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Edited by
Tom de Boer
Leiden University Medical Center, Leiden

Viviane van Kasteel
MC Haaglanden, Den Haag

Peter Meerlo
University of Groningen, Groningen

Roy Raymann
Philips Research, Eindhoven

Johan Verbraecken
University of Antwerp, Antwerp
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PREFACE

Dear colleagues,

The NSWO proudly presents its 2011 issue of our yearly proceedings, which is read in many international large institutes for sleep research.

Sleep in the public domain

This year NSWO was successful by increasing awareness for sleep and sleep disorders in the Netherlands. Our PR committee successfully performed an internet based survey which showed that 24% of the 1350 responders is suffering from hyper somnolence. All those 324 persons were not known to have any sleep disorder. The NSWO survey got widespread media coverage. Moreover, the Dutch National Sleep Day has become a major stimulant for many members to share their knowledge with the general public through activities organised in sleep centres. This year was exceptional since it is the first in which a three-day public exhibition was organised in cooperation with and at AHoy conference centre in Rotterdam. Many distinguished speakers all members of NSWO gave public presentations on sleep and sleep disorders. During all three days the audience greeted the lectures enthusiastically.

Sleep in the professional domain

All clinical specialties involved in sleep have at currently started their own committees to promote the importance of Sleep Medicine within their own societies. NSWO is happy with its representation in the board of the Taskforce for Sleep and Wake disorders of the Dutch Society for Neurology. This year the Federation for Sleep Medical Centres has been founded. The NSWO is intensively involved in the process of accreditation of Sleep Medical Centres through this Federation for Sleep Medical Centres. At the time of the appearance of this issue the first accreditation visits have taken place. Since the NSWO is the Dutch representative of the European Sleep Research Society, which oversees the European accreditation of sleep medical centres, we are in line with the rest of Europe in having such a process developing at present. Also the Dutch pulmonologists involved in sleep can be part of this federation. The main body of pulmonologists have at present chosen for their own system of accreditation of Sleep Apnea Centres. NSWO is pleased with this increased awareness for quality of diagnosis and treatment of apnea patients.

Sleep and teaching

The teaching committee of NSWO has formed a taskforce fore for the organization of the annual International Sleep Medicine Course, which will be held in the Netherlands for the second time. The present course is unique since it is the first time that two parallel courses will be held for beginners and advanced students in the science of sleep. An extensive programme, discussing all the main sleep disorders and its medical implications has been prepared with many distinguished speakers from home and abroad. It will take place November 7-10 2011, just before our yearly scientific meeting at the same location.
Future goal

The NSWO board will serve as a platform to promote the spreading of knowledge on scientific sleep research and its combination with clinical practice. We also aim to increase the understanding of sleep disorders and to develop better treatment options for patients. NSWO will continue to participate in the process of accreditation of Sleep Medical Centres in all its aspects. Finally, we aim to integrate the many specialties working in the field of sleep into one large scientific and clinical federation possibly under the umbrella of NSWO.

Hans Hamburger, president
Amsterdam, November 2011
EDITORIAL NOTE

This is the 22nd edition of the proceedings of the Dutch Society for Sleep-Wake Research, which is again full of Dutch sleep research pearls.

In this edition Wytske Hofstra and Jaap Lancee present the summary of their PhD thesis. Both defended their thesis successfully in the past year. We are much honored that Marijke Gordijn and Michael Schredl took the effort to write a comment on the thesis of the new PhDs.

A new feature of the book is a special mini-paper by the winner of the Piet Visser Posterprice of last years meeting in Nieuwegein. Henry Keijzer was willing to write a paper about the subject of his poster and I hope a new tradition for the proceedings is born in this issue.

Similar to last year not only mini-papers, but also research abstracts of work of the past year, published or in press, are included. In this edition you will find 14 mini-papers, followed by 26 abstracts. I am very happy that Ton Coenen found the time to write a mini-review about the importance of the bed and the bedroom for sleep. On behalf of the scientific committee, I would like to thank all NSWO members for their contributions. In addition, from my side, many thanks to my co-editors for reviewing the mini-papers, ensuring the highest quality possible.

The proceedings are completed by an updated member list. This list, together with a lot more information about sleep research and sleep medicine in the Netherlands is also available on the NSWO website (www.nswo.nl).

Finally, I gratefully acknowledge the support of Merck Sharp and Dohme who, for the second time, support the publication of our yearbook.

Leiden, September 2011

Tom de Boer

Chair Scientific Committee
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PhD Theses
In this thesis we investigated the influence of circadian rhythms on epilepsy. Circadian rhythms are endogenously mediated ~24-h cycles of physiological and psychological processes, including the sleep-wake cycle, core body temperature, blood pressure, task performance and hormone production. These circadian rhythms in mammals are generated and maintained by a biological clock in which the master circadian pacemaker is formed by the cells of suprachiasmatic nuclei (SCN). In addition to the master pacemaker in the SCN, there is convincing evidence for the existence of peripheral circadian oscillators in the human body. More or less independent peripheral oscillators are found in several organs, including the liver, skeletal muscle and testis; all are under the influence of the SCN (Lamont et al., 2007). To synchronize the circadian system to the 24-h day, the SCN need to adjust daily. This is termed entrainment and this is accomplished by external cues, so-called Zeitgebers (“time givers” in German), such as scheduled sleep, activity, temperature and by far the most important the solar light-dark cycle (Duffy and Wright, Jr., 2005).

Several genes have been discovered that are at least partly responsible for this characteristic activity of the individual SCN and the interindividual differences. The activity depends on the expression of auto regulatory translation-transcription feedback loops of genes including the Period genes (Per1, Per2, Per3), the Clock gene and two Cryptochrome genes (Cry1, Cry2). It has been demonstrated in several animal studies that deletion or mutation of these genes leads to rhythms with abnormal periods or even arrhythmic phenotypes when tested under constant conditions. Moreover, dysfunction of these clock genes might be important in the development of various diseases, including cancer (Lamont et al., 2007).

In Chapter 2 the relatively poor knowledge on the interaction between circadian rhythms and human epilepsy is discussed. If this relationship exists, this interaction may be of value for better knowledge of pathophysiology and for timing of diagnostic procedures and therapy, as therapy adjusted to individual circadian rhythmicity (an example of chronotherapy) might improve seizure control. It appears that human seizure occurrence may have 24-h rhythmicity, depending on the origin. These findings are supported by animal studies. Rats placed in constant darkness showed spontaneous limbic seizures occurring in an endogenously mediated circadian pattern. More studies are available on the influence of epilepsy on circadian rhythms. One group studied chronotypes in patients with different epilepsy syndromes and found significant differences in the distribution of chronotypes between these two groups. Numerous studies have described influences of epilepsy and seizures on sleep and vice versa. In contrast, knowledge on circadian (core) body temperature patients is minimal as is the knowledge on clock genes in patients. Reduced heart rate variability and changed hormone levels, which are under the influence of the biological clock, have been observed in people with epilepsy. In short, large gaps in the knowledge about the interaction of circadian rhythm and human epilepsy still remain.

In Chapter 3 the methodology of measuring the circadian rhythm in humans is explored. An overview of widely used methods includes protocols used to desynchronize circadian rhythm
and sleep-wake, such as the forced desynchrony protocol (i.e. living on a 20 or 28-h day),
constant routine protocol (in which factors influencing circadian rhythmicity are minimized or
kept as constant as possible). Also, biological markers are employed to determine the phase of
the circadian rhythm. Examples are the dim light melatonin onset (DLMO, i.e. the time the
melatonin level starts rising in the evening under dim light conditions), core body temperature
and cortisol. Sleep parameters are being used frequently, but fall short in comparison to the
other reviewed methods. Questionnaires are helpful in determining chronotypes and sleep
parameters and finally, actimetry is one of the most frequently used methods in animal
circadian studies, but in human studies merely a good additional tool. In conclusion, the
DLMO is the most robust and most widely employed method to measure circadian
rhythmicity in humans.

Very few studies have evaluated seizure occurrence in humans over the 24-h day; data from
children are particularly scarce. In the study described in Chapter 4 we have analysed clinical
seizures of 176 consecutive patients (76 children, 100 adults) who had continuous
electroencephalography (EEG) and video monitoring lasting more than 22 hours. Several
aspects of seizures were noted, including classification, time of day, origin and sleep stage
and seizure numbers were compared to numbers expected when seizures would occur
randomly (binomial test). More than 800 seizures were recorded. Significantly more seizures
than expected when occurring randomly were observed from 1100 to 1700h and from 2300 to
0500h significantly fewer seizures than expected were seen. The daytime peak incidences
were observed in all types of seizures, but also in subgroups with complex partial seizures (in
children and adults), seizures of extratemporal origin (in children) and seizures of temporal
origin (in adults). Incidences significantly lower than expected were seen in the period 2300
to 0500h in all types of seizures, complex partial seizures (in children and adults) and in tonic
seizures (in children). In addition, significantly fewer seizures of temporal (in children and
adults) and extratemporal origin (in children) were observed in this period. The results
suggest that certain types of seizures have a strong tendency to occur in true diurnal patterns.
These patterns are characterized by a peak during midday and a minimum in the early night.

As mentioned above, few studies have evaluated human seizure occurrence over the 24-h day
and only one group has employed intracranial electrocorticography monitoring to record
seizures. We have analysed spontaneous seizures in 33 consecutive patients with long-term
intracranial EEG and video monitoring. This study is described in Chapter 5. Several aspects
of seizures were noted, including time of day, origin, type and behavioural state
(sleeping/awake). We recorded 450 seizures that showed an uneven distribution over the day,
depending on lobe of origin: temporal lobe seizures occurred preferentially between 1100 and
1700h, frontal seizures between 2300 and 0500h and parietal seizures between 1700 and
2300h. In the awake state, larger proportions of clinical seizures were seen from 0500 to
1100h and from 1700 to 2300h. During sleep, larger proportions occurred from 1100 to 1700h
and from 2300 to 0500h. Our results suggest that seizures from different brain regions have a
strong tendency to occur in different diurnal patterns.

It is conceivable that seizure timing could influence timing of daily activities, sleep and wake
(i.e. chronotype). Therefore, we performed a questionnaire study to compare the distribution
of chronotypes and sleep parameters in 200 epilepsy patients to the distributions in the general
population. This study is described in Chapter 6. To determine chronotypes and subjective
sleep parameters the Morningness Evennessness Questionnaire and the Munich Chronotype
Questionnaire were used. Significant differences were found between people with epilepsy.
and healthy controls. Epilepsy patients were more morning oriented, had an earlier mid sleep on free days and sleep duration on free days was longer ($p<0.001$). However, the distribution of chronotypes and subjective sleep parameters between patients with temporal lobe epilepsy, frontal lobe epilepsy and juvenile myoclonic epilepsy was found not to be different. Also, patients that had been operated on temporal lobe epilepsy had similar chronotypes and sleep duration when compared to patients who were not operated, but mid sleep on free days was earlier ($p=0.035$). In conclusion, this is the first large study focusing on chronotypes in epilepsy patients. We show that the distribution of chronotypes and subjective sleep parameters in patients in general is different from that of controls. Nevertheless, no difference is observed between patients with specified epilepsy syndromes, although they exhibit seizures in different diurnal seizure patterns. Our results suggest that epilepsy in general, but not seizure timing has significant influence on the chronotypes and sleep parameters.

Almost one-third of epilepsy patients continue to have seizures despite adequate drug treatment. Chronotherapy (based on dynamic changes in drug pharmacology and disease-related processes) could be a promising new treatment option. In the study described in chapter 7, we aimed to explore whether different circadian types (i.e. morning, intermediate and evening types) already adjust administration times of their anti-epileptic drugs (AEDs) as a first step in exploring chronotherapeutic possibilities. Therefore, we performed a questionnaire based study to compare the behaviour of patients with different circadian types in relation to the times of taking drugs. Circadian type (morning, intermediate or evening type) was determined by the Morningness/Eveningness Questionnaire. Results clearly show that morning types are taking their AEDs significantly earlier than evening types do on free days, that is 100 minutes earlier for the morning dose ($p<0.001$) and 55 minutes earlier for the evening dose ($p=0.019$). Also, times of taking AEDs in the morning on work days differ significantly between morning and evening types (55 minutes, $p<0.001$). Regardless of circadian type, drugs on free days are taken significantly later than on working days, which is most pronounced in evening types (up to 90 minutes delay in the evening types, $p=0.005$). Age and gender did not influence times of taking AEDs. In conclusion, this is the first study to show that patients adapt times of taking medication to their circadian type.

As mentioned, there is strong evidence that epileptic seizures occur in diurnal patterns. A study in rat models of partial epilepsy showed circadian seizure patterns and in humans circadian rhythmicity in interictal discharges has been found, suggesting that circadian rhythm may play a role in epilepsy. Circadian influences on human seizure patterns have not been investigated. In chapter 8 the study is described in which we performed a pilot study to ascertain influences of the circadian rhythm on seizure occurrence. We prospectively outlined circadian rhythms of patients admitted for long term EEG-video monitoring, using measurement of the dim light melatonin onset (DLMO). Seizures during admission were recorded with continuous EEG and video monitoring. The DLMO ranged from 1846h to 2313h (mean 2122h). One hundred and twenty-four seizures of 21 patients were analysed. Seizures of temporal lobe origin occurred mainly between 1100 and 1700h and frontal seizures were seen mostly between 2300 and 0500h. When correlating seizure timing to the individual circadian phase as measured by the DLMO, the following was seen: temporal seizures occurred most frequently in the six hours before DLMO and frontal seizures mainly in six to twelve hours after the DLMO. The results of this pilot study suggest that temporal and frontal seizures not only occur in diurnal patterns, but are time locked to the circadian phase.
CONCLUSIONS

Based on the studies presented in this thesis the following conclusions can be drawn:

- Seizures in epilepsy patients do not occur randomly over the 24-h day, but follow certain temporal patterns. These patterns depend on the origin and type of seizure. Temporal seizures occur most frequently during midday, frontal seizures are observed mainly at night and parietal seizures mostly in the evening. Complex partial seizures are seen most frequently during daytime.

- When referenced to the individual circadian phase, temporal seizures are mostly observed in the six hours preceding the dim light melatonin onset (a robust marker for the circadian phase) and frontal seizures occur most frequently in the six to twelve hours after the dim light melatonin onset.

- Epilepsy in general, but not seizure timing has significant influence on the chronotypes and subjective sleep parameters. People with epilepsy are more morning oriented and have an earlier mid sleep on free days than people without epilepsy.

- In our patient population we have shown that people adapt the times they take their drugs to their level of morningness or eveningness. Also, times of taking medication are delayed significantly on free days as compared to work days.

Overall, the results of our study strongly suggest that there is interaction between epilepsy and circadian rhythmicity.
Commentary on the dissertation of Wytske Hofstra

CIRCADIAN RHYTHMICITY AND EPILEPSY: THE SIGNIFICANCE OF BIOLOGICAL TIME

Marijke C.M. Gordijn

Centre for Life Sciences, Department of Chronobiology, University of Groningen, The Netherlands

Wytske Hofstra received her PhD with the defence of her thesis entitled “Circadian Rhythmicity and Epilepsy: The Significance of Chronobiological Time” in Amsterdam (VU) on March 4, 2011. The work was performed at Sleep Centre SEIN in Zwolle under supervision of her co-promotor Dr. A.W. de Weerd. Promotor at the VU was Prof. Dr. C.J. Stam. The work was financially supported by a grant of the “Christelijke Vereeniging voor lijders aan epilepsie”.

The thesis contains 9 chapters, including the introduction and general discussion. Of the seven main chapters, five were already published prior to the defence in international peer reviewed journals. Of the remaining two, one was published in May 2011 and the last one has been submitted. On all papers, Wytske is the first author. In addition, she published two book chapters as a first author and was co-author on several other papers. This is quite a comprehensive scientific output, especially if you realize that this PhD project lasted only two years and four months! During these 2.3 years at SEIN she collected a large amount of data in several groups of epileptic patients; she worked as a sleep specialist, participated in other research projects, analyzed all the data and wrote the papers. Immediately after this period she left with an almost complete manuscript to Enschede to start her specialisation in Neurology and one year later she got her PhD.

The purpose of the study was to give a thorough description of the role of biological time in the occurrence of epileptic seizures and the possible implications of this knowledge for improving therapies. The important role of the biological clock - generating 24h rhythms in the body - for our daily life is recognized by a selected group of scientists working in chronobiology and an even smaller group of interested clinicians. In some way, everybody is aware of this biological clock, e.g. people know they are more a morning type or evening type person and they feel the consequences of desynchronization between internal and external rhythms if they fly over time zones. Some people experienced the unexpected return of alertness in the morning, even after a full night without sleep. Nevertheless the consequences of the existence of the biological clock for clinical measurements, diseases or therapies have been mainly neglected for a long time. This was not foreseen when already in the 70-80s of the last century one of the godfathers of chronobiology, Prof. Jürgen Aschoff wrote in a chapter “The Circadian System of Man” (Aschoff and Wever, 1981) - quote: “The response of an organism to any stimulus usually depends on circadian phase in a systematic manner. In medicine, such rhythms of responsiveness are of relevance with regard to action of drugs…..chronotherapy may soon become of general usage after its start in endocrinology with the properly timed administration of corticosteroids…possibilities for chronotherapy in other fields (such as cancer) have been discussed…”. Not that much happened since then, although some recent papers might indicate a turn to the better (e.g. Hermida et al 2010, Levi...
2006, Wirz Justice et al 2009). Wytske’s studies fit perfectly well in this growing interest of the clinical field in the relevance of biological time.

In the first two chapters of her thesis, Wytske starts with a nice overview of how to measure circadian rhythms and what is already known about circadian rhythms and epilepsy. She covers both the literature dealing with epilepsy in animals, mainly rats, and studies involving humans. In rats a clear circadian rhythm in limbic epileptic seizures has been shown both under a light-dark cycle, with seizures occurring predominantly in the light phase, and under constant dim light. There are indications of daily patterns of epileptic seizures depending on lobe origin in patients as well. However whether these rhythms are endogenously generated or more related to the alternation of sleep and wakefulness or light and darkness is not a simple thing to study. Two of the best protocols to study human circadian rhythms are time consuming and not very suitable for epileptic patients. A constant routine, in which subjects stay awake under constant conditions - constant posture, environmental light, temperature and food intake – should last longer than 24h and therefore involves sleep deprivation. Since sleep deprivation is known to increase seizure occurrence this is not the best choice in epileptic patients. An alternative is a forced desynchrony-protocol. In this protocol subjects stay for at least 5 days under constant conditions with an imposed sleep-wake cycle deviating from 24h, for instance 20 h. This protocol could be carried out in patients but for this purpose one needs a time isolation unit with clinical care and highly motivated subjects and personnel.

