR change (%). A significant group x genotype interaction was found, as depicted in Figure 2., \((F(2,39) = 3.71, p = .036, \text{partial-}\eta^2 = 0.19)\).

Conclusions: Although a significant genotype x group interaction was observed, main effects of group and genotype were not statistically significant. The small number of T/T samples \((n = 3)\) suggests that any conclusions are highly tentative. Should individuals with SAD and/or OPN4 variations demonstrate lower sensitivity to stimuli designed to trigger responses by melanopsin containing cells, this could indicate a less sensitive light entrainment pathway for the circadian clock in SAD, and a specific role for melanopsin signaling in the disorder.

Figure 1. Example of PLR(ON) & PIPR(OFF) responses to red and blue stimuli. Pupil diameter (mm) plotted against time in response to the control (red) and test (blue) LED stimuli. Bar represents stimulus duration (30s).

Figure 2. Net PIPR change (%) = [Blue PIPR – Red PIPR] genotype x group comparison. PIPR is the difference (mm) between baseline and sustained response after stimulus off, Net PIPR is Blue PIPR – Red PIPR.

Keywords: Seasonal affective disorder, Melanopsin, Pupillometry, Polymorphisms.
THE IMPACT OF POLYCHROMATIC LIGHT MIXTURES ON EARLY MORNING SLEEP INERTIA IN ALERTNESS AND WAKING MEMORY

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Objectives: Sleep inertia is a state of reduced alertness and impaired performance that occurs soon after awakening. It dissipates rapidly and asymptotically, although it can last as long as 2 hours for some cognitive tasks. Light has a potent effect on alertness and brain function which is mediated by a multi-component photoreceptive system, consisting of rods, cones and melanopsin-expressing intrinsically-photosensitive retinal ganglion cells (ipRGC). Because this effect of light varies in an intensity and wavelength dependant manner, we can ask whether artificial light can be modified to minimize sleep inertia and thereby improve the wake-up experience.

Methods: We assessed the acute effects of four polychromatic light conditions on the dissipation of sleep inertia in working memory in a four-way laboratory cross-over design, in eleven healthy young volunteers. We assessed subjective sleepiness (Karolinska Sleepiness Scale) and measured response time (RT) and accuracy (aprime) in an auditory 1-back (low difficulty) and 3-back (high difficulty) task, 2 hrs before the laboratory sleep episode (Baseline), and at regular intervals during a 4-h morning light exposure following the sleep episode. The effects of three fluorescent lighting conditions differing in intensity and spectral composition, viz. Blue-Intermediate (BI; 200 Lux), Blue-Enhanced (BE; 194 Lux) and Bright Blue-Enhanced (BBE; 750 Lux), were compared to that of Dim light (D; 19 Lux).

Results: Subjective sleepiness and response speed in both n-back tasks showed a significant effect of sleep inertia (p < 0.001) while accuracy did not. Participants rated themselves as being significantly sleepier (p<0.001) (KSS score: 6.1 vs. 3.3) immediately upon awakening when compared to Baseline. Similarly, median RT in both n-back tasks was significantly slower (p<0.01) upon awakening when compared to Baseline (1-back: 911.13 vs. 722.47 ms; 3-back: 947.9 vs. 847.4 ms). Notably, in the high difficulty task there was significant Time x Light Condition interaction (p = 0.008) such that the speed of responding to a target after 4 hours was at least 200 ms faster than at wake time in both BE and BBE; no such change was observed in the BI and D conditions. However, we observed no significant differential (p>0.05) effect of light condition on subjective sleepiness levels.

Conclusions: Our results indicate that the effects of sleep inertia on cognitive performance are not transitory but last well over an hour. This has significant implications for jobs e.g. medicine, law enforcement and transportation, where personnel need to perform at peak efficiency immediately upon awakening from a nap or sleep. Notably, our results imply that modifying the composition of artificial light may provide an avenue for reducing sleep inertia in effortful cognitive tasks, a finding which has implications for the design of work environment that would be conducive to safety, well being and efficiency.