Wytske was highly motivated for sure and considered to run a forced desynchrony protocol in epileptic patients, but it was decided that the lack of an isolation unit with clinical care made it too difficult to perform. But Wytske had more than one string to her bow. In chapters 4 and 5 she describes two large studies in which she recorded daily patterns in seizure occurrence in large groups of patients suffering from various types of epilepsy. She used different techniques, both electroencephalography, video monitoring and intracranial electrocorticography. It was concluded that indeed seizures from different brain regions have a strong tendency to occur in (different) 24h-patterns. In an attempt to identify whether the pattern of seizures over the day was (also) related to the internal phase of the biological clock or only to the external world she decided to take advantage of differences in biological timing between individuals. In chapter 6 she first analyzed individual differences in diurnality in epileptic patients. It was clear that also within the group of epilepsy patients clear differences in chronotypes exist; there are early birds and late types. This has even consequences for the timing of their drug intake as is shown in chapter 7; early birds take their anti-epileptic drugs 1-2 hours earlier than late types do on days off, but not on workdays. In chapter 8 she uses the differences in chronotypes to study the relationship between seizure occurrence and endogenous phase, measured by the up to now golden standard in chronobiology: the timing of the onset of melatonin in the evening (DLMO = dim light melatonin onset). As expected from the existing differences in chronotypes, timing of DLMO showed a wide range, varying from 18:46 to 23:13h. The occurrence of seizures from temporal origin and frontal origin showed a non-random pattern related to DLMO, with seizures from temporal origin being more abundant in the period 6h prior to DLMO and frontal seizures occurring predominantly 6-12h after DLMO.

In the last chapter Wytske summarizes the results and discusses the two main questions that evolve from her work: What is the origin of the circadian pattern of certain types of epileptic seizures and what are the possible implications for clinical practice. An interesting fact is that seizures from temporal origin are phase locked to the light phase in both the diurnal human
being and the nocturnal rat. This suggests a direct involvement of the biological clock itself, since SCN activity and some of its output parameters such as vasopressin and melatonin are also in phase with the light-dark cycle and not with the rest-activity cycle. One obvious practical outcome for the clinic is the possibility to optimize the planning of diagnostic monitoring of seizures by adjusting the timing to specific times of the day, in accordance with the expected type or origin of the seizure. And last but not least the fact that patients differ in the timing of their drug intake between days off and workdays may contribute to poor seizure control. Since almost one third of the patients continue to show seizures under medication, chronotherapy – i.e. individualized optimal timing of drug intake at the same time each day - may very well improve treatment success.

As usual some questions on the role of the biological clock in epilepsy are answered, others appear, but this thesis is a clear step towards a better understanding of the relevance of biological time in a severely disabling disease. As far as I understood, Wytske will come back to SEIN at a certain moment as part of her specialisation in neurology. Let’s hope that this topic is so much near to the heart of her interest that the field will benefit from her spirit and energy to continue and test the efficacy of chronotherapy in epileptic patients.


COGNITIVE-BEHAVIORAL SELF-HELP TREATMENT FOR NIGHTMARES AND INSOMNIA

Jaap Lancee

Department of Clinical and Health Psychology, Utrecht University

INTRODUCTION

Nightmares and insomnia are prevalent sleep disorders with serious consequences. Both nightmares and insomnia have a large psychological component and they can be effectively treated by cognitive-behavioral therapy.⁴ Nightmares and insomnia receive relatively little attention in the general health care and a minority of all sleep-disordered persons seek face-to-face treatment; most likely because the general public, as well as professionals are not sufficiently aware of sleep disorders and the possibilities for its treatment.³

Because of its cost-effectiveness and promising effects, self-help CBT has been proposed as a first option within a stepped-care framework. CBT for insomnia and nightmares primarily consists of psycho-education about sleep and exercises to improve sleep-wake habits that are relatively easy to explain. Therefore, the use of CBT self-help manuals for sleep problems within a stepped care approach framework seems promising. This dissertation describes three large randomized controlled trials concerning self-help CBT for nightmares or insomnia. The main goal of this dissertation was to assess whether self-help CBT can be effective in treating nightmares and insomnia.

NIGHTMARES

To date, the amount of published nightmares treatment studies is relatively modest. For this dissertation, all controlled nightmare intervention studies prior to May 2008 have been addressed in a systematic review (Chapter two⁴); only nine controlled nightmare CBT studies had been performed. The methodological quality of these studies varied; almost all studies had small sample sizes. This systematic review could reveal that two intervention types, Imagery Rehearsal Therapy (IRT) and exposure, demonstrated the largest effects. However, exposure and IRT were only once compared in a comparative trial, with a small sample size. Another problem was that the efficacy of IRT was only demonstrated by one research group and therefore did not meet the APA criteria for a well-validated treatment. A direct comparison with sufficient statistical power was needed.

The design of the two RCTs carried out in this thesis was primarily based on the conclusions of the systematic review (Chapter two⁴) and on the cognitive model for recurrent nightmares.⁵ According to the cognitive model, nightmares are represented in a fixed expectation pattern called a script. Cognitive avoidance is thought to prevent the emotional normalization of the script. Desensitization through exposure (prolonged imagination of the feared image) is supposed to break through this cognitive avoidance. Moreover, techniques that break through the cognitive avoidance and change the fixed expectation pattern by introducing new nightmare elements are supposed to work even better (e.g., IRT).

We therefore aimed to examine the hypothesis that IRT would be superior to exposure, which in turn would be superior to simple recording of nightmares (with some but very few
exposure elements). Moreover, of clinical interest was whether self-help CBT for nightmares is an appropriate treatment-delivery method (Chapter four\(^6\) and five\(^5\)). This is important because very few psychologists are properly trained to give nightmare treatment. If effective, self-help could be a low-cost and easy-to-deliver method to address this disorder. The second RCT was a logical consequence from this comparison by including two other familiar interventions types (addressing sleep hygiene; lucid dreaming; Chapter six\(^8\)).

The baseline data of the two RCTs were used to evaluate the associations between nightmares and psychopathology measures. According to the literature, nightmares are correlated with general psychopathology in clinical samples and samples of college students. However, in a previous study on the general population, no such correlations were found, which suggests that these associations might be different within subsamples. In this study (Chapter three\(^9\)), we found that nightmare frequency is not associated with psychopathology but with sleep quality. This supports the idea that nightmares are a relatively independent mental disorder and that nightmares should be specifically targeted from a sleep medicine perspective.

In the first nightmare RCT (Chapter four\(^6\)), 399 participants were randomized into IRT (\(n = 103\)), exposure (\(n = 95\)), recording (\(n = 106\)) or waiting-list condition (\(n = 95\)). Compared to the waiting-list, IRT and exposure were effective in ameliorating nightmare frequency and distress, subjective sleep quality, anxiety (after imagery rehearsal), and depression (after exposure; \(\Delta d = 0.25 - 0.56\); \(p < .05\)). Compared to recording, IRT reduced nightmare frequency while exposure reduced nightmare distress (\(\Delta d = 0.20 - 0.30\); \(p < .05\)). The recording condition was more effective compared to the waiting-list in ameliorating nightmare frequency, nightmare distress, and subjective sleep quality (\(\Delta d = 0.19 - 0.28\); \(p < .05\)).

Results were sustained in the long run (Chapter five\(^7\)). Moreover, IRT has now been tested by a second research group, so it meets the criteria for a well established treatment.\(^{10}\) IRT alleviated nightmare frequency faster, but, unexpectedly, was equally effective to exposure. It seems thus that the desensitization to the feared image is the crucial element in nightmare treatment.

In the second nightmare RCT (Chapter six\(^8\)), 278 participants were randomized into IRT (\(n = 70\)), IRT+ (with sleep hygiene; \(n = 76\)), Lucid Dreaming Therapy - LDT (\(n = 70\)), or waiting-list condition (\(n = 62\)). Results showed that in addition to IRT, sleep hygiene or lucid dreaming did not have a beneficial effect. Contrary to our expectations, the original IRT was more effective than the treatment conditions with additional sleep hygiene and LDT sections. It seems therefore that –at least in a self-help format- diversifying the treatments confuses nightmare sufferers.

Overall, the nightmare treatments tested in this thesis were found to be effective. A rather large part of the studied sample did not benefit (enough) from this treatment, leaving considerable room for improvement. An explanation might be that we used a format that did not motivate the participants sufficiently. Previous studies concluded that providing feedback to the self-help enhances efficacy\(^{11, 12}\); future studies should consider including support. Self-help CBT for nightmares is promising and with the proposed addition of feedback, treatment could possibly be enhanced, which would eventually allow implementation of nightmare self-help treatment into general healthcare.

**INSOMNIA**

Self-help for insomnia has been proposed as a good first option for insomnia in a stepped care model.\(^{13}\) The problem was that the effectiveness of self-help CBT for insomnia appears only
Moreover, large-scale self-help studies found no effect on diary sleep measures (e.g., sleep duration). For Chapter seven, a self-help CBT protocol for insomnia was developed and its effectiveness was evaluated in a large RCT \((N = 623)\) which compared Internet delivered self-help CBT to bibliotherapy and a waiting-list condition. Multilevel regression intention-to-treat analyses showed that, at 4-week follow-up, Internet and bibliotherapy conditions were superior \((p < .05)\) compared to the waiting-list condition on daily sleep measures \((\Delta d = 0.20–0.64)\), global insomnia symptoms \((\Delta d = 0.54–1.00)\), depression \((\Delta d = 0.36–0.41)\), and anxiety symptoms \((\Delta d = 0.33–0.40)\). The Internet and bibliotherapy groups demonstrated equal effectiveness 4 weeks after treatment \((\Delta d = 0.00–0.22; p > .05)\). However, the Internet condition had a higher dropout. Effects were sustained at 48-week follow-up, but surprisingly, symptoms of insomnia and secondary complaints decreased more in the Internet compared to the bibliotherapy condition.

This large-scale RCT showed that insomnia can be effectively treated through self-help CBT. Observed effects were larger than previously published moderate- to large-scale self-help studies, comparable to the most effective smaller scale \((N < 50)\) self-help CBT studies, and almost similar to several face-to-face intervention studies. Furthermore, long-term outcomes were better than sleep medication. This study showed that self-help CBT for insomnia is not only effective on global insomnia symptoms (such as an insomnia rating scale), but also on diary sleep measures (such as total sleep time, sleep onset latency, etc.). This means that insomnia self-help now proved to be effective in a large trial on primary outcome measures.

The results in this thesis moved insomnia research one step forward into the direction of implementing this type of treatment into the general healthcare. Interestingly, these large effects were found with unsupported self-help CBT. This is surprising because it has been suggested that some rudimentary form of support is essential in self-help. The current findings suggest that a majority of persons suffering from insomnia do not need support in order for self-help to have positive effects. The unsupported self-help CBT is very cost-effective and might be an interesting option to employ in large groups for prevention purposes (e.g., insomnia is a predictor for developing major depression and other health problems in later life).

Notwithstanding the positive results, the fact remains that after treatment, 50-60\% still fulfilled the diagnostic criteria for an insomnia disorder. Unsupported self-help may have been sufficient for large parts of the sample but might have been too complicated for other participants. Especially the intrusive and difficult-to-perform method of sleep restriction could have been too challenging. So although unsupported self-help showed good results, providing additional therapist support on progress and the actual exercises might encourage more patients to complete the most intrusive modules of sleep restriction and paradoxical intention.

CONCLUSION

In conclusion, in this dissertation we found that unsupported self-help CBT can successfully ameliorate nightmares and insomnia. Sleep disorders can be specifically targeted and self-help treatments have an effect on primary sleep complaints. The nightmare studies demonstrated that self-help CBT decreased nightmare frequency. The insomnia study showed that CBT increased total sleep time, and decreased sleep onset latency as well as waking time after sleep onset. Moreover, indirect effects were found on affective complaints such as depression and anxiety. The effects were sustained in the long run, suggesting that not only face-to-face but also self-help CBT has better long-term effects than sleep medication. The self-help
format is promising because it appears to be a cost-effective way to reach a large number of people with sleep disorders.

REFERENCES

Nightmares and insomnia share three features; both sleep disorders are very prevalent in the general population (prevalence of nightmare disorder about 5% (1); prevalence of insomnia varies between 5 and 20% depending on the criteria of the studies (2)); both disorders are most effectively treated by cognitive behavioral therapy (for nightmares see (3) and for insomnia see (4)) and, lastly, both conditions are under-diagnosed and undertreated (for a discussion on nightmares see (5)).

Within this context, the work of Jaap Lancee and his supervisors Jan van den Bout and Victor Spoormaker is groundbreaking and very beneficial to patients suffering from these disorders. Sleep medicine is still a young discipline and including courses on sleep medicine in the course of the training of physicians is only a recent accomplishment. In the training of psychotherapists, treatment of insomnia often is part of the training to become a cognitive-behavioral therapist but far from common knowledge within the psychotherapy community. In our experience, the treatment of nightmares is rarely known to professionals in the field. This contributes, at least partly, to the fact that these disorders are undertreated. Therefore, the idea of Jaap Lancee to reach out to the patients directly and offer them a self-help approach is great. Showing moderate to large effect sizes of his program clearly indicate that these techniques, Imagery Rehearsal Therapy for treating nightmares, and a multi-modal cognitive-behavioral intervention for treating insomnia can be brought to patients who otherwise very likely would not have received any help for their specific problems.

In view of the stepped care model, the development of self-help programs and making them available to the general public is very important. I hope that Jaap Lancee and Jan van den Bout continue their good work in this area to find way to minimize drop-out rates and maximize the percentage of fully recovered patients. It should be kept in mind that research on self-help programs, e.g., what works and what doesn’t work, will also help to improve therapist-based treatment approaches for nightmares (see (6), a manual for therapists recently published in Germany) and insomnia.

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Mini review
SLEEP, THE BEDROOM, AND THE BED

Anton Coenen

Department of Biological Psychology, Donders Centre for Cognition
Radboud University Nijmegen
a.coenen@donders.ru.nl

PROLOGUE

A main factor facilitating sleep is the bed. Although most people can sleep sitting up in a chair, it is most comfortable to sleep lying in a bed. A lying position demands the least energy, and is most relaxing. The pressure on the vertebrate column is small and the heart can easily pump blood through the body. Until far in the nineteenth century, humans slept with pulled up knees in a tiny bed located in an alcove, a closed, windowless small, dark space (Figure 1). Building separate sleeping rooms came to The Netherlands when the ‘Woningwet’ ['Law on houses'], was introduced, in 1901. The design of good beds started some years earlier in 1888 when Johannes Auping, a blacksmith from Deventer, designed a bed with a flexible mesh base. The Auping company is still the leading bed and mattress manufacturer in The Netherlands. A good bed, plus appropriate bed materials, located in an adequately arranged room, is invaluable, because we spend one third of our total life asleep. But what is a good bed and what is a good sleeping environment? Until now there is no scientific consensus on these points. A large distance existed between bed manufacturers and sleep scientists, and a cautious approach between these two groups of experts emerged only recently \(^1\), \(^2\), \(^3\). The sleep industry came to the conclusion that they could use the results of sleep researchers, and researchers noticed that the physical properties of beds, and bed materials, played a role in the quality of sleep.

THE BEDROOM

A quiet bedroom is positive for sleep. The threshold for arousal varies according to the age of the subject, the stage of sleep, as well as the nature of awakening stimuli. Children sleep through more stimulation than adults, and older people have the lowest awakening thresholds. The threshold for arousal increases from stage 1 to stage 4 of sleep. Sudden intense stimuli, such as loud noises, light flashes or firm touches, can disturb sleep considerably. Awakening from sleep follows from two kinds of stimuli: intense stimuli passing the awakening threshold and soft ones which are relevant to the sleeper. A suspicious thumping in the house or the smell of burning can arouse us, even at a low intensity. A young mother can wake up by the soft noise of her newborn baby. The sudden barking of a dog in the dead of night, may warn a sleeper that something is wrong. All these kinds of awakenings is functional. An evaluation mechanism is at work in sleep and the, scarce, incoming information is still subconsciously evaluated. If the result of this information is relevant, then it is likely that the sleeper will be aroused. Often the sleeping subject is unaware of what exactly causes the awakening. This evaluation process is a vital process and this distinguishes sleep fundamentally from non-physiological low-conscious states, such as coma or anesthesia \(^4\). Obstruction of this
evaluation process, for example by wearing earplugs to dampen noises, is not recommended, since it isolates the sleeper physically from the environment. Normally occurring noises, for example, the softly ticking of a clock or the humming of a fan, do not disturb sleep at all, which is also true for familiar house sounds. The situation changes when the sounds are experienced as annoying. In that case the stimulus is experienced negatively, and is relevant. That is what often happens around airports. Several people living in the neighborhood of an airport, often wake up easily when an aircraft approaches, even when the noise is gentle. In the bed situation, this frequently occurs with the snoring noises of a bed partner.

Figure 1. The French caricaturist Honoré Daumier sketched in 1839 the sleeping environment of a human. Often pets slept in the same alcove. Note the usual nightcap.

Darkness is a sleep stimulus and the bed room needs to be dark. Many people prefer not to have complete darkness, but rather a weak light in the sleeping room, which allows proper orientation at a nightly awakening. The daylight in the morning, is a trigger for waking up. In the spring and summer, with early daylight, sleep tends to be shorter than in autumn and winter with longer darkness. Sleep duration can be somewhat modulated by the transparency of the curtains which let through more or less morning light. Fresh air is important since we consume oxygen and produce carbon dioxide during the entire night. Ventilation with open windows, keeps the air in a good condition. Ventilation is also good for proper humidity in the bedroom. Humidity in the room has to be around 40 till 60 percent. When the air is too dry, waking up with a hoarse throat can occur, and when the room is too humid, awakening with a clammy feeling can occur. A humid climate also attracts moulds and other vermin. Humidity can be regulated by the window opening and by vaporizing water.
The environmental temperature in the bedroom should not be too high. The best temperature ranges between 16 and 18 degrees Celsius, with an ideal of 18 degrees, although variations can be large. When the temperature is higher, the body cannot easily get rid of its warmth. The drop in body temperature, with darkness acting as a trigger for sleep, is thus not as easy during the day, but also during the night, and cooling pillows are already on the market. Recent summers in The Netherlands are characterized by heat waves. Nightly temperature in sleeping rooms after some tropical days may increase up to 26 degrees Celsius in the airco-less Dutch houses. During such a period, many people complain about their sleep, which is shallow and accompanied with many arousals. Ambient temperature is too high and the necessary cooling of the body cannot adequately take place. Conversely, the environmental temperature should not be too low. Below 12 to 14 degrees can be problematic, because the internal temperature can sink under the ideal nightly body temperature, or the weight of blankets becomes uncomfortable heavy. In early times when sleeping rooms were much colder a nightcap was usually worn, to prevent too much cooling (Figure 1).

THE BED

The temperature in the bedroom is important, but the temperature in the bed under the blankets is even more critical. The best temperature in the microclimate of the bed lies in the thermo-neutral zone of 27 to 31 degrees, with an optimal value of 29 degrees. The thermo-neutral zone is characterized by a zero exchange between the skin and the surroundings. When the bed temperature is too high the body starts sweating, whereas at a too low temperature the warmth production by shivering begins. A fine adjustment between room temperature, blankets and night cloths is required. Also the bed partner plays a role in this adjustment, because this person acts as a moving stove and may disturb the fragile equilibrium in the bed climate. There is also evidence that sexes have their own temperature preference, since women tend to prefer a higher bed temperature than men. During REM sleep the thermoregulation is inhibited, since the complete muscle relaxation prevents the production of warmth. However, the effects on body and skin temperature are small, since the periods of REM sleep last relatively short. Nevertheless, recent investigations performed by van Someren and colleagues at the Free University of Amsterdam show that subtle changes in skin temperature might have quite considerable consequences for the depth and quality of sleep.