Keywords: Sleep Inertia, Working Memory, Alertness, Polychromatic Light.

Funding: Philips Lighting, The Netherlands
BRIGHT LIGHT IMPROVES VIGILANCE IN THE MIDDLE OF THE NIGHT INDEPENDENTLY OF THE PRESENCE OF SHORT WAVELENGTHS.

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Introduction: Blue light was shown to be more efficient than other wavelengths to improve vigilance. However, it is still unclear if this difference can have a noticeable impact at a time when vigilance is low. We investigated if blue blockers would impact the possible alerting effect of a blue-enriched white light in the middle of a sleep deprived night.

Methods: 20 participants (9M, 11F) were maintained awake in dim light through two consecutive nights. Vigilance was assessed subjectively with a battery of four visual analogue scales (VAS): 1) alertness, 2) energy level, 3) mood, anxiety, 4) Stanford sleepiness scale (SSS). Vigilance was also assessed objectively with the Conners’ continuous performance test 2 (CPT-II) at 23:30 h, 1:30 h and 3:30 h. The first night served as baseline and the second as the experimental night. Group B (n=10, 4M) was exposed first to 500 µW/cm²/s of blue-enriched white light (provided by two Litebook Élité) at 3:00 h. At the same time, participants from Group A (n=10, 5M) were exposed to 1500 µW/cm²/s from the same light device while wearing blue-blockers (500 µW/cm²/s behind the glasses).

Results: There was a significant effect of time in the VAS for alertness (p < 0.001), energy level (p < 0.001), mood (p < 0.001) and SSS (p < 0.001), but not anxiety. Moreover, the VAS for alertness was lower on experimental night at 1:30 h (p = 0.02) and 3:30 h (p = 0.002). Energy level was also lower on experimental night at 3:30 h (p = 0.005). As for SSS, it was lower on experimental night at 3:30 h (p = 0.02). For all VAS assessments, no group difference was observed. With the CPT-II, a group by night interaction in errors of omission (p = 0.02) was observed. Here, group A made more errors on the baseline night than experimental night (p = 0.04). Also, all participants made more errors of commission at 23:30 h on experimental night (p = 0.02). As for the hit reaction time by block, there was a main effect of time (p < 0.001), with 23:30 h being lower than 1:30 h (p < 0.001) and 3:30 h (p < 0.001). There were, however, no differences for reaction time, standard error of the reaction time and standard error of the reaction time by block. Again, no difference between groups was observed.

Conclusions: In the subjective vigilance battery, alertness, energy level and the SSS were improved at 3:30 h, on the experimental when compared to the baseline night, which could be attributed to the effect of light. However, since the 1:30 h test was also better on the second night in alertness (when no light was present) this could imply that the participants were also less affected by sleep deprivation on experimental night. In fact the wake period was probably longer on the first night than on the second night since subjects slept during the day between the two nights. As for the objective measurements, the differences observed at 23:30 h can be attributed to training effect. The time effect in hit reaction time by block reflects the growing sleep deprivation as in subjective measurements. Since no group effect was observed, we can think that the effect of light observed on subjective vigilance is independent of the presence of short wavelengths. It might also be independent of melatonin since those glasses were shown to prevent its suppression (Sasseville et al. 2006).

Keywords: Blue-enriched light, Vigilance, Sleep, Blue-blockers.

Funding: FRSQ, CIHR, IRSST

SIGNALING WITHIN THE MAMMALIAN CIRCADIAN TIMING SYSTEM

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In mammals, most physiological processes are subject to daily oscillations that are coordinated by a complex circadian timing system with a hierarchical architecture. The master pacemaker resides in the suprachiasmatic nucleus (SCN) of the ventral hypothalamus. It is composed of two small aggregates of neurons, whose self-sustained and cell-autonomous oscillators are tightly coupled. In the absence of external timing cues the SCN generates rhythms with a period length of approximately 24 hours, and it must therefore be synchronized every day by light-dark cycles in order to stay in resonance with geophysical time. Most peripheral cells also possess circadian oscillators, but in contrast to those operative in SCN neurons, they are not coupled and rapidly lose phase coherence in the absence of systemic timing cues (Zeitgebers) controlled by the SCN.