In the course of the time beds became more spacious. It is recommended that a bed is 20 cm longer than the length of the sleeper. Currently, the standard bed length is 2 meters, but in the future it is expected that it will be extended to 2.20 meters. The width has to be 80 to 90 cm per person. This allows sufficient room for movement in the bed. A sleeper has not a fixed position in the bed, although he has a favorite posture. A subject goes to bed, take his favorite posture, and will fall asleep. Soon, however, the sleeper will change his position and turns from his favorite posture, to another position, for example changes from the right side to the left side. All sleeping persons move in their sleep. Changes in bodily position are part of a healthy sleep, otherwise the sleeper would wake up in the morning with stiff muscles and joints. Bodily movements are also necessary for a proper blood circulation. The sleeper’s favorite position is, however, dominant and most sleeping time is in this position. The number of body shifts is variable, but a realistic estimation is between 20 to 40 times. A higher
motility is associated with insomnia (‘tossing and turning’), while a lower activity points towards alcohol or drug use.

The favorite postures of many people are the left and right side, which also seem the best sleeping positions. The supine position, lying on the back, is more problematic since snoring occurs more frequently in this position, while the prone position, lying on the belly, is the least favorite posture, because the heavy body presses on vital organs such as the heart. The position of the head relative to the body, is in both prone and supine posture, less favorable. A normal pillow is mostly designed for a side lie, and just fills up the space between the head and the shoulder (Figure 2). Pillow manufacturer Jade from Deventer, has tried to solve this problem by designing a pillow with three compartments of different thickness. The middle, less thick, compartment is thought to be used in the prone and supine position, while the two, thicker, side compartments are thought to be used in the two lateral positions. However, practice and theory do not always agree with each other.

Figure 2. The pillow has to fill up the distance between the head and the shoulder, to support optimally the head and neck spines. Sleeping subjects mostly crumple up the pillow and also use an arm to fill up this space.

THE MATTRESS OF THE BED

The mattress of the bed is particularly important for a healthy sleep, because the mattress influences the lying posture in the bed. The firmness and elasticity are especially relevant given the fact that a straight horizontally positioned cervical spine facilitates relaxation and minimizes bodily problems (Figure 3). The elasticity cannot be equally divided over the mattress surface, because the pressure of the body is not the same across the mattress surface, and is largest at shoulders, hips and pelvis. The mattress must tolerate body movements and both isolation and ventilation must be adequate. Finally, the mattress must not attract mites and bed bugs. Most mattresses loose their good qualities in the course of years and should be replaced after 8 to 10 years.

It is often thought that sleep motility is associated with a shallow sleep, considering the association of insomnia with tossing and turning. Soft mattresses, such as those composed of the temperature sensitive visco-elastic material that gives a sleeper a deep lying position and encloses the body, should not to favour nightly movements. This should be in contrast to mattresses with a firm surface, such as the pocket spring mattresses, which enables a subject to lay on top of the mattress, allowing for sleep movements. Recent research on this issue,
However, revealed that modern comfortable mattresses have no direct effects on sleep motility. Sleep movements seem to fulfill an intrinsic physiological need, and only in quite extreme situations, effects of the sleeping surface on sleep motility can be noticed.

Figure 3. An optimal support of the cervical spine is shown in the upper part of the figure. When the firmness of the mattress is too small (middle part) or too high (bottom part), the spine is not lying in a straight way. Back pain and irritation of the nerves can occur.

Sleep movements can also influence, or even disturb, the sleep of a bed partner. This is accepted in the beginning of co-sleeping, but after a while the feelings of acceptance may change in feelings of irritation and annoyance. To minimize disturbance the bed partners can choose for one bed with two separate mattresses. The intimacy of sleeping together is then maintained, while the inconveniences are greatly reduced. Unfortunately, this two-mattresses-in-one-bed solution is not a solution for annoying snoring sounds. Earplugs or separate sleeping rooms are then, though less optimal, good solutions.

SNORING AND SLEEP POSITION

Interest for the position in bed increased when it appeared that snoring was modulated by the sleep position. Muscles are relaxed in sleep and snoring is associated with obstruction of the upper airway. The noise is produced by vibration of the soft tissue of the back of the mouth. Snoring may be affected by a number of factors, such as increased body weight, alcohol consumption, the use of hypnotics and body position in bed. Although, most loud snorers tend to snore in any position, sleeping on the back is liable to induce snoring in a person who otherwise does not snore when sleeping on the side. An old trick is to attach a tennis ball to the shirt of the pajamas, to facilitate sleeping on a side. In the side position the air can stream more easily through the airway, than in the supine and prone positions. Lying on something
uncomfortable ensures you of lying on your back. This anti-snoring ball helps in many cases, although also people often complain that this uncomfortable approach can disturb sleep.

Figure 4. The American Liebhardt introduced and patented the trick with the tennis ball in the pajamas already in 1908. Soldiers fighting in the American War of Independence had to sew a small cannonball in their uniform to prevent that loud snoring kept the entire army awake.

A better approach is to arrange bed materials so that a side lie is facilitated and a supine position is counteracted. Head pillows are already designed doing this, such as the American ‘anti-snoring pillow’ which helps to adjust the position of neck and chin to easing the flow of air. The efficacy of this pillow, however, is still not clear. In Scandinavia, experiments are going on to lift the head side of the bed when a microphone indicates snoring. It seems that in a half upright position snoring is reduced, since the airway is less obstructed. A future approach might be that a bed or mattress is designed in such a way that a lying position on the side will be favoured and a supine position hindered.

Figure 5. Sleeping with a guling, as shown in a brochure of the company ‘Topslapen’. The guling is also known as the ‘Dutch wife’, for the reason that the Dutch in their former colony Dutch Indies, now Indonesia, often slept singly and took the sleep habits of the inhabitants. It cannot be denied, however, that also other versions of this designation exist.
In Indonesia people like to sleep with a guling (Figure 5). That is a long roll shaped pillow or bolster. Basically the guling is hugged between arms and legs and seems a comfortable way of sleeping. The reason that such a pillow is particularly used in a tropical climate is that perspiration fluid is readily taken up by the bolster. A second advantage is that bare legs do not touch each other, and prevent the sweaty feelings. A few years ago this roll pillow was introduced in The Netherlands as the ‘sleep mate’. The most important reason for this is that such a pillow favors a side lying position and could therefore serve as an anti-snore pillow.

EPILOGUE

Sleep begins when body temperature decreases and darkness comes, while sleep ends when light returns and body temperature increases. The temperature in bed is particularly relevant for sleep and must be in the thermoregulatory zone of 27 to 29 degrees Celsius, while the environmental temperature fluctuates around 18 degrees. In falling asleep a preferable sleeping posture is chosen. Despite this main position, there are relatively many movements during the night. This keeps the body in a proper condition during the long period of sleep. Bed, pillow and mattress have to permit these movements and the bed must be large and wide enough. The best positions in bed are the left and right side positions and these positions are preferable above the prone and supine body positions. In particular snoring is minimal in a side position. Future approaches are to develop bed materials which facilitate a lying position on the side. Good sleep is also facilitated by an optimal arranged sleeping room, without too much noise, a suitable light-dark regime and a proper ventilation, as well as humidity.

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Henry Keijzer (l) receives the Piet Visser Poster price 2010 (picture by C. Donjacour)
EVALUATION OF SALIVARI MELATONIN MEASUREMENTS FOR DIM LIGHT MELATONIN ONSET CALCULATIONS IN PATIENTS WITH POSSIBLE SLEEP-WAKE RHYTHM DISORDERS

Henry Keijzer¹, Marcel G. Smits², Twan Peeters¹, Caspar W.N. Looman³, Silvia C. Endenburg¹, Jacqueline M.T. Klein Gunnewiek¹ and Leopold M.G. Curfs⁴

1) Gelderse Vallei Hospital, Department of Clinical Chemistry and Hematology
2) Gelderse Vallei Hospital, Department of Sleep-Wake Disorders and Chronobiology
3) Erasmus MC Rotterdam, Institute of Public Health
4) Academic Hospital Maastricht / University Maastricht, Department of Clinical Genetics,

INTRODUCTION

The endogenous 24-hour melatonin rhythm is one of the most reliable biological clock markers of circadian phase. The time at which the melatonin concentration starts to rise in blood or saliva under dim light conditions (Dim Light Melatonin Onset or DLMO) is an important marker in assessing circadian phase¹. Determining DLMO plays a key role in the diagnosis of Circadian Rhythm Sleep Disorders (CRSD) and is needed for successful treatment of CRSD with exogenous melatonin, a potent chronobiotic drug². Circadian phase can be assessed by measuring DLMO in serum or saliva³ or by measuring of 6-sulfatoxymelatonin levels excreted in urine⁴. In healthy young adults, studied in sleep-labs DLMO correlates well with sleep onset⁵. In contrast, in sleep onset insomniacs DLMO correlates only moderate with sleep onset time⁶. In the Dutch National Referral Centre for sleep-wake disturbances and chronobiology at the Gelderse Vallei Hospital in Ede, the Netherlands, DLMO is measured in about 1500 patients annually. Patients collect saliva conveniently in their home environment and send it to the laboratory for analysis of endogenous melatonin concentration. To evaluate the success rate of DLMO measurements we retrospectively analyzed the melatonin measurements performed in the year 2008 patients’ sample size. Furthermore, in patients with a completed sleep diary and in patients where sleep architecture was assessed using ambulatory polysomnography (PSG), we studied whether DLMO can be correctly predicted by diary or PSG sleep-onset time.

METHODS

Patients with a sleeping difficulty referred to the sleep centre at the Gelderse Vallei Hospital completed an online questionnaire at www.slaapstoornissen.nl. If this questionnaire points toward a Delayed Sleep Phase Disorder (DSPD), i.e. falling asleep late or having trouble waking up at a conventional time in the morning, these patients received saliva collection devices Salivette® (Sarstedt, Nümbrecht, Germany) for measurement of a 5-point partial melatonin profile. Sample collection occurred at the patient’s home in dim light. Melatonin was measured using a radioimmunoassay (Bühlmann laboratories, Schönenbuch, Switzerland), as described previously and DLMO was defined as the time at which the increasing melatonin concentration in saliva reached 4 pg/mL³. The 5-point partial profile was used as a diagnostic test to determine possible CRSD. Based on the 5-point profile results the
sleep centre physician started treatment or ordered additional saliva samples (i.e. a 24-hour profile), a sleep diary during at least one week or an ambulatory multichannel portable polysomnography (PSG) during one night.

Melatonin data from January 1st 2008 until December 31st 2008 were retrieved from the Laboratory Information Systems and exported in a Microsoft Excel datasheet. In addition to the melatonin results, the datasheet contained information about date of birth, gender, personal hospital number, date / time of sampling. DLMO was calculated by linear interpolation of 4 pg/mL melatonin value to the corresponding time. Extrapolation was done when the highest point was between 3 and 4 pg/mL.

Data were analyzed with SPSS version 17 (SPSS Inc, Chicago, Illinois) for descriptive statistics, independent t-test for comparison of means and Pearson correlation between DLMO vs. sleep onset. The study was conducted in accordance with the ICH-GCP guidelines and local law. Ethical approval was not required; this study was a secondary analysis of a de-identified data set.

RESULTS AND DISCUSSION

In 2008 a total of 1848 5-point partial curves were analyzed and included is this study. Other curves were omitted because these curves were not used in our clinical practice for diagnosing sleep problems.

DLMO was calculated in these 5-point partial curves (n=1848) and could be determined in 76.2% (n=1408). Table 1 summarizes the results. Table 1 also shows a subdivision in cases where DLMO calculation was not possible.

Table 1: Different DLMO outcomes from 5-point partial melatonin curve with frequencies (n) and mean age

<table>
<thead>
<tr>
<th>DLMO outcome</th>
<th>n</th>
<th>Percentage (%)</th>
<th>Mean age (y)</th>
<th>SD (y)</th>
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<tbody>
<tr>
<td>DLMO determined</td>
<td>1408</td>
<td>76.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Calculated</td>
<td>1316</td>
<td>71.2</td>
<td>27.9</td>
<td>19.2</td>
</tr>
<tr>
<td>- Extrapolated (values ≥3 - &lt;4 pg/mL)</td>
<td>92</td>
<td>5.0</td>
<td>39.3</td>
<td>19.5</td>
</tr>
<tr>
<td>No DLMO determined</td>
<td>440</td>
<td>23.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Values ≥0.5 - &lt;3 pg/mL</td>
<td>162</td>
<td>8.8</td>
<td>43.4</td>
<td>19.7</td>
</tr>
<tr>
<td>- All values &lt;0.5 pg/mL</td>
<td>51</td>
<td>2.7</td>
<td>31.4</td>
<td>21.0</td>
</tr>
<tr>
<td>- All values exceed 4 pg/mL</td>
<td>136</td>
<td>7.4</td>
<td>30.6</td>
<td>20.9</td>
</tr>
<tr>
<td>- Unexplained curve fluctuation</td>
<td>53</td>
<td>2.9</td>
<td>27.5</td>
<td>20.6</td>
</tr>
<tr>
<td>- Insufficient sample amount</td>
<td>38</td>
<td>2.1</td>
<td>18.7</td>
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</tr>
<tr>
<td>Total</td>
<td>1848</td>
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</tbody>
</table>

Failure of DLMO determination was mainly due to profiles with melatonin values between 0.5 – 3 pg/mL (8.8%) or profiles where melatonin levels were already above the threshold of 4 pg/mL (7.4%). The low evening melatonin levels are consistent with late melatonin onset or with persistent low melatonin secretions. Mean age of the “no-DLMO” (values ≥0.5 - <3 pg/mL) group was significantly higher (p<0.001) compared to that of the “DLMO calculated” group. This can be explained by the fact that melatonin production declines with increasing age. In these low melatonin secretors, DLMO threshold could be redefined at a lower fixed threshold or at an individually calculated threshold: 2 standard deviations above the basal mean. Mean age of the patients with all values above 4 pg/mL did not significantly differ (p=0.14) from the mean age of the “DLMO calculated” group. High evening melatonin levels might also be caused by recent intake of high doses of melatonin or be due to slow melatonin metabolism. Fluctuating curves were seen in 2.9% of the total sample size. This percentage increased to 43.7% in patients with high evening melatonin levels. These fluctuations are also
often seen in patients taking exogenous melatonin. It may take about three months after stopping melatonin treatment before pre-treatment melatonin levels are reached again.\textsuperscript{11}

Figure 1 shows the age distribution among included patients (n=1848): 41.2% were children aged between 0 and 17; 6.9% were young adults aged between 18 and 24; 38.5% were adults aged between 26 and 54 and 13.4% were adults above the age of 55.

![Age Distribution Histogram](image)

Figure 1: Histogram of age distribution of the 2008 patient sample size where a diagnostic 5-point curve was measured (n=1,848). Age is plotted on the X-axis while numbers of included patients are plotted on the Y-axis.

For the correlation study 130 patients were randomly selected (SPSS). Of those 130 patients, 54 underwent a PSG (mean age: 40.5 years, SD 17.2 range 5 – 70 years and consisted of 33 women and 21 men) and 20 online diaries were available (mean age: 23.2 years, SD 20.5 range 4 – 63 years and consisted of 11 women and 9 men). Sleep onset time retrieved from PSG was a one day measurement and sleep onset from sleep diary was a 6.5 day average (range 1 – 12 days). The Pearson correlation was significant moderately positive between DLMO and the sleep onset time in PSG and sleep diary, as seen in Table 3.

<table>
<thead>
<tr>
<th>DLMO time (PSG)</th>
<th>Sleep onset time (PSG)</th>
<th>r</th>
<th>DLMO time (diary)</th>
<th>Sleep onset time (diary)</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>22:26</td>
<td>23:49</td>
<td>0.514</td>
<td>22:07</td>
<td>23:10</td>
<td>0.653</td>
</tr>
<tr>
<td>(80)</td>
<td>(59)</td>
<td>p&lt;0.001</td>
<td>(112)</td>
<td>(89)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>n=54</td>
<td>n=54</td>
<td>n=54</td>
<td>n=20</td>
<td>n=20</td>
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</table>

(SD in minutes)
CONCLUSIONS

DLMO can be reliably measured in saliva that is conveniently collected at home. DLMO correlates moderately with sleep onset determined with diary or PSG. Therefore caution is advised when predicting DLMO in patients with a sleeping difficulty.

ACKNOWLEDGEMENTS

We would like to thank the technicians of the Gelderse Vallei Hospital Isotope Laboratory for the measurements of the many melatonin samples.

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THE EFFECT OF EMOTIONAL STIMULI ON SLEEP ARCHITECTURE IN HEALTHY SUBJECTS

Laura F. Bringmann, Winni F. Hofman & Lucia M. Talamini

Department of Psychology, University of Amsterdam, The Netherlands

INTRODUCTION

A growing body of evidence suggests an intimate relation between emotions and sleep. For example, the majority of dream reports have an emotional content and emotional experiences have a high probability of popping up in dreams\(^1\). Accordingly, recent studies indicate a selective activation of the amygdala during REM sleep,\(^2,3\) in which most emotional dreaming occurs. Furthermore, chronic sleep loss or selective REM sleep deprivation make people bad-tempered and irritable. Finally, nearly all affective disorders are associated with sleep disturbances involving alterations of REM-sleep and SWS\(^4-6\).

Such observations have led to the hypothesis that emotional memories may be reprocessed in sleep, possibly as part of some coping mechanism\(^1\). However, direct evidence for this notion is limited. Most pertaining studies use acutely arousing stimuli. The few studies that address more complex and persistent negative emotions typically regard life events. Interpretation of these studies is complicated by lack of a baseline or, in clinical studies, because of the pathology. Polysomnographic studies are particularly scarce and tend to focus on REM sleep. Here, we use a laboratory procedure to induce a persistent, negative emotional state in healthy subjects, and assess its effects on light sleep, slow wave sleep as well as REM sleep. To assess whether reactive changes in sleep architecture are adaptive or rather maladaptive, sleep architectural parameters are correlated with attenuation of the emotional response over sleep.

METHODS

Thirty-two healthy, good sleepers (23F/8M; mean age=20.09; SD=1.5) participated in the experiment. Subjects stayed overnight in the sleep laboratory for two nights, separated by at least a week. On one of the nights sleep was preceded by viewing of an emotional film fragment (extract from ‘The Passion of the Christ’, Mel Gibson); on the other night a neutral film fragment (extract from ‘March of the Penguins’, Luc Jacquet) was presented. Both film fragments were 10 minutes long. The order of the film conditions was counterbalanced across subjects. During sleep (at least 6 hours), EEG (F3, F4, C3, C4, O1, referenced to A1/A2), EOG and EMG were recorded. The next morning subjects returned to the lab and were presented with 5 stills from the film (1s per still, inter-still interval 9s) to cue emotions experienced during the original event. Emotional response to the film fragments was scored both directly after the film and after cueing, using the Dutch shortened version of the Profile of Mood Scales (POMS)\(^8\). The depression, tension/anxiety and anger scales differentiated best between the emotions induced by the two film fragments and were used in all analyses. Memory for film content was tested, through multiple-choice questions, to exclude differences in sleep architecture being due to
differential declarative memory load at sleep onset. Sleep stages were scored manually according to the standard criteria of Rechtschaffen and Kales\textsuperscript{9}. For each night, total sleep time, light sleep\%, SWS\%, REM sleep\% and REM sleep latency were calculated. The percentages of REM sleep, light sleep and SWS were also determined separately for the first and second halves of the night.

RESULTS AND DISCUSSION

Effects of negative emotional experience on sleep architecture
Initial memory for film content was similar for the emotional and the neutral film fragment. The emotional film induced a strong, significant shift towards a negative mood state, which could be reactivated, in weakened form, 24 hours later at cueing. The neutral film induced a slight mood elevation, which was marginally reproducible at cueing.
Comparisons of sleep architecture between film conditions showed a trend level increase of SWS\% in the emotional condition ($t (30) = 1.94, p = .062$). Furthermore, the natural increase in REM sleep from the first to the second half of the night was reduced (see fig. 1; repeated measures ANOVA, film (emotional, neutral) * part of the night (first half, second half):

\[ F(1,30)= 4.62, p = .04 \]

Figure 1. Mean percentage REM sleep in the first and second half of the night after the emotional and neutral film.

There was no difference in average subjective sleep quality after the emotional or neutral film ($t (31) = -.40, p = .70$). However, a histogram of the Sleep Quality Scale scores in the emotional condition revealed a clear bimodal distribution (fig. 2), suggesting the existence of two subgroups. A division of subjects based on the mean score of 9 on the Sleep Quality Scale resulted in 18 “poor sleepers” (scores ≤9, 9F/5M) and 14 “good sleepers” (scores ≥10, 14F/4M).

Poor sleepers had significantly lower subjective sleep quality after watching the emotional film in comparison to the neutral film ($t (17) = -3.43, p = .003$). Good sleepers had slightly but significantly higher subjective sleep quality after watching the emotional in comparison to the neutral film ($t (13) = 2.65, p = .02$). While good sleepers had higher subjective sleep quality than poor sleepers on the emotional film night ($t (30) = -9.38, p < .001$), they had equal subjective sleep quality on the neutral film night ($t (30) = .95, p = 0.35$), indicating that the groups differ in their sleep response to negative emotional experiences, rather than in general sleep quality.
A re-analysis of the polysomnographic data shows that the two groups differ significantly with respect to their sleep architectural response to the emotional event. Indeed, the good sleepers display a significantly higher SWS% in the emotional than in the neutral film night \((t(12) = 2.19, p = .048)\), while the low sleep quality group appears to be responsible for the reduction in REM sleep % in the second half of the night \((F(1,17) = 6.45, p = .021); T-test \(REM\) in second night half: \((t(17) = - 2.19, p = .043))\).

Interestingly, poor sleepers displayed a stronger emotional response to the distressing film than good sleepers, as reflected in the depression \((z = 2.0, p = .045)\) and tension/anxiety \((z = 2.03, p = .043)\) mood scales.

Thus, our data suggest the existence of two subpopulations with a different sleep response to negative emotional stimuli. One of these shows increased SWS% and a higher subjective sleep quality the following morning; the other shows a stronger emotional response to the stimulus, reduced REM sleep% in the second half of the night and a lower subjective sleep quality the following morning.

**Sleep alterations and emotional attenuation**

Adequate coping with emotional responses to a distressing stimulus would result in an attenuation of the emotional response over the 24-hour retention period between the emotional film and cueing. To evaluate a possible relation between the alterations in sleep architecture and emotional coping, the percentages spent in light sleep, SWS and REM sleep were correlated with attenuation of the emotional response over the retention period (score after film – score following stills). In the sample as a whole, SWS% correlated positively with attenuation of depression (Spearman’s \(r = .580, p = .001\)), while negative correlations were found for light sleep% with depression attenuation (Spearman’s \(r = -.378, p = .033\)) and REM% with anger attenuation (Spearman’s \(r = -.388, p = .028\)). When good sleepers and poor sleepers were considered separately, SWS% correlated strongly with attenuation of depression in both groups (Good sleepers: Spearman’s \(r = .618, p = .019\); Poor sleepers: Spearman’s \(r = .475, p = .046\)), while REM% correlated negatively with anger attenuation only in the poor sleeper group (Spearman’s \(r = -.499, p = .035\)).

**CONCLUSIONS**

In conclusion, our results show that even a relatively brief emotionally distressing experience alters the electrophysiological patterning of subsequent sleep. Moreover, findings suggest the
existence of two subpopulations that differ with respect to the sleep response after an emotional challenge. Interestingly, these subpopulations also differ with respect to emotional responsiveness to negative stimuli. One group shows a more moderate emotional response to a distressing stimulus and responds with elevated SWS% and good subjective sleep quality during the subsequent night; the other shows a stronger emotional response to the distressing stimulus, and responds with reduced REM% in the second night half and lowered sleep quality. In comparison, several studies regarding sleep disturbance in an affective disorder like major depression have shown reductions of SWS% and REM sleep shifts from the second to the first half of the night. The combined results indicate that negative influences of emotional experience on sleep are specifically accompanied by REM sleep changes. On the other hand, increases in SWS, without negative effects on sleep quality, may reflect a compensatory response to negative stimuli. Importantly, individual subjects tended towards either one or the other sleep response. The bimodality in the way sleep is affected by negative emotional stimuli may be of importance with respect to recovery from emotional trauma and individual sensitivity to develop affective disorders, such as post traumatic stress disorder (PTSD).

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BODY POSTURES IN SLEEP
Anton Coenen and Margreet Kolff

Department of Biological Psychology, Donders Centre for Cognition
Radboud University Nijmegen

INTRODUCTION

Generally four postures of the sleeping human body can be identified: two lateral side positions (sleeping on the right and left side), sleeping on the back (the supine position), and sleeping on the belly (the prone position). Studies related to sleep postures are scarce. Only some qualitative, incidental, observations can be found \(^1,2\), with one recent quantitative study \(^3\). In the last few years interest for the posture of the sleeping body is growing, which is particularly due to the renewed attention for the classic observation that certain sleeping positions are more accompanied by snoring than others \(^1\). However, the characteristics and details of sleeping postures are still not sufficiently known. In this paper body postures are studied in regularly sleeping men and women. Questions are in which postures subjects fall asleep and wake up, which body positions are dominant, whether people have a favorite sleep position, and how many times sleeping people change their body position. In brief the characteristics of body postures are studied in a quantitative way.

METHODS

Twenty eight healthy subjects, who were self pronounced good sleepers, 11 men and 17 women, aged between 23 and 80 years (mean age 52 years) and body weights between 65 and 90 kg, signed an informed consent and participated in the study. Sixteen subjects were investigated in a sleeping room of the University of Amsterdam \(^4\), and twelve, elderly, subjects in their homes in a nursery institution \(^5\). No differences between the two subgroups appeared, reason that the data were pooled. Temperature in the sleeping room was approximately 20 degrees Celsius, with a humidity of around 50 percent. Alcohol and drugs were prohibited on the days preceding the experimental nights. After a habituation night, two consecutive nights were studied. Subjects went to bed and got up to their own needs and wishes. The assessment of the sleeping posture in bed was performed with a body position sensor. Subjects got a belt around the chest containing the body position sensor (Pro-tech Embla), which was connected to a small data logger. These two minor pieces of equipment did not put any burden to the sleeping subject. Postures in bed, distinguishing supine, prone, and left and right lateral body positions, were measured during the entire night. Figure 1 shows a diagram of sleep postures occurring during a night of sleep. This graph uncovers not only the sleep postures, but also the position of falling asleep (in-sleep position), the position at waking up (out-sleep position), the times spent in the four postures, as well as the number of body shifts. It can also be inferred whether there is a favourite sleeping position. Subjectively, it was also asked to the subjects whether they had a favourite sleeping posture, while the sleep quality was obtained with a 14- points sleep quality scale \(^6\).
RESULTS AND DISCUSSION

Authors agree that healthy sleep requires the presence of body shifts and turns in the night. In the present paper body shifts were assessed by counting the number of level changes seen in the recording of the body position sensor. The number of shifts is variable and ranges between 8 and 34, with a mean of 14.1 and a standard deviation of 7.1. This is in good agreement with the study of Verhaert et al. 3, describing approximately 15 posture changes per night. It is remarked that the majority of shifts (approximately 80%) are half turns, i.e. from a lateral side to the back or vice versa. Complete turns, from the right side to the left or vice versa, occur less frequently (20%), what is understandable since the random chance for a half turn is much larger then for a complete turn. The relationship between sleep movements and sleep quality is a complex one, since a moderate number of sleep movements are necessary for maintaining a good body physiology and homeostasis, while too many movements are detrimental for sleep quality, and too less movements point towards alcohol or drug use.

![Figure 1](image.jpg)

Figure 1. The body postures during a night of sleep of one of the authors (AC), are shown in the recording of the body position sensor. Five levels correspond to the four sleep postures and one standing or sitting ‘up’ posture. Sleep starts around 00.30 and ends at 08.30. The in-sleep position is at the right lateral side, as well as the out-sleep position. The time spent in the right lateral position is 38%, in the left lateral position 44%, in the supine position 12%, in the prone position 5%, and in the up position 1%. The right lateral side seems the favorite sleep posture, what also subjectively is indicated, although even a bit more time is spent on the left side. The number of body shifts during the night is approximately 10.

In Table 1 the in-sleep and out-sleep position data are given of the two experimental days. The two consecutive nights follow approximately the same pattern with respect to the in-sleep and out-sleep positions. The most preferred in-sleep position is the supine position, followed by the right side, than the left side, while the least preferred position for sleep is the prone position. The out-sleep position follows quite well the in-sleep position. Most people (approximately 80%) regard the in-sleep position as their favorite sleep posture. Generally, subjects judge their favorite sleep posture in a correct way, even when they also spent a considerable amount of time in the non-favorite position. Hence, the objective dominancy of the favorite position over the non-favorite position is less strong as most subjects believe.
Regarding the prevalence of sleep postures during the night, most time is spent in the supine sleep position. This is remarkable since in the rare literature about this topic, information is obtained that the two lateral sleep postures are the most preferential postures, followed by the supine posture. The least attractive posture is in the prone position, which is in full agreement with the literature. It is also acknowledged that this position is the least beneficial position since the heavy body presses on vital organs. It could be that the age of people influences the favorite posture in bed, since it is known that sleep quality in the elderly diminishes and that poor sleepers consistently spent more time on their backs \(^7\). A comparison between the younger and older subgroup, however, did not confirm this view. While the sleep quality on a 14-points scale for young adults is 11.9 ± 1.8 (mean and SD) \(^4\), it decreases to 8.6 ± 1.0 in elderly people \(^5\), but the posture data, including the supine position data, are exactly the same in the two subgroups.

| Right side | 7 | 7 | 9 | 10 |
| Supine (back) | 13 | 15 | 14 | 11 |
| Left side | 7 | 3 | 4 | 6 |
| Prone (belly) | 1 | 3 | 1 | 1 |

Pearson’s r 0.87 0.94

Table 1. Data of the in-sleep and out-sleep positions. The numbers indicate the number of persons. The left two rows are the in-sleep positions of day 1 and day 2, while the right two rows show the out-sleep positions of the two days. Pearson’s r (correlation coefficient) merging the data is 0.88 with \(p = 0.004\).

The time spent in the several sleep postures is calculated. The supine position is mostly seen with a percentage of total sleep time of 55.3 ± 15.8% (mean and SD). This is followed by the left lateral side with 21.8 ± 26.2%, and the right lateral side with 17.3 ± 21.1%. The remaining time is for the prone and the up positions. Despite the high variation it can be stated that there is a tendency, though not statistically significant, for the favorite position to occur most of the time. Just as the supine position is the favorite position prior to sleep, this position is the most occurring position during the night. The dominance of the supine position, with more than fifty percent higher scoring than the two lateral positions together, is remarkable and surprising, since it is not completely in agreement with the recent data obtained by Verhaert and colleagues \(^3\). These authors mention an occurrence of 30.2% in the supine position and of 56.2% in the two lateral positions. The group of Verhaert established the sleep postures with the indirect method of mattress indentation \(^3\), while in the present study postures were directly assessed with a body position sensor. Nevertheless, the discrepancy of 55% against 30% regarding this relevant issue has to be cleared up in future research. It cannot be denied, however, that the large variations in the data, found in both studies, might play a role in the supine versus the lateral position dominancy. Both in the Verhaert et al. study \(^3\), and in the present study, large intra- and inter-individual variations are found. Sleepers show a large variation in in-sleep positions, as well as in the time spent in the several postures. Many studies have shown the strong effect of the sleep position on snoring, resulting from the collapsibility of the upper airway. Snoring occurs most easily in the supine position \(^8\). It is shown that a change in body posture from the supine to the lateral position significantly
decreases pharyngeal collapsibility. Given the relative high incidence of the supine position found in a recent study and in the present study, the back lying position seems rather problematical with respect to breathing in sleep. Preliminary investigations in which subjects were trained by instructions to take a lateral sleeping position, showed an improvement of sleep.

Unfortunately, the common state of art of positional training is currently still a tennis ball in a pocket in the back of a shirt. Great efforts could be made by the bedding industry to design beds and bedding materials in such a way that subjects prefer a lateral position as their favorite sleep position, without affecting sleep quality.

CONCLUSIONS

Despite large variations the following main lines can be extrapolated concerning sleep postures and posture changes during the night. Most people have a favorite body position. They start to sleep and to wake up in this position, and despite a considerable number of body shifts they spent most time in this posture. Most preferential position of humans is the supine position (lying on the back), followed by the two lateral positions (lying on the left and right side). As already stated, intrapersonal as well as inter-individual variability and variance is high. Since sleeping in the supine position favors snoring, and since sleeping on the back is a frequently occurring sleeping posture, it seems worthwhile to develop methods to tempt people to sleep in a lateral position.

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RETENTION-DEPENDENT INCREASES IN SLEEP SPINDLE DENSITY: A SPECIFIC SWS PHENOMENON

Roy Cox, Winni F. Hofman & Lucia M. Talamini
Department of Psychology, University of Amsterdam, The Netherlands

INTRODUCTION

The role of sleep in episodic memory consolidation has gained increasing support over recent years. Non-rapid eye movement (NREM) sleep and its signature neuro-oscillatory events, sleep spindles and slow oscillations, have been shown to be of particular importance in this respect. Sleep spindles are transient, waxing and waning, rhythmic brain signals with a core frequency between 11 and 16 Hz. A role of spindles in learning-related processes is supported by their plasticity-inducing properties. Indeed, spiking patterns underlying spindles are capable of potentiating cortical synapses. Furthermore, various spindle measures increase after learning, and/or correlate with memory retention over sleep.

While spindles occur throughout NREM sleep, spindles during slow wave sleep (SWS) might be particularly relevant for declarative memory consolidation. Indeed, several studies suggest that the benefits of sleep for declarative memory performance are specifically related to SWS and to slow oscillations, the hallmark oscillatory events during SWS. The neural mechanisms underlying these memory benefits may include temporal coupling of hippocampal ripples, cortical slow oscillations and sleep spindles, which have been suggested to serve a hippocampo-cortical dialogue underlying memory consolidation during sleep.

Considering the established role of slow oscillations in memory consolidation, it is noteworthy that previous studies linking spindle measures with memory retention do not distinguish between sleep stages with and without these slow waves. Therefore, the current study investigates the relation between memory retention and sleep spindles for NREM sleep epochs containing sleep spindles, but no slow oscillations (stage 2 sleep), and NREM episodes involving both types of oscillation (SWS). In addition, power for different frequency bands was correlated with memory retention.

METHODS

Nineteen healthy, good sleepers (16F/3M; mean age=21.3; SD=5.2) participated in the experiment. On the night prior to the experiment, subjects were deprived of 1/3 of their normal sleep period. The next morning, sleepiness (Stanford Sleepiness Scale or SSS) and fatigue (Dutch version of the Profile of Mood States or POMS) were assessed. Then, at 9.30 AM, subjects viewed a film fragment (10 minutes extract from ‘March of the Penguins’, Luc Jacquet). Memory for film content was tested, through multiple-choice questions (three alternative answers and ‘I don’t know’) both five minutes after the film and 11 hours later (8.30 PM). Retention of film content was expressed as (delayed recall / immediate recall) * 100.
During the retention interval all subjects took a nap (onset 12 AM) under polysomnographic registration (F3, F4, C3, C4, O1, referenced to linked mastoids, EOG, EMG). After entering stage 2 sleep, they were allowed to sleep for a maximum of two hours. If they failed to reach stage 2 sleep within an hour, or if they failed to sleep for at least one hour, they were excluded from the experiment.

Sleep stages were scored manually according to the standard criteria of Rechtschaffen and Kales\(^9\). In addition, the frequency content of the EEG between 0.75 – 50 Hz was analyzed using FFT power spectral analysis. This was done for stage 2 sleep and SWS separately. The power in the following frequency bands was determined: Slow oscillations (0.75 – 1.5 Hz), delta (0.75 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), sigma (11 – 16 Hz), beta (15 – 25 Hz) and gamma (25 – 50 Hz).

Sleep spindles were identified by an algorithm closely similar to the one used by Ferrarelli\(^10\). Sleep spindle density was calculated as the amount of sleep spindles per minute. Spindle density measures from C3 and C4 were averaged.

For stage 2 and SWS separately, Pearson correlations were determined between memory retention and spindle density, and also between retention and power measures.

**RESULTS**

Two subjects were outliers with respect to memory retention and were excluded from further analyses. For two additional subjects there were no POMS values available, and for one subject EEG power estimates were not available. Therefore, our total number of included cases ranges from fifteen to seventeen. Table 1 displays average sleep parameters for all subjects. All subjects spent time in SWS and all except one reached REM sleep.

Table 1. Sleep parameters (times are in minutes).

<table>
<thead>
<tr>
<th>N = 17</th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td><strong>Total sleep time</strong></td>
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</tr>
<tr>
<td><strong>Sleep latency</strong></td>
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<tr>
<td><strong>Time spent in stage</strong></td>
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<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>21.6</td>
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</tr>
<tr>
<td>Stage 2</td>
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<tr>
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<tr>
<td>Stage 4</td>
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<tr>
<td>Rem</td>
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<td>11.2</td>
</tr>
<tr>
<td>SWS (stage 3+4)</td>
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<td>25.3</td>
</tr>
<tr>
<td><strong>Proportion spent in stage</strong></td>
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<tr>
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<tr>
<td>SWS (stage 3+4)</td>
<td>15.4</td>
<td>8.4</td>
</tr>
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</table>

**Sleep spindles**

We found no significant relation between spindle density during stage 2 sleep and memory retention ($r = -0.08, p = 0.77, n = 17$). In contrast, we found a strong and highly significant
positive correlation between spindle density during SWS and memory retention (r = 0.75, p = 0.001, n = 17; Figure 1). Given subjects’ partly sleep-deprived state, it is possible that the aforementioned correlations are influenced by pre-nap sleepiness and fatigue. Therefore, partial correlations between spindle density and memory retention were calculated, controlling for these variables, as indexed by the SSS (sleepiness) and the POMS (fatigue) scale. Again, no correlations were found between spindle density during stage 2 sleep and memory retention (covariate sleepiness: r = −0.11, p = 0.70, n = 17; covariate fatigue: r = −0.29, p = 0.32, n = 15), while in SWS this relation remained significant (covariate sleepiness: r = 0.74, p = 0.001, n = 17; covariate fatigue: r = 0.66, p = 0.011, n = 15). Finally, we re-calculated correlations while controlling for initial (pre-sleep) memory performance, to rule out possible influences of encoding success on subsequent spindle density. Once again, we found no significant correlations during stage 2 (r = −0.03, p = 0.91, n = 17), while a strong link during SWS was maintained (r = 0.60, p = 0.015, n = 17).