According to the currently held molecular model, circadian rhythms are generated by interlocked negative feedback loops in gene expression. The major feedback loop consists of two period genes, Per1 and Per2, and two cryptochrome genes, Cry1 and Cry2, whose transcription is activated by the transcription factors BMAL1 and CLOCK. PER and CRY proteins form complexes with additional proteins, and once these complexes have reached a critical activity, they inhibit Per1/2 and Cry1/2 gene expression by attenuating the activity of BMAL1-CLOCK/NPAS2 heterodimers. As a consequence, the levels of PER and CRY mRNAs and proteins decrease, and a new cycle of CRY and PER expression can ensue. This feedback circuitry also affects the expression of BMAL1 through an accessory loop involving transcriptional activators of the Retinoic acid-related Orphan Receptors (ROR, ROR, and ROR) and repressors of the REV-ERB orphan receptor family (REV-ERB and REV-ERB). Many posttranslational modifications, including phosphorylation, sumoylation, ubiquitination, and acetylation, modulate the activity and stability of core clock components and thereby contribute to circadian rhythm generation.

The SCN uses a variety of indirect and direct pathways to synchronize peripheral clocks. Daily feeding-fasting cycles, driven by daily rest-activity cycles, are strong Zeitgebers for many peripheral tissues (including liver, kidney, pancreas, heart, and skeletal muscle). In the first part of this lecture I shall present novel whole body imaging approaches that allow the long-term recording of circadian gene expression in peripheral tissues (such as the liver) in real time and in freely moving animals. These experiments revealed that the SCN synchronizes peripheral clocks through direct and indirect signals that are in conflict when feeding rhythms are changed. In the second part of the lecture I shall present novel experimental strategies allowing the identification of signaling pathways that participate in the synchronization of circadian clocks by blood-borne signals. STAR-PROM (for Synthetic Tandem Repeat Promoter screening), a technology we recently developed, should eventually afford the detection of most immediate early transcription factors that serve as sensors of blood-borne signals. One of the pathways revealed by STAR-PROM involves a diurnally active signaling protein that generates daily oscillations of actin polymerization. Thereby it regulates diurnal rhythms in transcription by Serum Response Factor (SRF) and probably other transcription factors.
THE RELATIONSHIP BETWEEN SLEEP QUALITY AND PREFERENCE FOR MORNING/EVENING, SEASONALITY AND ACTIVITY LEVELS IN DEPRESSED PATIENTS WITH BIPOLAR DISORDER

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Objective: We examined the relationship between night-time sleep quality and the preference for morning or evening, seasonal variation in depressive symptoms and activity levels during the day and at night in depressed patients with Bipolar Disorder (BD). Also we explored dim light melatonin onset (DLMO) in BD patients with a current major depressive episode. We hypothesized that reduced sleep quality is associated with an evening preference, increased seasonality and reduced daytime activity levels in depressed bipolar patients.

Methods: Study patients were enrolled in the ongoing parent investigation to explore the efficacy of bright light therapy vs inactive comparator for bipolar depression: a randomized control trial. We obtained assessments at baseline, prior to randomization. We confirmed the diagnosis of BD Type I or II and a current major depressive episode (duration ≥4 weeks) with the Semi-Structured Clinical Interview for the DSM-IV. We assessed sleep quality with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al, 1989), morning/evening preferences with the Morningness Evenness Questionnaire (MEQ; Horne and Östberg, 1976), seasonality with the Personal Inventory for Depression and SAD (PIDS; Terman et al, 1998) plus the component Global Seasonality Score (GSS) to quantify the seasonal variation in the mood and energy of depressed patients (Rosenthal et al, 1987); and one-week activity levels with the Respironics actiwatch (model#AW16 and AWLP, Mini-Miller Co, Inc). We collected 9 serial evening salivary melatonin samples to estimate DLMO.