Figure 1. Correlation between spindle density and memory retention in stage 2 sleep (left panel) and SWS (right panel).

Power measures
We observed a correlation between power in the theta band during SWS and memory retention (r = 0.51, p = 0.046, n = 16). Correcting for sleepiness reduced this association to a trend (r = 0.45, p = 0.09, n = 16), as did correction for fatigue (r = 0.46, p = 0.10, n = 15). Finally, controlling for pre-sleep memory performance reduced significance of this relationship as well (r = 0.45, p = 0.10, n = 16). Although we found trends towards relations between memory retention and slow oscillation power (r = −0.47, p = 0.065, n = 16), and between retention and gamma power (r = 0.44, p = 0.086, n = 16), controlling for sleepiness, fatigue or initial memory score abolished all such links (all p values > 0.11). No other frequency band, including sigma, showed a correlation between power and memory retention.
CONCLUSIONS

In summary, our findings show a strong and specific correlation of declarative memory retention with spindle density in SWS. Such a correlation is to no extent apparent in stage 2 sleep. There is also a moderate correlation between theta power in SWS and retention, but this relation may, at least in part, be related to factors other than retention itself. Notably, no robust correlations were found between retention and slow oscillation power, or between retention and sigma power. This suggests that, while both slow oscillations and sleep spindles likely play a role in memory consolidation, general power measures may not always sufficiently reflect the functional relevance of these brain rhythms. These findings indicate that, for declarative memory, SWS-related spindles may play a central role in the neural mechanisms underlying consolidation.

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SYNCHRONIZATION LIKELIHOOD IN HEALTHY RATS: DIFFERENCES BETWEEN CORTEX AND THALAMUS DURING SLEEP AND ACTIVE BEHAVIOR

Maik Derksen\textsuperscript{a}, Emanuel van den Broeke\textsuperscript{b}, Kris Vissers\textsuperscript{b}, Clementina M. van Rijn\textsuperscript{a}

\textsuperscript{a} Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, The Netherlands
\textsuperscript{b} Pain and Nociception Neuroscience Research Group, Department of Anaesthesiology, Pain and Palliative Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

INTRODUCTION

The synchronization likelihood (SL) is a measure of the statistical interdependencies between two time series, for instance two EEG channels\textsuperscript{1}. The SL takes on a value between a number close to zero in the case of independent time series, and 1.0 in the case of fully synchronized time series\textsuperscript{2}. SL is sensitive to linear as well as non-linear interdependencies and can be computed with a high time resolution.

A growing body of research concerning SL is available in the field of human studies, where SL is mostly used to determine functional connectivity between cortical areas in pathologies such as Alzheimer’s disease, Parkinson’s disease, or epilepsy, and in working memory and semantic processing tasks.

However, data on SL between subcortical areas and different sleep/wake stages in animals is virtually absent. Therefore we present data on the SL between the left and right frontal cortex, and between the left and right thalamic bodies of rats during active behavior and sleep. We will discuss the differences between those SLs with respect to active and sleep states, in delta ($\delta$), theta ($\theta$), alpha ($\alpha$), and beta ($\beta$) frequency bands of the EEG.

METHODS

Ten male Sprague Dawley rats were used with an age of 3 months and a mean weight of 394 grams (SD = 22). The animals were housed individually and kept on a reversed light-dark 12-12h cycle with lights on at 8h p.m. The experiment was approved by the Ethical Committee on Animal Experimentation of Nijmegen University (DEC 2008-191).

For EEG recording, four electrodes were implanted in each rat under isoflurane anaesthesia. Two electrodes were implanted bilaterally in the frontal region of the cortex, at coordinates -0.26, 2.70 and -0.26, -2.70 from bregma, on the surface of the cortex. Two electrodes were implanted in the thalamus, also bilaterally, at coordinates -2.30, 2.92 and -2.30, -2.92 from bregma, both at a depth of 5.7mm. The rats were allowed to recover for 17 days.

EEG was recorded from the four electrodes while observing the freely moving animals, showing spontaneous behavior. The behavior was scored and labeled accordingly as being active or sleeping. The EEG signal was recorded in a frequency range of 1Hz to 500Hz at a sample rate of 2048Hz using Windaq (DATAQ Instruments, Akron, OH) and stored for
offline analysis. The recordings were downsampled to a sample rate of 512Hz, and epochs were extracted from the data in Brainvision (Brain Products, GmbH). In the active periods, 8 second EEG epochs from all 10 rats were collected. In the sleep state 8 second epochs from 8 rats were collected for analysis of the cortical EEG signals, and epochs from 9 rats for the analysis of the thalamic EEG. On average, per animal 5 epochs were used for analysis of the active state, and 2 epochs for the sleep state.

SL between the two EEG signals recorded bilaterally from the cortex, and between the two bilateral signals from the thalamus, was computed from afore mentioned epochs using the SL method as defined by Stam and van Dijk (2002). These SL values were computed separately for the frequency bands of δ (1.0 – 3.9Hz), τ (4.0 – 8.9Hz), α (9.0 – 12.9Hz), and β (13.0 – 29.9Hz). In this study Pref was fixed at 0.05, and for the state space embedding a time lag of 10 samples and an embedding dimension of 10 was used.

Data were analyzed using a two-way repeated measures ANOVA with the brain area (cortex, thalamus), the state (active, sleep), and the frequency band (δ, τ, α, and β) as within factors. For post-hoc analysis ANOVAs with Bonferroni correction were used.

RESULTS

A large global difference between the SL computed from the two thalamic EEG signals and the cortical EEG signals was found: the SL between the thalamic areas (0.32; SEM = 0.06) is more than twice the value of the SL between the cortical areas (0.13; SEM = 0.03), (F(1,7) = 113; P < 0.001).

Therefore subsequent analyses were performed on the signals recorded from the thalamic areas and the cortical areas separately, or, when comparing active and sleep states, the relative difference was computed (Fig. 1).

For the SL between the two cortical EEG signals, main effects for state (F(1,7) = 8.29; p = 0.02), band (F(3,21) = 17.6; p < 0.001) and a state x band interaction (F(3,21) = 10.3; p < 0.001) were found. Post-hoc analysis revealed that i) the SLs found in the two lower frequency bands (δ, τ) were higher than those found in the higher frequency bands (α, β) but ii) that only in the delta band the SL during sleep was higher than the SL in the active state.

All the SLs between the two thalamic EEG signals are higher in the sleep state than those found in the active state (F(1,8) = 107; p < 0.001). Since also a main band effect (F(3,24) = 36.8; p < 0.001) and a state x band interaction (F(1,8) = 22.2; p = 0.002) were found, post-hoc analyses were performed. These show that i) the SL found in the τ-band is higher than those found in the other frequency bands, and ii) that the difference in SL between the active and sleep state is the highest in the δ-band.

Post-hoc analysis shows that the relative difference in SL between the sleep and active state in the δ-band of the cortical EEG signals equals that of the δ-band of the thalamic EEG signals.
**DISCUSSION**

Functional connectivity in the brain can be measured in EEG studies with coherence measures and SL measurement. In contrast to coherence measures, SL picks up non-linear as well as linear correlations between time series\(^1\) and does not depend on amplitude or power measurement in quantitative EEG\(^3\). In humans, synchronization in the \(\tau\)-band is associated with working memory processes\(^2,4\). It is hypothesized that the lower \(\alpha\)-band reflects attention processes\(^5\), that the upper \(\alpha\)-band reflects long-term semantic memory\(^5\), and higher frequencies such as gamma may reflect the representation of complex information processing\(^6\).

The values of SL between the cortical areas in the awake state of our rats, are comparable with those reported previously\(^7\). The SL between the two cortical signals is higher in the two lower frequency bands (\(\delta, \tau\)) than in the two higher bands (\(\alpha, \beta\)). Whether the SL values in these bands are comparable to those in humans is not clear.

Data on SLs between left and right thalamic regions have not yet been reported. Our data show that the SL between the thalamic areas is much higher, in all bands, than the SL between the cortical EEG signals. It seems unlikely that this higher SL is due to a higher volume-conductivity, since the absolute distance between the two thalamic electrodes is larger than...
the distance between the two cortical electrodes (5.84mm versus 5.40mm). Anatomically, commissural axonal projections between the two thalamic bodies exist\textsuperscript{8}, but the function of these commissural fibers is unclear. That these connections may indeed be functionally important is suggested by the high values of SL found between the two thalamic bodies and its modulation by behavioral state. The SL between the left and right thalamic areas is higher in the sleep state than in the active states in all frequency bands, with the biggest difference between those states in the δ-band. On the other hand, the SL between the two cortical signals is only in the δ-band higher in the sleep state than in the active state, no differences between states were found in the other frequency bands.

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LIGHT AND SLEEP WITHIN HOSPITAL SETTINGS

M.C. Giménez\textsuperscript{a}, L.M. Geerdinck\textsuperscript{a}, M. Versteylen \textsuperscript{b}, P. Leffers\textsuperscript{c},
G.J.B.M. Meekes\textsuperscript{a}, H. Herremans\textsuperscript{a}, B. de Ruyter\textsuperscript{d} and L.J.M. Schlangen\textsuperscript{a}

\textsuperscript{a}Philips Lighting, Eindhoven, the Netherlands
\textsuperscript{b}Maastricht University Medical Center, school CARIM, the Netherlands
\textsuperscript{c}Maastricht University Medical Center, school CAPHRI, the Netherlands
\textsuperscript{d}Philips Research, Eindhoven, the Netherlands

INTRODUCTION

Light is the most important signal that entrains the human circadian system. Hence, light strongly influences the 24 h sleep-wake pattern and has a broad impact on our physiology and behavior. Not surprisingly, light affects performance, health and well-being\textsuperscript{1} in society, also within the healthcare settings\textsuperscript{2-5}.

Lighting standards for hospitals prescribe a horizontal illuminance of at least 300 lux measured at bed level. This is relatively modest as compared to the natural, much higher illuminance outdoors (2000-100000 lux). During daytime, the indoor environment leaves us relatively light deprived, whereas in the late evening, indoor lighting limits our exposure to darkness. Both effects are not optimal for our sleep and health\textsuperscript{6-8}.

Impaired sleep is known to have negative consequences for human health\textsuperscript{9}. Unfortunately, sleep within most hospital settings is less optimal as compared to the home situation\textsuperscript{10}. Improving sleep in the hospital can contribute positively to the clinical care.

The aim of the present study was to investigate the effects of an artificial patient room lighting system that simulates certain aspects of natural daylight and its dynamics on sleep duration, sleep quality, depression, and satisfaction within a group of hospitalized cardiovascular patients.

METHODS

From December 2009 until September 2010, 171 patients (average age 65.9 ±14.9 SD) of the cardiology ward of the Maastricht University Medical Center (MUMC, NL) enrolled in the study. Typically patients on this ward were stable cardiology patients diagnosed with heart failure, heart infarction, heart rhythm disturbances, or angina pectoris. All patients gave written informed consent. The experimental protocol was approved by the local Medical Ethics Committee of the Maastricht University Medical Center.

Patients were assigned according to normal hospital procedures and irrespectively of their health status, to a control room with standard lighting conditions, or to an intervention room with dynamic and enhanced lighting. Four rooms (having 1, 2 or 4 beds) were available per condition. In total 9 beds were available per condition. One control room had all windows facing west, the other 7 rooms had windows facing north only. The intervention rooms were equipped with a prototype of the Philips HealWell lighting system. This system provides general lighting with automated gradual changes in correlated colour temperature (2700K-6500K) and illuminance across the day, mimicking elements of dawn and dusk. Every day contained a fixed timeslot of more than 1 h in the late morning where the vertical illuminance at eye level exceeded 750 lux. Moreover, the system comprises (multicolour) lighting elements for a pleasant ambience with bedside control for the patients.
Sleep was measured by means of Actiwatch-Spectrum® (Philips Respironics). Subjects wore the Actiwatch on their non-dominant wrist throughout their hospital stay. Movement-induced acceleration counts were stored on a 1-min basis. Total sleep duration, sleep onset latency and sleep efficiency were analyzed by means of Respironics Actiware 5 software. Questionnaires were used to probe depression (Hospital Anxiety and Depression Scale\textsuperscript{11}, HADS) and satisfaction scores on the lighting system of the patient room (using a 7 point scale: 0 = very unsatisfied, 3 = neutral, 6 = very satisfied).

Mixed-effects regression analysis using MLwiN software (MLwiN 2.23, Centre for Multilevel Modelling, Institute of Education, London, UK) was used to test the statistical significance of the intervention and its time dependent effects. This analysis takes into account the interdependency of the data points inherent to the hierarchical structure of the data, in our case the daily measurements \(i\), nested within subjects \(j\). It further allows to use of all available data, even when some observations are missing for a subject \textsuperscript{12} as is the case in the present study. The following model equation was used:

\[
\text{Outcome}_{ij} = \beta_0 + \beta_1 \times \text{DaysAtHospital}_{ij} + \beta_2 \times \text{light}_j + \beta_3 \times (\text{light} \times \text{DaysAtHospital})_{ij}
\]

The betas (\(\beta_{0-3}\)) represent the intercept and the effect estimates. \(\text{DaysAtHospital}_{ij}\) is the number of days a patient \((j)\) has spent at the hospital at any time point \((i)\) that a particular \(\text{Outcome}_{ij}\) value is measured. \(\text{Light}_j\) represents the condition, using 0 for the control group and 1 for the intervention group.

**RESULTS AND DISCUSSION**

Actiwatch data of 107 subjects were available for analysis. In the dataset the number of subjects present per night was variable and decreased considerably with increasing length of stay. The maximum number of nights that any subject stayed at the hospital was 19. On average subjects stayed in the hospital for 8 ± 5 (SD) days (Figure 1).

![Figure 1](image-url) Raw data overview. Mean (± 95% CI) total sleep duration per night of hospitalization for the control (black line) and the intervention (grey line) group. The number of subjects per group contributing to a given mean is indicated next to each point. The dotted line reflects data after the 7th night in the hospital, after this night the majority of the subjects are dismissed.

The control and the intervention group hardly differed in their medication usage. Virtually all patients were on \(\beta\)-blockers and hypnotics were used very restrictively. Whether the different
diagnoses, and the slight differences in their distribution across the control and intervention group, could trigger different responses to light remains to be analyzed. For the sleep parameters, the regression analyses showed that there were no significant differences between the control and the intervention group in the first hospital night (p = 0.42). Moreover, there was no significant effect (p = 0.12) of DaysAtHospital (β1). However, a significant interaction effect between light exposure and DaysAtHospital (β3) was observed (Table 1). When a given patient is hospitalized in an intervention room on the first night and remains hospitalized in that room for 6 more nights (i.e., totaling to 7 nights, chosen to match the average stay-duration of 8 days), total sleep duration (TSD) in the 7th night increases by an average of 50.5 min as compared to the situation where this patient would have spent the 6 additional nights in a standard room. When expressing this change as % of the TSD during the first night in the hospital, this corresponds to a relative increase of 13%. Similarly, a reduction by 9 minutes (or a relative 55%) is observed for sleep onset latency, whereas sleep efficiency improved by 3% (or a relative 3.3%). A large part of the patients was dismissed before the 8th night of hospitalization. In view of the small sample size, the regression output after this period should be interpreted with caution. We tested how our model responds towards a reduction in the follow-up time by analyzing the data collected during those first 8 days only. This yielded similar findings as compared to the analysis over all 19 nights, see Table 1. These results indicate that, despite of the negative effects that β-blockers could have on sleep, sleep was more consolidated and rapid for patients in the intervention group. The increased daytime light exposure and the dawn and dusk elements of the intervention could stand at the basis of this effect. It is generally accepted that sleep is necessary to remain healthy9. Therefore, improving sleep can be deemed to be of clinical relevance.

HADS scores have been collected for 154 patients. Regression analysis for the depression score of the HADS (7 items, each with a 0-3 point scale) showed a modest interaction effect (β3). This effect results in a reduction of the depression score by 1.0 points after 8 days of hospitalization (p = 0.08). Moreover, no significant differences were observed between the control (4.7 ± 0.4 SEM) and intervention (5.4 ± 0.6 SEM) group at the onset of the study (p = 0.28), nor was there an effect of DayAtHospital (β1, p = 0.11). Satisfaction scores were collected for patients (N = 90) and staff (36 questionnaires returned). In both groups satisfaction scores for the intervention lighting system are higher by about 1.2 points as compared to the standard room lighting system. The reduced depression scores and the increased satisfaction may be supportive for a positive effect of lighting on recovery13, 14.

Table 1.: Regression model estimates (±SEM) for actigraphy data on total sleep duration, sleep onset latency and sleep efficiency within the intervention group. The intercepts correspond to the first night of hospitalization. The slopes give the light by DaysAtHospital interaction (β3) representing the average absolute change for every extra night spent at the hospital beyond night one. Values are given for the overall analysis (up to 19 nights of hospitalization) and for the analysis restricted to the first 7 nights of hospitalization. All p-values are 2-sided.

<table>
<thead>
<tr>
<th>Output</th>
<th>Analysis over all 19 nights</th>
<th>Analysis over the first 7 nights</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intercept (±SEM)</td>
<td>slope (β3)</td>
</tr>
<tr>
<td>Total sleep duration (min)</td>
<td>403.0 (±14.5)</td>
<td>8.4 (±2.7)⁎</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>16.8 (±3.2)</td>
<td>-1.5 (±0.7) **</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>83.5 (±1.4)</td>
<td>0.5 (±0.2) †</td>
</tr>
</tbody>
</table>

⁎ p < 0.01  ** p < 0.05  † p = 0.06  †† p = 0.3
CONCLUSIONS

This preliminary analysis shows that the present lighting intervention achieves modest benefits on various sleep parameters and depression scores of cardiovascular patients. Moreover the intervention is positively appreciated by patients and nursing staff. More evidence based research with larger sample size and different patient populations is needed to identify how patient room lighting can help optimizing the healing environment.

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REFERENCES

SLEEP YOURSELF HAPPY? THE ASSOCIATION BETWEEN SUBJECTIVE SLEEP AND EVERYDAY AFFECT

Jessica Hartmann\textsuperscript{a,b}, Marieke Wichers\textsuperscript{a}, Lex van Bemmel\textsuperscript{a,b}, Catherine Derom\textsuperscript{c}, Evert Thiery\textsuperscript{d}, Claudia Simons\textsuperscript{a,b}

\textsuperscript{a} Department of Psychiatry and Psychology, School of Mental Health and Neuroscience, European Graduate School of Neuroscience (EURON), Maastricht University, Maastricht, the Netherlands; \textsuperscript{b} GGzE, Institute of Mental Health Care Eindhoven en de Kempen, P.O. Box 909, 5600 AX Eindhoven, The Netherlands; \textsuperscript{c} Association for Scientific Research in Multiple Births, Ghent, Belgium; \textsuperscript{d} Department of Human Genetics, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium

INTRODUCTION

Sleep and affect regulation appear closely tied together. In the general population, sleep loss has been associated with emotional dysregulation, e.g. increases in negative affect\textsuperscript{1} and, more recently, decreases in positive affect\textsuperscript{2, 3}. In the psychiatric setting, sleep appears to be disturbed in the vast majority of patients suffering from a mood disorder, especially in patients diagnosed with major depression\textsuperscript{4}. In contrast to former, unidirectional views, insomnia is currently not merely considered a consequence of depression, but also regarded as a robust risk factor for the development of depression\textsuperscript{4}.

The dynamics of sleep-affect regulations in natural circumstances have received little research attention. Most studies have relied on cross sectional, single-point, retrospective assessments of affect and sleep in an artificial setting, thereby possibly inducing memory bias and not taking into account the variability of affect. In order to systematically explore the hypothesized reciprocal associations between subjective sleep and everyday affect in healthy participants, the Experience Sample Method (ESM) was deployed, assessing sleep and mood prospectively and repeatedly in an ambulatory setting. This design allows exploring and comparing the temporal association between nocturnal sleep and subsequent daytime affect as well as daytime affect and subsequent nocturnal sleep.

METHODS

In a sample of 621 female healthy participants, positive affect (PA) and negative affect (NA) was assessed ten times a day over a period of five days, exploiting the Experience Sampling Method (ESM), an extensively validated momentary assessment technique (for a detailed description of this technique see Myin-Germeys et al\textsuperscript{5}). Furthermore, subjects filled in a morning and evening questionnaire, assessing the following self-report sleep variables: Sleep quality, sleep latency, sleep period (time between falling asleep and awakening in the morning), number of awakenings. Subclinical depressive symptomatology was assessed at baseline using the Symptom-Checklist-90-Revised (SCL-90-R\textsuperscript{6}). Due to the hierarchical nature of the data, multilevel regression analysis was applied, (1) using subjective sleep variables as predictor of subsequent daytime affect and (2) using daytime affect as predictor of subsequent nocturnal sleep.
RESULTS

Multilevel regression analysis yielded the following results:

(1) Subjective sleep reported upon awakening as predictor of subsequent daytime affect, assessed repeatedly during the day. As can be seen in Table 1, almost all subjective sleep variables were significantly associated with PA, except for sleep latency, which only showed a statistical trend. Similarly, almost all sleep variables were significantly associated with NA, except for sleep period. Standardized regression coefficients revealed the strongest association between subjective sleep quality and PA (Figure 1).

(2) Daytime affect, assessed repeatedly during the day, as a predictor of subsequent sleep reported upon awakening the next day. There was a significant association between PA and subjective sleep quality ($\beta=-0.03, \ p<0.001$), unexpectedly in negative direction, and between NA and sleep latency ($\beta=0.01, \ p=0.04$). None of the other variables were significantly related.

**Figure 1.** Effect sizes of subjective sleep quality as reported upon awakening on average positive affect (PA) during the day: increase of PA per category of sleep quality (1= very bad, 7= very good) relative to reference category sleep quality = 1.

**Table 1.** Standardized regression coefficients (p-values) of mixed regression analysis with sleep variables as predictors.

<table>
<thead>
<tr>
<th>Subjective sleep variables</th>
<th>Positive affect</th>
<th>Negative Affect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality</td>
<td>0.09 (&lt;0.001)</td>
<td>-0.04 (&lt;0.001)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>-0.01 (0.06)</td>
<td>0.02 (&lt;0.001)</td>
</tr>
<tr>
<td>Sleep period</td>
<td>0.02 (0.03)</td>
<td>-0.01 (0.75)</td>
</tr>
<tr>
<td>Times awake</td>
<td>-0.02 (&lt;0.001)</td>
<td>0.01 (0.02)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

The present study showed that subjective sleep quality and everyday affect are consistently associated. Interestingly, subjective sleep was a good predictor of subsequent daytime affect, while daytime affect itself was a less consistent predictor of following subjective sleep. In other words, sleeping worse was associated with greater affect dysregulation the next day. These findings support the concept of sleep disturbances reflecting a possible risk factor for subsequent depression rather than being merely a consequence of depression. In general, the association between subjective sleep and affect was greater for PA than for NA, which is in line with recent investigations. The findings of the present study call for more research attention towards sleep and positive affect regulation.

REFERENCES

INTRODUCTION
Shift work is associated with several health problems including insomnia, cardiovascular diseases, chronic infections and cancer. From October 2009 the coffee factory of Sara Lee changed the 5-shifts schedule into a 3-shift schedule, resulting in an increase of health problems and complaints of the shift workers. This stimulated the company doctors to develop a program aimed to give the shift workers all possible information to prevent unnecessary decrease of health. In order to develop such an information program, we studied the literature to be able to answer the following questions: (a) What is the effect of three-shift work? (b) What is known about three-shift work in relation to age and gender? (c) What is the optimal rotation direction of shift work? (d) What are the appropriate start and end times? (e) What other factors increase the risk of health problems? (f) What kind of training is useful and what is their impact?

METHODS
Pubmed, Scholar and CDC (Center for Disease Control and Prevention) databases were searched using the terms shift, 3-shift work, shift work AND affects, influence AND shifts, shift work AND effect AND health, rotating shift, shifts direction or rotation, coping and shift work, influence age at shift work, training shift workers, prevention training shift work, implementation training shift work.

RESULTS AND DISCUSSION
Shift work is associated with several health problems including insomnia, sleeping disorder, cardiovascular diseases, chronic infections and cancer. The consequences of health problems due to shift work are increase of irritability, accident risk, errors at work. Furthermore shift work has important social consequence as shift workers have little time for socializing. Age, gender, coping style, heredity of disease, morning- or eveningness person and health condition affect the onset of health disorders due to shift work. Elderly people (50 +) have more problems with irregular working hours than younger people. Women experienced shift work more damaging than men, perhaps due to home environment (housekeeping, child care and the like). Furthermore coping behavior (how people deal with their problems and events) increases problems in shift workers. Heredity of disease, like cardiovascular disease and obesity, also affects the onset of health disorders due to shift work. It also varies per person which shift is stressful for them. Morningness persons have more problems with the night shift and the eveningness persons feel morning shift heavier.
Furthermore lifestyle (physical activity, meals and drinking habits, smoking and degree of relaxation) plays an important role in the onset of symptoms. The more healthy the employee, the smaller the risk of health problems due to shift work. Our literature search showed that shift work is associated with insomnia, sleeping disorder, cardiovascular diseases, chronic infections and cancer. Shift workers have little time for socializing. Age, coping style, morningness versus evenningness, lifestyle and health condition increase the risk of health problems, Furthermore backward rotation of the shift induces more health problems than forward direction. The literature review revealed a great deal of research on the effects of the shift work, but not specific for 3-shift. As a result, the measures are in general for all types and not specifically for 3-shift. This may affect the impact of preventive measures. Preventive measures that can be taken to reduce health problems due to shift work are:

a) Forward rotation of the shift work;
b) Starting time of the morning service at 7 am;
c) Self scheduling;
d) Provide healthy meals during the shift work and encourage for physical activity;
e) Power nap;
f) Light and temperature;
g) Light therapy;
h) Cognitive therapy.

Optimal rotation direction of shift work is a forward rotation (morning, noon and night service) as the body adjusts better when the service starts later. Backward rotation goes against biological clock which rhythm is slightly more than 24 hour. Suitable time for a morning service is at 7 am, because it deviates least from the regular working hours.

According to literature, personal influence on the shift schedule (self-scheduling) would enhance the employee satisfaction. Self-scheduling means that employees make their own schedule, by making their own schedule which allows planning their social activities around it. Employer can also contribute to a healthy lifestyle of the employee by providing healthy meals, especially during the night shifts (fewer snacks, greasy bites etc), and encourage them for physical activity.

Power nap is defined as a short nap. Duration of power nap is a minimum 15 to maximum 30 minutes. Most efficient time of a power nap for day shift is between 13.00 and 15.00 pm and for night shift between 19.00 and 21.00 pm. Power nap increases productivity and alertness of the employees. Not everyone react the same to power nap, so each person must find out for himself what is pleasant.

Light and temperature control at work and at home may also be important to reduce sleep disorders. It’s suitable that the bedroom is dark and with a temperature around 15 to 18 degrees Celsius. Increase the light during the night shift would help employees to keep awake. At night drops the body temperature of human, so it is convenient during night shift to enhance the workplace temperature.

Light therapy involves exposure to intense levels of light under controlled conditions. Cognitive therapy is a form of psychotherapy that emphasizes the important role of thinking in how we feel and what we do. These therapies have a positive impact in reducing fatigue. The above list of preventive measures is a list of measures that can be taken to reduce health problems due to shift work.
According to the literature, there are training courses for shift workers, but we did not find effect studies of those training courses. So, whether training has effect in preventing the health effects from shift work is not yet known. This will in future appear after completing the training.

Based on our literature search we are developing a training for shift workers which is intended to start at the end of 2011.

Aim of the training is to make both employees and their family aware of the effects of shift work and how they can deal with it. The training will consist of various topics, themes, namely:

- The effects of shift work
- Sleep Hygiene
- Healthy lifestyle
- Coping with social pressure and how to create social support.

The effect of the training will be measured by questionnaires, which will measure quality of life of the employees. The measurement takes place on several moments, the first measurement point is at the beginning of the training and the same questionnaire will be filled at the end.

REFERENCES
RECORDING LIGHT AND SOUND IN AMBULATORY PSG

Bob Kemp, Daniel Wahid, Rob van den Bogert, Marco Roessen

Sleep Centre, Medical Centre Haaglanden, Den Haag, The Netherlands

INTRODUCTION

Some ambulatory PSG or actigraphy recorders have sensors for ambient light on board. These sensors are not calibrated and can easily become covered by clothing and bed linen. Therefore the light intensity cannot be measured reliably, which implies that circadian and sleep-hygienic factors remain largely unknown. Also, lights-off time needs to be estimated from the subjects report or indirect information such as fading EMG activity. In contrast, a calibrated light sensor at a less vulnerable site would greatly improve the assessment of circadian and behavioral sleep disorders and of sleep onset latency.

Most ambulatory PSG recorders have snoring sensors at the trachea or the nasal cannula. These are not calibrated either and the results strongly depend on the anatomical site where snoring occurs. Therefore they cannot accurately record snoring sound. In contrast, a calibrated sound sensor at a less vulnerable site would quantify the burden that snoring causes to the bedroom partner.

Both alternative sensors would also quantify any ambient sound and light sources that may cause sleep-disturbances.

We developed calibrated light and sound sensors that are to be placed on the forehead. The sound sensor is based on earlier described electronics\textsuperscript{1,2} but uses a less expensive and smaller microphone. The light sensor has not been reported before. This contribution describes a few technical details and the type of results that were obtained in the first half year.

Figure 1. Sound and light sensors connected to an ambulatory PSG recorder and attached to the forehead
METHODS
Tiny and low-cost sensor chips for light (APDS-9007) and sound (MAA-03A-L60B-B) were connected to unused inputs of our ambulatory PSG recorders (Fig. 1, left). They are to be placed on the forehead, next to the Fpz electrode (Fig. 1, right). Small electronic circuits integrated in their cables were tuned until recorded ranges were 3 till 10,000 Lux (full moon till clear daylight) and 30 till 90 dBA (breathing till very heavy snoring), respectively. The circuits draw less than 1 mA of current from the recorder battery and therefore do not jeopardize the 24 hr recording time.

The light sensor has logarithmic sensitivity. Sound amplitude is also converted to a logarithmic scale, using a plug-in in the review software. Because of these logarithmic scales, variations in both weak and strong levels are clearly shown (Fig. 2).

RESULTS AND CONCLUSION

Hundreds of routine recordings have shown that the sensors are accurate and easily connected to the patient. They appear to be about as robust as an EEG electrode. Calibration is checked every three months. Some microphone sensors then show somewhat (about 5-20%) degraded sensitivity for which we do not yet know a cause. Malfunctioning sensors are repaired by replacing the actual sensor chip at the tip. This costs about one Euro and one hour.

Snoring, circadian actors, lights-off time and sleep disturbers such as the bed partner, dawn or ambient sounds can now reliably be quantified in ambulatory PSG (Fig. 2).

REFERENCES

INTRODUCTION

Gifted and talented people differ from people with an average intelligence in several ways: mentally (cognitive, emotional) and probably also physical. The definition of giftedness we use is as follows:

A gifted person is a quick and clever thinker, able to deal with complex matters. Autonomous, curious and passionate. A sensitive and emotionally rich individual, living intensely. He or she enjoys being creative. 

Perkins states that giftedness can be seen as having a neural system with special properties (with regard to efficiency and precision) in which the nerves transport information in a faster and more effective way compared to people who are less intelligent.

In literature on giftedness we often read that gifted and talented people (children and adults) have problems in sleeping. The arguments that are given are that gifted people do a lot of thinking, leading to worrying, they are ‘too much in their head’. Another argument is that gifted people (also children) may need less sleep than average. A well known example is Sir Winston Churchill who only slept a few hours at night. When parents do not know that gifted people may need less sleep, they may think their child is a bad sleeper.

Literature on sleep quality in gifted people is very scarce and the studies are not always methodologically sound. A psychological study in children aged 7 – 11 yr. showed a reverse correlation between IQ and sleep duration. In a longitudinal study of 70 gifted children Freeman compared gifted children with two control groups of children from the same school class. One control group was equally intelligent, but not labelled as gifted, the second control was taken at random. Children with IQs over 140 were neither found to sleep less nor more fitfully. At all levels of ability the length of a child’s sleep was found to be directly related to both age and emotional problems.

In order to get an impression whether gifted people differ from people with average intelligence in their sleep quality we performed a survey among a group of gifted adults asking for sleep quality, the amount of hours of sleep needed, the kind of sleep disorder and reasons for the sleep disorder. We used data from published studies to compare with average people with average intelligence.

METHODS

We asked users of a LinkedIn group, where about 400 gifted people discuss topics about giftedness in daily life, to fill out a questionnaire that was made on a free site on the internet where surveys up to n=100 can be conducted. We also asked for gender and age. The questions were:

1. How do you rate the quality of your sleep: good/moderate/ bad?

2. How many hours of sleep do you need on average at night?
3. Do you think you have a sleeping disorder, yes or no? If yes, what kind of sleeping disorder do you have? (sleep onset insomnia, sleep maintenance insomnia, other; combinations were allowed.)

4. What do you see as reasons for you sleeping disorder?

The survey was open for about 3 weeks in January/February 2011. By that time 46 people had responded: 34 female (73.9%) and 12 male (26.1%). The average age was 45.5 year (female 44.4, male 48.6) with a range of 28 to 63 year.

The data were analysed using SPSS version 15.0 using independent sample t-test, 2-tailed testing. Significance was set at $P<0.05$

**RESULTS**

The results on the first four questions are given in the tables 1-4.

**Table 1.** Quality of sleep in general.

<table>
<thead>
<tr>
<th>Quality of sleep</th>
<th>n</th>
<th>%</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bad</td>
<td>4</td>
<td>8.7%</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>18</td>
<td>39.1%</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Good</td>
<td>24</td>
<td>52.2%</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>100%</td>
<td>34</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table 2.** Hours of sleep respondents need (n = 45) by gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>All</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needed average hours of sleep (range)</td>
<td>7.2 (2.5 – 10)</td>
<td>7.5 (4 – 10)</td>
<td>6.6 (2.5 – 9)*</td>
</tr>
<tr>
<td>* Difference female – male is significant: $p = 0.04$.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Sleep disorder in relation to quality of sleep.

<table>
<thead>
<tr>
<th>Sleep disorder?</th>
<th>n (%)</th>
<th>Bad sleeper</th>
<th>Moderate sleeper</th>
<th>Good sleeper</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19 (41.3%)</td>
<td>4 (8.7%)</td>
<td>12 (26.1%)</td>
<td>3 (6.5%)</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>27 (58.7%)</td>
<td>0 (0.0%)</td>
<td>6 (13.0%)</td>
<td>21 (45.6%)</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>46 (100%)</td>
<td>4 (8.7%)</td>
<td>18 (39.1%)</td>
<td>24 (52.2%)</td>
<td>34</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table 4.** Sleep disorders in 29 gifted persons.

<table>
<thead>
<tr>
<th>Sleep disorder</th>
<th>n</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merely sleep onset insomnia</td>
<td>11</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Merely sleep maintenance insomnia</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Both sleep onset and sleep maintenance insomnia</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Both sleep maintenance insomnia and other</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Both sleep onset insomnia, sleep maintenance insomnia and other</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| Total | 29† | 23   | 6    |

† The 29 respondents consisted of 4 bad sleepers, 15 moderate sleepers and 10 good sleepers.
Sleep quality of 47.8% of the gifted people was rated moderate to bad (table 1). Average hours of sleep (table 2) was higher in females than in males (p=0.04). Four out of 19 respondents with a sleep disorder (21% of this subgroup) rated their sleep quality as bad (table 3). Merely sleep onset insomnia was mentioned by 19 and merely sleep maintenance insomnia by 12 respondents (table 4).

As reasons for the sleep disorders were mentioned (a) not being able to stop thinking (including having ideas): 16 respondents, (b) medical/somatic reasons (apnoea, depression, pain in legs, PTSD, cold feet, light sleep): 10 respondents and (c) other factors (light, noise), irregular life style, dreams, nightmares: 8 respondents.

DISCUSSION
This first survey measuring sleep quality in gifted people showed that about 40% of this group had sleep problems. This is more than expected, as we found that self reported sleep problems occur in about 30% of the general population (in which about 2% is considered to be gifted). It might be possible that from the gifted people we asked to participate in our study those with sleep problems were more inclined to fill out the questionnaire which in turn might explain the higher percentage of sleep complaints observed as compared to the average population. Therefore we need to repeat the survey in a group of gifted while minimizing the possibility of selection bias.

Sleep onset insomnia was reported as being the major sleep problem. However also sleep maintenance insomnia was reported frequently.

Chronic sleep onset insomnia is associated with the delayed sleep phase syndrome. This circadian rhythm disorder, characterized by late endogenous dim light melatonin onset (DLMO) occurs in 30% of children with ADHD. Giftedness may overlap ADHD as giftedness shares high activity level, boredom, not following rules with ADHD. Possibly a subgroup of gifted people with sleep onset insomnia has a similar circadian rhythm pattern as people with ADHD. This hypothesis can be tested by measuring DLMO.

Our finding on male female differences supports another study on self reported sleeping quality, where sleeping problems are reported by women twice as much as by men. Suggested origins for this difference are that women do worry more on work and family and that they are facing problems with hormonal functioning, but to confirm these hypotheses more studies in this area have to be conducted. We cannot compare our findings with other studies as we did not find studies to compare. The study by Geiger et al who found that children with higher IQs need less sleep, may be an indication of the required amount of sleep by the gifted. However, in this study only 2% of the participants were gifted children. Freeman’s study showed no correlation between intelligence and sleep disturbances. However the results could have been biased by questioning the parents rather than the children.

Gifted people are extraordinary for instance by their very sensitive way of perceiving and their very fast associations. This can lead to overstimulation. Their nervous system may be different from others which could have implications in sleep quality. Studies have to be done to support or reject this hypothesis.

Based on the high prevalence of sleep disorders found in the present study, we are now assessing sleep quality, circadian rhythmicity and co-morbidity in gifted people with sleep problems. Gifted people with sleeping disorders can be referred to the sleep centre of the Gelderse Vallei Hospital in Ede by sending the selftest sleepdisturbances at www.slaapstoornissen.nl to the sleep centre, mentioning ‘hoogbegaafden slaaponderzoek’.
Many questions that gifted asked themselves on this topic are still unanswered, for instance about the influence of dreams, food and the biological blueprint.

The importance of more information on this theme is evident. A well rested mind in a rested body can mean a lot for society. A rested gifted person could offer even more. Further study is justified.