Results: We included 16 women and 7 men ranging in age from 18-66 (mean=47.7) years; 17 pts had BD-I and 6 had BD-II. The racial distribution comprised of 18 - white, 4 – African American and 1 – multiracial. For sleep quality (PSQI), 20 patients scored ≥5 and 14 scored ≥7. On the MEQ, 17 patients had an intermediate preference; 4 preferred the morning (3-moderately, 1-definitely) and 2 preferred the evening (moderately only). The association between sleep quality and MEQ was not significant [estimate of slope of the regression = 0.0189, 95% confidence interval- CI (-0.190, 0.229), p-value= 0.8526]. On the PIDS-GSS, 10 patients reported increased, 5 – moderate and 8 – no seasonal component to their depressive symptoms. Analysis of variance indicated a significant association between sleep quality and seasonality (p = .0333). Sleep duration from the self reported PSQI and the actigraphs was consistent. There is a significant linear association between sleep quality and wakeful activity [linear regression estimate = -0.0107, 95% CI (-0.0219, 0.0005), for p=0.10 level only; p = .0594]. DLMO and the possible relationship with circadian outcome measures will be discussed.

Conclusion: Patients with bipolar depression may have an increased or moderate seasonal component to their depressive symptoms. Sleep duration may be estimated with the PSQI or actigraphy. Even during a depressive episode, bipolar patients with better sleep quality tend to be more active during the day. Increased daytime activity likely is related to improved physical health. Future research on new bipolar treatments should include measures to assess sleep and sleep quality as possible clinical markers of illness episode and physical health.

Key Words: Sleep, Seasonal, Bipolar Disorder, Depression

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A RANDOMIZED CONTROLLED TRIAL OF COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA IN EUTHYMIC PATIENTS WITH BIPOLAR DISORDER

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Background: Sleep disturbances in euthymic phases of bipolar disorder (BD) are risk factors for new episodes of (hypo)mania or depression. Cognitive behavioural therapy for insomnia (CBT-I) to euthymic patients with BD has not been evaluated in a randomized controlled trial (RCT).

Aims: In a RCT to compare CBT-I and treatment as usual (TAU) in improving quality of sleep, stabilizing mood variations and preventing new mood episodes in euthymic patients with BD I and II and insomnia. To compare sleep in BD with sleep in ordinary insomnia, delayed sleep phase syndrome and healthy controls.

Methods: First a three weeks screening phase with sleep diary and diary of mood, seven consecutive days with actigraph (ACG) and two nights with polysomnography (PSG) before randomization to an eight week treatment trial. TAU consists of pharmacological and supportive psychosocial treatment. CBT-I consist of sleep restriction, psychoeducation about sleep, stimulus control, challenging beliefs about sleep, stabilization of the circadian rhythm, challenging and correcting sleep state misperception in 3-6 sessions.

Conclusion: The RCT could document a new treatment for insomnia in BD with possible effects on sleep and on stability of mood.

Key Words: Bipolar disorder, insomnia, CBT for insomnia
Objectives: Based on recent animal laboratory studies a melanopic spectral efficiency function (melanopic lux or mlux) has been developed to predict the activation of melanopsin containing ganglion cells in the retina by polychromatic light. Adapted to the human eye this function integrates brightness and sensitivity to blue wavelength light. Still it remains unknown whether this function can predict melatonin suppression i) in humans; ii) after short-term light exposure; iii) in a naturalistic setting. In this context the aim of the current study was to investigate whether the melanopic efficiency function is associated with melatonin suppression.

Methods: Thirteen light conditions were tested in 31 healthy men and women (18 - 35 years of age) in 4 sessions; every session included 9-11 participants and lasted 12-14 days. Dim light was applied four to one hours before individual bedtime, followed by a 30 minute light exposure and again 30 min dim light. Light conditions during light exposure varied between 79–2955 mlux (80-600 lux, 1500-12000 Kelvin). Experimental light condition plus a control condition were presented in a randomized order. Experimental light conditions plus a control dim light condition in each session were presented in a randomized order. Saliva was sampled in 10 and 30 min intervals.