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INVESTIGATING THE TWO-TRIAL Y-MAZE AS A PERFORMANCE ASSAY FOR SHORT-DURATION SLEEP DEPRIVATION STUDIES IN C57BL/6 MICE

Marcella Oonk¹, Christopher J. Davis¹,², James M. Krueger¹,², Jonathan P. Wisor¹,², Hans P.A. Van Dongen¹

¹Sleep and Performance Research Center, Washington State University, Spokane, WA, USA
²WWAMI Medical Education Program, Washington State University, Spokane, WA, USA

INTRODUCTION

The two-trial Y-maze is a simple recognition task that measures spatial recognition memory in rodents¹,². It is based on the innate preference of rodents to explore novelty and does not require the use of appetitive, aversive or complex associative conditioning¹,². As such, it provides a quick and relatively easy assessment of spatial recognition memory. The present study evaluated the usefulness of the two-trial Y-maze for short-duration (6 h) sleep deprivation (SD) studies in mice. Specifically, we investigated whether Y-maze performance reliably reflects the impairment of waking functions associated with SD³,⁴.

METHODS

N=21 male C57BL/6 mice were used; twelve were 11 weeks old and nine were 21 weeks old. They were housed under standard vivarium conditions (22° C; 12-12 h light-dark schedule) with food and water available ad libitum. All experiments were conducted during the light phase.

The Y-maze consisted of three arms (width x length x height: 8.5 x 35.5 x 15.0 cm), with a 120° angle between each arm. One arm was designated as the ‘Start’ arm, in which the animals began the trials; the other two arms were randomly assigned to be the ‘Open’ and ‘Novel’ arms. Pictures of geometric shapes were placed on the walls furthest from center of the Open and Novel arms as visual cues. The influence of distal visual cues and the presence of the observer was minimized with a black drape surround. The floor of the maze was covered with corn cob rodent bedding, which was renewed after each trial to minimize olfactory-based traces from the previous mouse.

The Y-maze experiment consisted of two trials separated by a 6 h inter-trial interval. During the first trial, the mice were allowed to explore the Start and Open arms for 10 min; the Novel arm was blocked. Following the first trial, seven 11 week-old mice and five 21 week-old mice were subjected to 6 h SD, in their home cage, through gentle handling. The other five 11 week-old mice and four 21 week-old mice were allowed to sleep uninterrupted for 6 h.

After the 6 h inter-trial interval, the second trial was conducted, during which the mice were allowed to explore all three arms for 5 min (experiment 1). After 2 weeks, the Y-maze experiment was repeated with the same mice assigned to the same conditions to determine the reproducibility of the assay (experiment 2).

The percentages of duration and number of entries in the Open and Novel arm during the second trial were calculated and analyzed by 2×2 mixed-effects ANOVA with a between-
subject factor of condition (SD vs. control), a within-subject factor of arm (Novel vs. Open), and both age and the age by arm interaction as covariates. Planned contrasts were computed to further examine significant effects and interactions.

To analyze the performance of individual mice, the difference in duration and number of entries between the Novel and Open arms in the second trial, expressed as the percentage of the total for the Open arm subtracted from the percentage of the total for the Novel arm, was calculated for each experiment.

RESULTS AND DISCUSSION

Fig. 1A shows duration spent in the Open and Novel arms expressed as a percentage of total time in the Y-maze during the second trial of the first experiment. Fig. 1B shows number of entries in each arm expressed as a percentage of total number of entries in the first experiment. Statistically significant differences between the SD and control groups are indicated in the figures.

In the first experiment, when comparing duration in the SD group vs. the control group, there was no significant condition by arm interaction (F[1,18]=0.1, P=0.98). Both the SD group (t[18]=2.5, P=0.023) and the control group (t[18]=2.2, P=0.042) spent more time during the second trial in the Novel arm than in the Open arm. The age by arm interaction covariate was statistically significant (F[1,18]=5.0, P=0.038). Further analysis showed that the 11 week-old mice spent more time in the Novel arm than the Open arm (t[18]=4.2, P<0.001), whereas the 21 week-old mice did not (t[18]=0.7, P=0.49).

Number of entries likewise showed no significant condition by arm interaction (F[1,18]=2.2, P=0.16) in the first experiment. Both the SD group (t[18]=2.6, P=0.020) and the control group (t[18]=4.2, P<0.001) entered the Novel arm significantly more often than the Open arm in the second trial.

Fig. 1C shows duration spent in each arm expressed as a percentage of total time in the Y-maze during the second trial of the second experiment. Fig. 1D shows number of entries in each arm expressed as a percentage of total number of entries in the second experiment. Statistically significant differences between the SD and control groups are indicated in the figures.

In the second experiment, when comparing duration in the SD group vs. the control group, there was no significant condition by arm interaction (F[1,18]=0.1, P=0.72). Neither the SD group (t[18]=1.7, P=0.11) nor the control group (t[18]=1.0, P=0.34) spent more time in the Novel arm than in the Open arm.

With regard to number of entries, there was again no significant condition by arm interaction (F[1,18]=1.4, P=0.26). The SD group exhibited a trend of greater preference for the Novel arm (t[18]=1.8, P=0.081), and for the control group this effect was significant (t[18]=3.2, P=0.005).

Figs. 2A and 2B show the difference scores for duration of the individual mice in the SD and control groups, respectively. Figs. 2C and 2D show the difference scores for number of entries. Notice the inconsistencies between the two experiments. Although group performance appeared to be similar between the two experiments, 75% of the mice showed inconsistent performance with respect to duration and/or number of visits in the second experiment compared to the first experiment. It is unlikely that this can be attributed to a learning effect, as the 2-week interval between experiments is believed to exceed the Y-maze retention capability of rats. Moreover, at the individual level, increases as well as decreases in performance were observed.
When specifically comparing the performance of the 11 weeks old mice in the SD condition between experiments 1 and 2, a uniform decline in performance (i.e., a decrease in the extra time spent in the Novel arm relative to the Open arm) was observed for duration (see Fig. 2A). This resembles a finding in humans of sensitization to SD following repeated exposure\(^5\). Why it was not observed for the 21 weeks old mice is unclear; larger samples would need to be studied to further examine age-related differences.

![Figure 1](image)

**Figure 1.** Effects of sleep deprivation (SD) on spatial recognition memory in the two-trial Y-maze. **A.** Duration of visits to each arm (mean and standard error) during the second trial of the first experiment. **B.** Number of entries in each arm (mean and standard error) during the second trial of the first experiment. **C.** Duration of visits to each arm during the second trial of the second experiment. **D.** Number of entries in each arm during the second trial of the second experiment. Comparisons between Novel and Open arms: *P<0.1, *P<0.05, **P<0.01, ***P<0.001.

**CONCLUSIONS**

In our study, C57BL/6 mice showed the expected preference for the Novel arm in the second trial of the two-trial Y-maze assay, particularly in the first experiment. In an earlier report\(^6\), 12 h SD decreased this exploratory behavior significantly, whereas 6 h SD did not. In agreement with that study, we found that Y-maze performance was not significantly affected by 6 h SD compared to control. Furthermore, we observed that performance changes from the first to the second trial were inconsistent between mice as well as within mice between the two experiments. As such, the two-trial Y-maze did not prove to be a reliable assay of spatial recognition memory for short-duration SD studies in C57BL/6 mice. Whether this finding generalizes to other strains with different baseline performance on the two-trial Y-maze\(^2\) remains to be examined.
Figure 2. Difference between the Novel and Open arms in the individual mice. A. Difference in duration of visits between the Novel and Open arms for experiments 1 and 2 in the sleep deprivation (SD) group. B. Difference in duration of visits between the Novel and Open arms for experiments 1 and 2 in the control group. C. Difference in number of entries between the Novel and Open arms for experiments 1 and 2 in the SD group. D. Difference in number of entries between the Novel and Open arms for experiments 1 and 2 in the control group.

ACKNOWLEDGEMENTS

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WHY DIM LIGHT MELATONIN ONSET (DLMO) SHOULD BE MEASURED BEFORE STARTING MELATONIN TREATMENT

M.Smits\textsuperscript{a}, H. Keijzer\textsuperscript{a,b}, W. Braam\textsuperscript{b,c}, R. Didden\textsuperscript{b,d,e}, A. Maas\textsuperscript{b,f}, & L.M.G. Curfs\textsuperscript{b,h}

\textsuperscript{a} Gelderse Vallei Hospital, Ede, The Netherlands
\textsuperscript{b} Governor Kremers Center, University Maastricht, Maastricht The Netherlands
\textsuperscript{c} ‘s Heeren Loo Zuid-Veluwe, Wekerom, The Netherlands
\textsuperscript{d} Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands
\textsuperscript{e} Trajectum, Zutphen, The Netherlands
\textsuperscript{f} GROW School for Oncology and Developmental Biology, University Maastricht, Maastricht, The Netherlands
\textsuperscript{g} Institute for Management Research, Radboud University Nijmegen, Nijmegen, The Netherlands
\textsuperscript{h} Department of Clinical Genetics, Academic Hospital Maastricht/University Maastricht, Maastricht, The Netherlands

INTRODUCTION

At 12 and 13 May 2011 the Castang foundation organized a workshop on sleep research needs for the problems of children with neurodevelopmental disorders in Vancouver. The Dutch multidisciplinary expert team for persons with intellectual disabilities who present with sleep disturbances was invited to discuss their ideas on future research. This article summarizes their vision on the value of Dim Light melatonin Onset measurements in patients with possible circadian sleep-wake disturbances.

Melatonin is a chronobiotic drug\textsuperscript{1} which is increasingly prescribed for patients with insomnia. It is usually administered 1 or 2 hours before desired bed time, as recommended by several pharmacopoeias.\textsuperscript{2} However a meta-analysis showed that melatonin is not effective if administered in this way.\textsuperscript{3} On the contrary, if melatonin is administered at a time which is related to Dim Light Melatonin Onset (DLMO), it is remarkably successful in improving sleep.\textsuperscript{4,5} This suggests that the advice how to administer melatonin should be adapted at the present knowledge. The more, because nowadays, DLMO can be measured easily in home situations.\textsuperscript{6}

The present review summarizes the arguments supporting measuring DLMO before starting melatonin treatment. We focus on the relevance of DLMO for diagnosis and optimal treatment of circadian rhythm sleep-wake disorders. Furthermore we explored if DLMO can be predicted by sleep onset and to what extent DLMO predicts effectiveness of melatonin treatment. Finally, we studied the reliability of DLMO measurement in clinical practice.

METHODS

The databases PubMed and Embase were searched as well as the abstracts of sleep and chronobiologic societies that were published between January 1990 and May 2011 using the key words ‘human’, ‘melatonin’, ‘dim light melatonin onset’, ‘treatment’ and their combinations. We also asked leading chronobiologists to inform us about studies on DLMO in humans, and which were in press in international journals.
RESULTS
The results of the literature search are summarized in table 1 and 2.

<table>
<thead>
<tr>
<th>Reason</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis circadian rhythm sleep disorder</strong></td>
<td></td>
</tr>
<tr>
<td>DLMO is the best characterisation of the 24-h melatonin rhythm, which is strongly associated with the circadian sleep-wake rhythm</td>
<td>8-13</td>
</tr>
<tr>
<td>Knowledge of DLMO increases the accuracy of the diagnosis of Delayed Sleep Phase Disorder with 32.5%.</td>
<td>7</td>
</tr>
<tr>
<td>Melatonin treatment before measuring DLMO may delay optimal treatment several months, as it may take several months after stopping melatonin treatment before a steady pre-treatment melatonin rhythm is reached again.</td>
<td>14,15</td>
</tr>
<tr>
<td><strong>Optimal treatment success.</strong></td>
<td></td>
</tr>
<tr>
<td>Meta-analyses of studies where melatonin was administered at a time related to DLMO showed that sleep in insomnia patients improved considerably, while a meta-analysis of studies where melatonin was administered without knowing DLMO did not show improvement of sleep(3).</td>
<td>3,16,17</td>
</tr>
<tr>
<td>Exogenous melatonin, administered 5 hours before DLMO maximally phase advances melatonin rhythm and the sleep-wake rhythm which is associated with it. Exogenous melatonin, administered 10 hours after DLMO, delays these rhythms maximally. These effects are dose-dependent.</td>
<td>18-20,20,21</td>
</tr>
<tr>
<td>More delayed pre-treatment DLMO is associated with stronger advances of sleep onset after melatonin treatment.</td>
<td>22,23 20,21</td>
</tr>
<tr>
<td>Knowing DLMO in children with chronic sleep onset insomnia and late DLMO is associated with a 92% treatment success rate.</td>
<td>ESRS congress Lisboa 2010</td>
</tr>
<tr>
<td>When patients who respond well on melatonin treatment delay the time of melatonin intake, treatment effect decreases. When they advance the time of melatonin intake treatment effect increases</td>
<td>Oral communication</td>
</tr>
</tbody>
</table>

Table 1. Reasons to measure Dim Light Melatonin Onset (DLMO) before starting melatonin treatment
Sleep onset measured with sleep log or polysomnography does not predict DLMO clinically reliable in patients with possible circadian sleep-wake rhythm disorder.

Clinical reliability of DLMO measurements
In home situations salivary DLMO can be measured reliably in 76.2% of patients with possible circadian sleep-wake rhythm disorders. In the remaining patients additional measurements reveal DLMO.

Influences on DLMO
Beta-blockers, antidepressants and neuroleptcs influence the secretion of melatonin. Their influence on DLMO is unknown

Sleep-wake rhythm

<table>
<thead>
<tr>
<th>Prediction of DLMO</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset measured with sleep log or polysomnography does not predict DLMO clinically reliable in patients with possible circadian sleep-wake rhythm disorder.</td>
<td>24 14</td>
</tr>
</tbody>
</table>

Table 2. Predictive value of measuring Dim Light Melatonin Onset (DLMO), clinical reliability and methods to measure melatonin and exogenous influences on DLMO.

DISCUSSION
Our literature search showed that DLMO is crucial for optimally diagnosing circadian rhythm sleep disorders and for optimally timing of melatonin treatment, an important pillar of treatment of circadian rhythm sleep disorders.

It is not yet known if knowing DLMO also helps the two other treatment pillars of circadian rhythm sleep disorders i.e. light treatment and strengthening time cues (zeitgebers). Light treatment delays or advances circadian and sleep-wake rhythm when administered at night and in the morning respectively. There are several reports showing that light treatment should be given during the increasing or decreasing phase of the melatonin curve, respectively. This suggests that knowing DLMO also might support effectiveness of light treatment.

The first pillar for circadian rhythm sleep wake disorders treatment is strengthening time cues. In patients with extreme DSPD or ASPD time cues might be shifted substantially. Knowing DLMO might help to shift time cues to times, which correspond with the patients’ actual biological clock (i.e. melatonin rhythm). After that these time cues can be shifted in the desired direction, eventually supported by bright light or melatonin treatment.

Several comments can be given on the conclusions of our review. The 24-hour melatonin rhythm, of which DLMO is the best characterization, correlates well with sleep-wake rhythm in healthy persons and in patients with well diagnosed circadian rhythm sleep disorders studied in sleep labs. However, it is not known if and to what extent DLMO correlates with sleep-wake rhythm in insomnia patients studied at home.

Knowing DLMO increased accuracy of DSPD diagnosis considerably. However this conclusion is based on outcomes of only one study.

According to several studies, measuring DLMO a few weeks after stopping melatonin treatment might influence DLMO. However, more accurate studies are necessary to support this finding and to connect clinical consequences to it.

The meta-analyses showing that melatonin treatment is effective if DLMO is known, were conducted on studies where DLMO was calculated, but in several studies melatonin treatment was given at a fixed time, which was not related to DLMO. Furthermore, DLMO was not known in all patients who participated. Nevertheless, the treatment effect was quite different from that reported in the meta-analysis of the studies where DLMO was not known.
Several clinical studies, performed by independent research groups, support the finding that exogenous melatonin advances sleep most when administered 5 hours before DLMO. The best way to assess to what extent DLMO indeed helps to establish best timing of melatonin treatment is to perform a randomized study in patients with severe DSPS, comparing the effectiveness of melatonin treatment given at a fixed time (i.e. one hour before desired bedtime) to melatonin administered 5 hours before DLMO.

The finding that a delayed pre-treatment DLMO is associated with stronger advances in sleep onset after melatonin treatment has important clinical implications. That is, when a patient with a delayed sleep-wake rhythm and an evident delayed DLMO without other co-morbidity does not respond to adequate treatment, hidden co-morbidity should be looked for. In these patients, we often find previously undiagnosed psychiatric co-morbidity, such as adult ADHD or autism.

The remarkably high effectiveness of melatonin treatment in children with sleep onset insomnia and late DLMO should be confirmed in future studies, and in studies with adults. The present review shows that the guidelines of the American Sleep Report should be adapted as to the value of DLMO in diagnosing and treating patients with circadian rhythm sleep disorders. Worldwide Facilitation of DLMO measurements (e.g. www.melatoninecheck.nl) will help these patients.

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HEMODYNAMIC, METABOLIC AND CARDIOVASCULAR COMPLICATIONS OF OBSTRUCTIVE SLEEP APNEA IN A LARGE POPULATION STUDY BEFORE AND AFTER CPAP THERAPY (ESADA STUDY).

Heleen Vrints\textsuperscript{a}, Amna Abdelgabar\textsuperscript{a}, Christine Mallegho\textsuperscript{a}, Michiel Broere\textsuperscript{a}, Michael Jonker\textsuperscript{a}, Olivier Vanderveken\textsuperscript{b}, Evert Hamans\textsuperscript{b}, Paul Van de Heyning\textsuperscript{b}, Wilfried De Backer\textsuperscript{a}, Johan Verbraecken\textsuperscript{a}

\textsuperscript{a}Department of Pulmonary Medicine, \textsuperscript{b}ENT, Antwerp University Hospital and University of Antwerp, Belgium

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterised by recurrent episodes of partial or complete upper airway obstruction during sleep. This manifests as a reduction (hypopnea) in or complete cessation (apnea) of airflow, despite ongoing inspiratory effort, followed by oxygen desaturation and arousal. Several studies have shown that OSAS can lead to hemodynamic and metabolic changes, hypoxemia and cardiovascular complications \citep{1-3}. CPAP therapy may have a beneficial effect on these consequences \citep{4-5}. However, the literature is inconclusive and contradictory. Hence, these studies were limited by power problems and short follow up periods. The European Sleep Apnea Database (ESADA) study, a multinational collaboration between sleep centres, can make a contribution in this area. This study evaluated the relationship between OSAS and anthropometric, polysomnographic and biochemical markers in a large population and provides a structured follow-up program which can help improve the understanding of the pathophysiological mechanisms involved in the development of OSAS. Moreover, the effect of Continuous Positive Airway Pressure (CPAP) treatment after one year was studied as well. This paper contains the results of the recruited patients in our multidisciplinary sleep disorder centre (Antwerp, Belgium). We evaluated the relationship between the apnea-hypopnea index (AHI) and metabolic parameters, such as cholesterol, triglycerids, C-reactive protein (CRP), creatinine, HbA1c and urinary albumin, and the influence of gender. After one year CPAP therapy reanalyses were assessed.