Results: Repeated measures ANOVA revealed that five out of 12 light conditions suppressed melatonin significantly (p<0.05), some already after 20 minutes. Subjective alertness was not associated with melanopic lux. Multiple regression analysis included factors melanopic lux, number of blue photons, lux and Kelvin. Melanopic lux was the best predictor for melatonin suppression (beta = -.41; p < 0.01). The relationship between mlux and melatonin suppression could best be fitted into a quadratic curve, revealing a significant relationship (p < 0.01) that explains 67% of the variance.

Conclusions: The current data demonstrates that melatonin suppression after short-term evening light exposure can be predicted by melanopic lux. This confirms results of a recent study that reported changes in melatonin and sleep after four hours of evening light. However, current data emphasizes the strength of the effect even after short-term light exposures. The quadratic relationship clearly underlines a strong dependency even in rather low mlux values indicating that the specific mlux value of commercially available lamps should be labeled.

Keywords: Melatonin Suppression, Melanopic Lux, Evening Light Exposure

The study was supported by the German Ministry for Education and Research (BMBF FKZ: 13N8973)
EFFECTS OF BRIGHT LIGHT TREATMENT ON PSYCHOMOTOR SPEED IN TOP LEVEL ATHLETES: RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

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Objectives: Bright light therapy improves cognitive performance in healthy young men. We tested the hypothesis that bright light therapy could improve psychomotor speed in top level ice hockey players during competition period at seasonal darkness.

Methods: Psychomotor speed tests with audio and visual warning signals were performed before and after 24 days bright light or placebo treatments for Finnish National Ice Hockey League team (team Oulun Kärpät, age 25±5, range 17-33 years). Treatments were performed during seasonal darkness (October) in Oulu region (latitude 65 degrees north) whereas the strain of the players was also very high (10 matches during 24 days). A daily 12 min dose of bright light (n=11) or placebo (n=11) was administered every morning between 8-12 AM at home by a novel bright light device via the ear canals (Valkee NPT100). Two components of reaction time: inspection time and motor response time were analysed separately from both psychomotor tests. Analysis of variance for repeated measures with time x group and interaction adjusted for age was performed for the measured variables.

Results: Motor time to visual warning signal decreased in treatment group from 127±43 to 94±26 ms, p=0.006, and did not change in placebo group 121±23 vs. 110±32 ms, p=0.077 (time x group interaction p=0.024). Inspection time to visual signal did not change in either group. Inspection or motor time to audio warning signal changed neither in treatment nor placebo groups after intervention.

Conclusion: Psychomotor speed, particularly motor time to visual warning signal, improves after bright light treatment in top level ice-hockey players during the competition season at the darkness time of the year.

Key words: Ice-hockey, Motor speed, Seasonal darkness
Light constitutes the principal synchronizer of circadian rhythms but it also conveys a direct stimulating signal which enhances alertness and cognition and thereby profoundly affects brain function. This non-visual or non-image-forming impact of light is more effective with shorter wavelength blue light and is mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin. We have investigated the brain mechanisms involved in the non-image-forming impact of light in several neuroimaging studies but many aspects remain to be studied.

Aging is associated with marked changes in sleep and wakefulness regulation which may influence the impact of light on non-image-forming cognitive brain functions or conversely be caused in part by change in light impact. Recent data seem to indicate that the impact of light on non-image-forming functions is reduced with aging but whether this could also be the case for cognitive brain responses was unknown. We conducted an fMRI study which provides the first evidence that the impact of light, and of changes in its irradiance, on brain responses to a non-visual working memory task decreases with healthy aging. This effect was found in key areas for arousal and cognition regulation and was not related to the reduction in pupil size.

The successful use of light therapy in Seasonal Affective Disorder (SAD) suggests that light affects emotion and mood regulation. However whether this could constitute a non-image-forming impact of light and whether light directly affects emotion processing was unknown. We conducted two studies which show that light influences the processing of auditory emotional stimuli both in healthy and clinical populations. In a first study we found that in healthy individuals and as compared to green light, blue light enhances the functional connectivity between the amygdala, hypothalamus and voice area of the temporal cortex for the processing of vocal emotional stimuli. In a subsequent study we observed that patients with SAD show a specific pattern of response to emotional auditory stimuli in the hypothalamus with increased activation under blue light and decreased activation under green light exposure.

These results provide neurobiological substrates through which light could exert its therapeutic impact in patients but also its positive impacts on cognition, emotion and mood in healthy younger and aging individuals.

**Funding:** FNRS, FRFC, IRSC, FRSQ

**Key terms:** Aging, SAD, cognition, fMRI, melanopsin, light
A NON-CLINICAL NIGHT SETTING FOR A TREATMENT OF MAJOR DEPRESSION WITH CHRONOTHERAPY IN A SMALL PRIMARY CARE PSYCHOLOGY PRACTICE ~AN EXPLORATION~

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Objectives: Nowadays in primary care the treatment of choice in patients with major depression is mostly based on cognitive-behavioral therapy alone, or combined with pharmacotherapy. Recent studies found promising effects of a combination of a night sleep deprivation (wake therapy) and bright light therapy as treatment by patients with major depression in a hospital setting. In comparison with treatment as usual, wake therapy is known to have a quick mood increasing effect. Some researchers found that these quick results of wake therapy could be kept, if at subsequent mornings bright light therapy was applied. The therapy effects were better obtained, and the wake therapy in combination with bright light therapy is found to have minimal negative side effects. Little to no research is done in general primary health care settings, with patients that have a Global Assessment of Functioning Scale of 55 or higher (according to the Diagnostic Statistical Manual of Mental Disorders 4th edition). We researched the effects of a night sleep deprivation, followed by 5 morning sessions bright light therapy by patients diagnosed with a major depression in a primary care psychology practice in the Netherlands.

Methods: Sixty patients from a primary care psychology practice who received the wake/light therapy were asked to take part in the survey. No control group has been used in this stage, since the survey took place in a general primary health care setting, where the expectation of patients is to receive care as soon as possible. Furthermore, this survey had an explorative character. The combined intervention consisted out of psycho-education about sleep hygiene, a single night sleep deprivation and bright light therapy of 30 minutes via a light box (10.000 lux) the following five mornings. Thirty-five clients with a major depressive disorder (73% female, mean age = 41.4) responded. Participants completed two self-report measures for the assessment of depressive symptoms (Beck Depression Inventory-II) and general level of complaints (Symptom Check List-90) at the evening of the deprivation night (t=0), a week after the last light therapy (t=1) and three months after the combined treatment (t=2).

Results: Data analysis are still to be done at the moment of writing this abstract. The first impressions are a major relief of general complaints and depressive complaints at t=1 in comparison of t=0. This seems to be significant. The data-analysis will be done by May 2012.

Conclusions: Until now, no conclusions can be drawn from this study as the data-analysis isn’t finished yet. The first impressions suggest that a major depression decreases within 2 weeks by a combination of sleep deprivation and bright light therapy in a population of primary care patients. We foresee that we can conclude that a treatment with one night sleep deprivation and bright light therapy can be used as a treatment in the primary care with patients with a major depressive disorder.

Keywords: Major Depressive Disorder, Sleep Deprivation, Bright Light Therapy, General Primary Health Care
CASE REPORT: A 76 YEAR OLD FEMALE REFERRED FOR ELECTROCONVULSIVE THERAPY, IMPROVED AFTER AN OUT-PATIENT CHRONOTHERAPY PROGRAM (WAKE-LIGHT THERAPY); ACUTE TREATMENT AND FIVE YEAR FOLLOW-UP

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Objectives: Chronotherapeutic treatments like sleep deprivation (wake therapy), sleep-phase advance and bright light therapy, influencing the biological clock in the SCN have been studied for their effect on mood. A combination of these interventions is successfully implemented clinically in bipolar depressions and is studied for out-patient use (Wirz-Justice et al 2005). This casereport shows that chronotherapeutic interventions can not only be useful in clinical bipolar and unipolar depression, but also in motivated elderly people with unipolar depression at home.

Methods: A 72 year old, single female with a pharmacotherapy refractory depression was referred for ECT treatment to our out-patient clinic for intake. She had a remarkable need for sleep, energy loss, concentration difficulties and a strong diurnal variation with improvement of mood during the day. Aged 60 she had her first depression, treated successfully with Paxil (paroxetine), but relapsed in 2005 despite continuous use. Changing medication to venlafaxine (Effexor), nortriptyline, lithium augmentation, MAO-inhibitors and CBT, had no effect or were not tolerated. Because of her being reluctant towards ECT and the remarkable diurnal variations we suggested an attempt with an additional chronotherapy program: 3 times a week wake-therapy, sleep-phase advance and lighttherapy from 7.30 to 8.00 a, with a lightbox of 10.000 lux after the reinstallment of Paxil.

Results: In the second week of the Wake-light therapy program she noticed a slight change, but in the third (!) week, she remitted. ("Doctor, a miracle has happened"). Chronotherapy was continued with lightbox and sleep-phase advance; for convenience she change light therapy to a light visor. In the following years, discontinuing lighttherapy or discontinuing sleep phase advance by getting up later, caused mild relapses, which could be managed quickly with intensifying the treatment (reinitiating light treatment after a week holiday, a few wake therapy nights and rising earlier in the morning). Our patient has recaptured the life she lived before: walking, bridge drives, painting, traveling, organizing trips for a group of friends.

Conclusion: Elderly patients with unipolar depressions can be effectively treated in an out-patient setting with intensive chronotherapy and can integrate these interventions successfully in their lives.

Keywords: Wake-light therapy; outpatient, elderly, unipolar depression.

References:
EFFECTS OF MORNING LIGHT ON COGNITIVE PERFORMANCE, MOOD AND MELATONIN DURING SLEEP RESTRICTION

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Introduction: Light exposure elicits numerous effects on human physiology and behaviour. However, it remains inconclusive whether morning light exposure has beneficial effects on cognitive performance, mood and circadian physiology following sleep restriction (SR). Here we investigated the role of morning light exposure as a countermeasure for impaired cognitive performance and mood during SR.

Methods: Seventeen participants were studied during 42h in the laboratory in a balanced cross-over design where 3 different light settings were administered each morning after SR (6h): blue light (BL) (20 min exposure 2h after wake-up; 200 lux of light at 470nm), dawn simulating light (DsL) (blue-enriched polychromatic light gradually increasing from 0 to 250 lux during 30min before wake-up time, with light around 250 lux for 20min after wake-up time) and Dim light (DL) (<8 lux). Cognitive tests were performed every 2h during the wake episode and questionnaires were hourly completed to assess subjective mood and well-being. Salivary melatonin and cortisol were collected during wake episode in regular intervals.

Results: Analysis of cognitive performance yielded a significant main effect of “light condition” (p<0.01), such that during the first day following SR, performance was significantly deteriorated during DL, while it maintained stable during BL and significantly improved with DsL. After the second SR night, these differences on cognitive performance did not further reveal significances between DsL and DL. Analysis of well-being revealed a significant main effect of “light condition”, such that morning DsL improves levels of well-being, and even more after the second SR night, as compared to DL and BL (p<0.001). Exposure to morning DsL did not significantly affect circadian melatonin phase, while, after morning BL, melatonin onset was significantly earlier as compared to DsL and DL. Furthermore, after DsL, salivary cortisol levels were significantly higher at wake-time as compared to BL and DL.

Conclusion: Our data indicate that exposure to morning light after the first and second day of SR alleviate decrements in cognitive performance under conditions of mild SR. This effect was more pronounced after dawn simulation, since the DsL was able to maintain higher well-being levels and did not affect circadian melatonin phase, whereas morning blue-light induced a phase advance of melatonin, and therefore impacted on the circadian system.
THE “LIGHT ROOM” – LIGHT THERAPY FOR PEOPLE WITH CHRONIC MUSCULOSKELETAL PAIN

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Objectives: People with chronic musculoskeletal pain are at increased risk to become depressed, and depressed people have an increased risk of chronic pain. Sleep disturbances are frequently observed in patients with both chronic pain and/or depression, and sleep-wake disruptions can increase the physical sensation of pain. Light therapy might be a useful adjuvant treatment to increase well-being in this group of patients. The “Light Room”, initiated by the Rheumaliga Basel/Switzerland in winter 2010, offers the opportunity to try light therapy and get informed about light treatment use at home to patients with chronic musculoskeletal pain. The Light Room is mainly addressed to patients with rheumatic diseases but open to everyone, on three mornings from 9 to 12 a.m. weekly during the winter months (October to March). It is equipped with four DayLight® therapy lamps (Uplift Technology Inc., Canada), which can be used by the visitors for 30min; newspapers and soft drinks are available. The room is attended by an instructor with professional background in psychotherapy and energy work and two social workers, who give new visitors information about bright light treatment, its function, risks, benefits and use. Moreover, the Light Room aims to promote social contacts and daily structure in the patients.

Methods: The Light Room was announced by flyers sent to general practitioners, rheumatologists and social institutions, and by media releases sent to the local press, radio and television stations in the region of Basel. It was well attended during the first winter 2010/11, and visitors were requested to fill in a questionnaire for evaluating the use of the Light Room during the winter months 2011/12. We collected data on gender, age, diagnosis, expectations of the Light Room, and where they heard of the Light Room. Weel-being state (mood, alertness, pain, tension, energy, last night sleep quality) and well-being during the preceding two weeks (mood, tension, feeling rested, energy) were rated on a Likert scale (1-5). Moreover, visitors rated with “yes” or “no”, whether they think to benefit from, as well as whether they liked the room, the light, and the social contacts.

Results: 117 questionnaires of 42 visitors were collected on 32 days from 5th October 2011 to 14th March 2012, among them 36 women, age range 33-91 years (61.9±14.1y (m±SD)) and 6 men, range 35-80 years (49.8±8.6y (m±SD)). Only 5% of the visitors were informed by their physicians about the existence of the Light Room, 24% by their relatives and friends, and 71% by public announcements. Visitors expected the Light Room to improve mood and well-being, mental balance, stress and pain relief, and lighten up wintertime. Eight visitors thereafter purchased a therapy lamp for regular use at home. 33% of the 42 visitors suffered from arthritis/rheumatism, 31% from arthrosis, 36% from back pain, 14% from osteoporosis (only women), 29% from fibromyalgia, 52% from depression, 48% from sleep disturbances, 36% indicated other disorders (multiple diagnosis). Most of the people (79%) liked the light at their first visit, 19% stated to like the social contacts, and 12% liked the room itself. 88% had the subjective impression to benefit from exposure to light, 31% thought to benefit from the social contacts and 31% thought to profit from the room itself. 22 visitors, who came repeatedly to the Light Room (4.1±3.3 visits (m±SD)), rated the benefit of the light with 100% at their last visit, 45% indicated to benefit from the social contacts and 23% profit from the room itself. Well-being scores at first visit were on a moderate level (e.g. mood=3.2±1.1 (5=very good mood); pain 2.7±1.3 (5= free of pain)). All well-being scores were not significantly improved in frequent visitors at their last visit compared to the first visit and to the preceding two weeks (n=22, p>0.12).

Conclusions: The Light Room of the Rheumaliga Basel enables access to light therapy and is well visited by patients with chronic pain, depression and sleep disturbances. The exposure to light is most important for the visitors and its effect is subjectively rated as beneficial for their well-being. However, data analysis of the well-being ratings did not show improvement after light exposure, which is not surprising considering the lack of regularity and rather few days of bright light exposure. Extending the number of open days of the Light Room would be indicated, as well as increased individual consulting and assessment of long and short term effects of bright light treatment in patients with chronic musculoskeletal pain.

Keywords: chronic musculoskeletal pain, depression, bright light treatment, social contacts, daily structure