METHODS

We recruited all untreated patients, between 18 and 80 years, independently of comorbidity, concomitant medication and degree of sleepiness, with complaints of snoring and/or suspicion of OSAS. The severity of OSAS was confirmed by a full polysomnography. Several variables (anthropometric, polysomnographic and clinical data) were entered into the database. The patients completed a questionnaire concerning their sleep pattern, the symptoms related to OSAS, alcohol consumption, smoking habits and medical history. The Epworth Sleepiness Scale (ESS) was included as well. Following biochemical markers were analysed in the total population, with a subanalysis concerning OSAS severity and gender: cholesterol, triglycerids, creatinine, CRP, HbA1c and urinary albumin. Subsequently, correlations between various variables were investigated. These analyses were repeated in OSAS patients with a AHI>20, after one year of CPAP treatment.
RESULTS AND DISCUSSION

Baseline
Six hundred-ninety-three patients (M/F 539/154; 49 ± 12 years, BMI 28.5 ± 4.56 kg/m², AHI 22 ± 20) were included in the study. Sleep apnea (AHI>5) was confirmed in 80% of the cohort and 29.15% were currently smokers. The biochemical markers were into normal ranges. Cardiovascular and metabolic diseases were present in 29% and 20% of the population (Table 1). Significant differences were found between males and females in neck circumferences, subjective total sleep time (sTST), subjective sleep latency, mean and minimum SaO\(_2\), creatinine and triglycerids levels, AHI, oxygen desaturation index (ODI) (p<0.05).

Linear regression showed an influence of age, BMI, abdominal, hip and neck circumference on AHI. The ESS score was mainly related to the BMI and was not significantly influenced by the AHI. Subjective total sleep time (sTST) was clearly related to age and HbA1c. Blood pressure in males was influenced by the BMI and AHI. In the female population only an effect of BMI was seen. The abdominal circumference was related to creatinine, HbA1c, CRP and triglycerids levels.

The AHI and BMI had a significant effect on CRP. For creatinine, urinary albumin and HbA1c, this effect was not significant. Age, neck circumference and sTST had a significant impact on creatinine, HbA1c and CRP levels. Urinary albumin concentration was significantly related to the abdominal circumference. The oxygen desaturation index (ODI) was positively related to age.

An AHI>30 compared to an AHI<20 was generally associated with higher values of age, BMI, anthropometric markers, HbA1c, triglycerids, urinary albumin and ODI.

Follow-up
Eighty-nine patients (AHI>20) (M/F 80/9, 53 ± 10 years, BMI 29.7 ± 4.31 kg/m², AHI 40 ±17) were treated with CPAP. CPAP compliance (minimum 4 h/night) was sufficient in all patients (6.6 ± 1.2 h/night).

There was a clear positive effect of CPAP treatment on the ESS score (p<0.01), creatinine (p<0.01), cholesterol (p=0.03) and baseline triglycerids levels (p<0.01). However, HbA1c level increased (p=0.04). The effect of CPAP on ESS and creatinine was significant, regardless of OSAS severity (p<0.05). The effect on cholesterol was significant from an AHI >30 (p<0.05). The effect on CRP was significant in patients with an AHI between 30 and 50 (p<0.05). Finally, a significant improvement of the triglycerid levels was observed in patients with an AHI between 20 and 30 (p<0.05). These results could be confirmed only in the male population (p<0.05).

CONCLUSIONS

OSA (AHI > 30), compared with an AHI<20, was generally associated with higher values of age, BMI, anthropometric markers, HbA1c, triglycerids, urinary albumin and ODI. Long-term CPAP therapy leads to a clear positive effect on the ESS, creatinine, cholesterol and triglycerid levels.
Table 1. Baseline patients characteristics.

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† significant difference between male and female (p<0.05)
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† significant difference between pre and post (p<0.05)

REFERENCES

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PRESENTING SYMPTOMS IN PEDIATRIC RESTLESS LEGS SYNDROME

Al de Weerd\textsuperscript{a}, Rosalia Silvestri\textsuperscript{b}

\textsuperscript{a}Sleepcenter SEIN Zwolle-Groningen, Zwolle, Netherlands
\textsuperscript{b}Centro Dipartementale per Medicina del Sonno, Messina, Italy

INTRODUCTION

The diagnostic criteria for Restless Legs Syndrome (RLS) in adults are well known\textsuperscript{1}. As an extension to these rules, criteria for pediatric RLS were coined in 2003. See below for criteria\textsuperscript{2}. Theoretically, these rules allow for a final diagnosis of RLS based only on the history as reported by the patient and physical examination. For adults, but in particular in children, this data is not always clear, neither for the four essential questions nor for the exclusion of mimics, leading to additional tests like polysomnography (PSG), neurography, etc.

As primary aim of the study we describe the presenting symptoms, i.e. what did the patient and parents tell at the first visit to the out-patients clinic, in a group of children who were finally diagnosed as having definite RLS. In 2008 a study was published on presenting symptoms in pediatric RLS\textsuperscript{3}. The number of patients in that study was limited. The results of our study will be compared to this earlier work. If possible, they will be added to the existing data and used to come to a proposal for consensus on presenting symptoms, based on the study performed in the US and on our European data.

Diagnostic criteria in children\textsuperscript{2}

Diagnostic criteria for definite RLS in children 2-12 years old
Definite RLS 1
An urge to move the legs: The urge to move begins or worsens when sitting or lying down, is partially or totally relieved by movement, is worse in the evening or night than during the day or only occurs in the evening or night (=adult criteria) \textit{AND} The child uses own words to describe leg discomfort.
Definite RLS 2
All four adult essential (see above) criteria are met \textit{AND} 2-3 supportive criteria are met: sleep disturbance appropriate for age, biological parent or sibling has definite RLS, the child has a sleep study documenting a periodic limb movement index $>5\text{h}$ of sleep.
Diagnostic criteria for definite RLS in adolescents 13-18 years old: all four essential adult criteria are met.
For all ages: the leg sensations are not solely accounted for as symptoms of another medical or behavioral disorder (so called “mimics”).

PATIENTS AND METHODS

The study was performed in patients who were primarily presented to two large sleepcenters (Zwolle and Messina) in 2007-2010, both with special interest in pediatric sleep disorders, in
particular RLS. A pilot study was presented in 2008. Before the start of the study, the investigators, who both have longtime experience in child neurology and in sleep, agreed on which data had to be gathered: a detailed history based on a standardized questionnaire derived from the guidelines of 2003, with special attention for the presenting symptoms, physical examination and tests tailored to the patient under study to exclude mimics, PSG in the sleep clinic according to the AASM rules for the children seen in 2008-2010 and the Rechtschaffen and Kales guidelines for children included in 2007, and the patient had a follow-up period which lasted at least one year. If data obtained during this period or findings from the PSG made the diagnosis doubtful, the patient was excluded post hoc from the study.

All patients who were suspected of RLS during the first visit underwent the examinations mentioned. Based on the results the patient was diagnosed as having definite RLS or not. The definite group (N=24) participated in our study. In addition seven children were included who were evaluated in other Dutch sleep centers. The work-up of these children was similar to that outlined above. All data obtained in these children was transferred to the study coordinators. The local ethical committee (SEIN) had no objections to the set-up of the study.

One of the major problems in a history based study in children is the communicative skill of the child under study. This factor was more than age important for inclusion. In this way even two five year old children could participate. Teenagers older than 16 years at the first visit were excluded from the study as well as children suspected of secondary RLS. Although the description by the parents was taken into account, the data provided by the child was most important.

**RESULTS**

Thirty-one patients (25 boys) from Italy and The Netherlands, met the inclusion criteria. The first visit to the sleepcenter was at a median age of 10 years (IQR: 9-12). The interval between this visit and the first manifestations of the disorder was estimated at a median of 3 years (IQR 2-5). In all patients the starting symptoms were still present at the first visit to the outpatient clinic.

The presenting symptoms were: strange feelings, urge to move, tired or even excessively sleepy during the day (EDS). Sixteen of the 31 patients had already at the first visit a history compatible with the diagnosis definite RLS. At referral growing pains were mentioned by twelve patients. Further details on the strange feelings are shown in table 1. Figure 1 depicts the differences between the presenting symptoms in our study and those from the previous study by Picchietti’s group. Our patients had a history of less insomnia and EDS, but complained more of being tired, an item that was not mentioned in the earlier study.

In 27 of the 31 patients another disorder was present. Remarkable differences with the previous study were shown for epilepsy (our group:19 vs Picchietti: 0%), ADHD (42 vs 72%), parasomnia (7 vs 39%), anxiety (10 vs 33%) and depression (0 vs 28%). Furthermore, the genetic component as expressed in involvement of first degree family members, appeared to be less in our study (16 vs 72%)

At a cut-off of 35 pg/ml, the serum ferritine level was abnormal in half of our patients and in 72% of Picchietti’s patients. As this data were available for only 20 of our patients, these percentages were not formally compared.
Table 1. Presenting symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N=</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Feelings”, see below</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>Tired during daytime</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>Urge to move</td>
<td>28</td>
<td>90</td>
</tr>
<tr>
<td>Excessive sleepiness during day</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19</td>
<td>61</td>
</tr>
<tr>
<td>“Growing pains”</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>RLS (all adult criteria)</td>
<td>16</td>
<td>52</td>
</tr>
</tbody>
</table>

“Feelings” were described as: Ants in the legs, Itchy, Hurts, Deep ache, Spiders on or in the legs, Just need to move, Funny, Too much energy, Legs want to kick, Need to stretch.

Figure 1. Comparison of our data with those of the study by Picchietti et al³.

DISCUSSION AND CONCLUSIONS

This study provides data on presenting symptoms of pediatric RLS from two different regions of Europe. Independent from the location, sensori-motor symptoms were expressed by the child under study in a variety of often fancy descriptions. The complaints of insomnia, tiredness during daytime and sometimes overt EDS were mentioned mainly by the parents. Disorders other than RLS or PLMS occurred in 27 of the 31 patients, in particular ADHD, anxiety and pervasive disorders. The high prevalence of epilepsy may be due to the nature of the participating centers. Both major contributing centers and one of the other centers are specialized in sleep and in epilepsy.

A limitation of the study is in the long interval between first manifestations of RLS and the visit to our out-patient clinic, as this implies that the description of the presenting symptoms are partly based on retrospective data. This potential bias is inevitable, but may be mitigated by the persistence of the starting symptoms during this interval, as was mentioned by all
parents. We think that the strong point of this study can be found in the consequent and comprehensive work-up for each patient, leading to a homogeneous group of children. The study group may be compared with the group of 18 patients described by Picchietti et al. The subjective measures of sleep and of daytime performance suggest less insomnia and EDS in our group. At the other hand the children in our group were more tired during the day. As a multiple sleep latency test may give doubtful information in the age group studied, we had to rely on answers of the parents in this respect, knowing that tired during the day and EDS may be difficult to differentiate. Most important is the similarity of presenting symptoms of the RLS per se. Although expressed in a large variety, abnormal sensations in the legs, together with the urge to move, were the major presenting symptoms in both studies. The description of these symptoms were already supportive for the diagnosis RLS at the first contact in 16 of our 31 cases. In the other half of the patients, the history had to be verified through additional examinations, the course of the disorder over time, or both. A similar picture emerges from the study by Picchietti et al.

In our opinion the findings in both studies allow for the statement that pediatric RLS in many cases can be detected by taking a detailed history as given by the parents, together with careful listening to the description of the symptoms by the child itself. Sensori-motor symptoms prevail in children, and are, just as in adults, the cornerstone for the diagnosis. However, more anamnestic pitfalls occur in children. When doubt remains even after a detailed history taking, the clinical course and results of additional tests (exclusion of mimics, PSG, iron status) should be taken into account before the final diagnosis of pediatric RLS is made.

ACKNOWLEDGMENT

Ineke Lunsing (UMC Groningen), Nele Vandenbussche (Kempenhaeghe, Heeze), Elsa Peeters and Lynn Rijsman (both: MCH Haaglanden, The Hague) have sent in patients for this study.

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TO HEAT OR TOO HOT, THAT’S THE QUESTION
Induction of cooling promoting behavior during sleep while applying bed warming

Tim EJ Weysen, Els IS Møst, Dmitri A Chestakov, and Roy JEM Raymann

Philips Research, Eindhoven, the Netherlands

INTRODUCTION
The interaction between sleep, core body temperature and skin temperature is an established phenomenon, but the details on the way how temperature affects sleep is an ongoing debate [1-3]. It has been shown that nocturnal sleep is linked to the drop in core body temperature [4] where others showed that an increase in skin temperature is related to the onset of nocturnal sleep [5-7].

One way to increase skin temperature is by means of an electrical blanket. However, it has been shown that sleeping with an electrical blanket, turned on in the second half of the night, resulted in an increased core body temperature. They concluded that a higher core body temperature might have been the primary cause of the observed sleep disturbances [8]. Recent studies that manipulated skin temperature without affecting core body temperature showed improvements in sleep. It has been shown that an increase of skin temperature shortened sleep onset latency, promoted deep sleep and minimized early morning awakening [6, 7].

In the current study, we investigated whether bed warming would result in skin warming and if skin warming in turn resulted in sleep improvements. We warmed the bed prior to, and during bedtime and explored the effects on skin temperature and sleep parameters measured with polysomnogaphy (PSG), wrist actigraphy and questionnaires.

METHODS
Eight participants without sleep complaints (1 female and 7 males, mean age 24) visited the sleep lab for two non-subsequent nights. Participants were subjected to a neutral condition (no temperature intervention) and an intervention condition, in which bed temperature was first preheated (30 minutes) and then kept at a minimum temperature of 33°C, in randomized order. Bed temperature was controlled via an electrical blanket, developed at our technical department.

Polysomnographic sleep recordings were obtained with a digital recorder (Vitaport-3, TEMEC Instruments B.V., Kerkrade) and included EEG (F3,F4,C3,C4,O1,O2) using the Sleep Brainet system (Jordan Neuroscience, San Bernardino, USA), EOG and submental EMG. The signals were recorded digitally with a sampling frequency of 256 Hz. PSG recordings were scored by the Siesta group (Vienna, Austria) according to the standard R&K criteria [9, 10].

Participants wore an Actiwatch 2 on their non dominant wrist; actigraphic sleep parameters were estimated using the Actiware software, (Philips Respironics, Inc, Murrysville, USA). Subjective sleep was measured using a short form of the Pittsburg Sleep Diary [11] with additional questions that examined thermal comfort [12].

Skin temperature was measured at nine places: both mid-thighs, abdomen, both infraclavicular areas, both hands and both feet using 9 Thermochron iButtons (DS1921H; Maxim/Dallas Semiconductor Corp, Sunnyvale, USA) and a weighted average was calculated.
Duvet temperature was measured using 16 Hydrochron (DS1923; Maxim/Dallas Semiconductor Corp, Sunnyvale, USA) iButtons equally distributed (4x4 matrix) on the downside (i.e. facing the body of the participant) of a duvet cover. Temperature data from 6 sensors from the area surrounding the trunk were averaged. Temperature was sampled every 30 seconds.

All data was aligned on lights off time and data was averaged into 10 minutes epochs. Paired t-tests ($\alpha = 0.05$, one sided) were performed over the whole night as well as hourly bins.

**RESULTS**

**Temperature**

Skin temperature data was not significantly higher in the first 2 hours of the intervention condition as compared to the neutral condition. However, contrary to our expectations and our intention, skin temperature was significantly lower (bin 120 – 180 minutes: $p = 0.04$; bin 300 – 360: $p = 0.05$; bin 360 – 400: trend level $p = 0.08$) for a significant part of the night in the warm condition as compared to the neutral condition (figure 1).

![Average skin temperature](image)

**Fig. 1** Average skin temperature in the neutral condition (dark line) and the intervention condition (grey line). Periods of significant differences are marked with the dotted, black line. Values are presented as means ± S.E.M. for every epoch of 10 minutes.

Duvet temperatures also showed an unexpected temperature profile, being significantly lower (bin 120 – 180 minutes: $p = 0.04$; bin 180-240; $p = 0.01$) in the middle part of the sleeping period as compared to the neutral condition (figure 2).
**Fig. 2** Average duvet temperature in the neutral condition (dark line) and the intervention condition (grey line). Periods of significant differences are marked with the dotted, black line. Values are presented as means ± S.E.M. for every epoch of 10 minutes.

**Sleep**
PSG data revealed an increased sleep onset latency at trend level in the intervention condition as compared to the neutral condition (34.1 ± 24.2 min versus 17.0 ± 9.1 min.; mean ± SD, $p = 0.06$). A higher percentage REM sleep was observed in the intervention condition as compared to the neutral condition, also at trend level (23.4 ± 5.0% versus 19.3 ± 5.1%, $p = 0.09$).
Actigraphy showed a higher number of wake bouts in the intervention condition, as compared to the neutral condition at trend level (37.8 ± 15.5 versus 30.6 ± 6.7, $p = 0.07$). The average sleep bout duration in the intervention condition was shorter as compared to the neutral condition at trend level (13.2 ± 5.0 min. versus 15.5 ± 4.5 min., $p = 0.08$).

**Subjective**
In the morning, participants reported a higher number of awakenings due to physical discomfort in the intervention condition as compared to the neutral condition at trend level (0.6 ± 0.9 versus 0.4 ± 0.7, $p = 0.09$). Participants reported more often in the intervention condition that they preferred a cooler bed over the temperature of the intervention condition at a trend level (1.5 ± 0.5 versus 1.1 ± 0.4, $p = 0.09$).

**DISCUSSION AND CONCLUSION**
In the current study, we showed that bed warming does not result in skin warming and subsequent sleep improvements per se. The data indicate that the applied skin warming intervention resulted in both thermal discomfort and sleep disruption.
In the intervention condition participants removed the blanket multiple times during the night (confirmed by video observations), most likely causing the observed drops in duvet and skin temperatures throughout the night, even below the level of the neutral condition (see figures 1 and 2). After removing the blanket, both duvet and skin were exposed to the room temperature of 20°C. The removal of the blankets can be interpreted as a behavioral response to increase heat loss from the bed and the body. These disruptions might explain the tendency towards a lower sleep quality in this condition. Next to that, participants frequently reported after waking up that the bed temperature was too warm during the night.

Preheating the bed followed by continuously warming resulted in behavioral responses of the participants to cool down. It might be postulated that the heat content in the bed due to the preheating, together with the heat loss of the body during the first hours of the night result in a total heat load in bed that triggered thermoregulatory responses and subsequently disturbed sleep.

Although it has been shown that skin warming clearly improves sleep [7] our results show that both the timing and the amount of heat are critical for sleep improvement. Incorrect timing and heat overload easily trigger thermoregulatory responses, which in turn provoke behavioral responses counteracting the heat overload as shown in our data.

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SLEEP-WAKE
Research in The Netherlands

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Abstracts
ORAL APPLIANCE THERAPY VERSUS NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE IN OBSTRUCTIVE SLEEP APNEA: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Ghizlane Aarab\textsuperscript{a}, Frank Lobbezoo\textsuperscript{a}, Hans L. Hamburger\textsuperscript{b}, Machiel Naeije\textsuperscript{a}

\textsuperscript{a}Department of Oral Kinesiology, Academic Center for Dentistry Amsterdam, Research Institute MOVE, University of Amsterdam and VU University Amsterdam, and
\textsuperscript{b}Department of Clinical Neurophysiology and Center for Sleep-Wake Disorders, Slotervaart Medical Center, Amsterdam, The Netherlands

\textbf{Background:} Previous randomized controlled trials have addressed the efficacy of mandibular advancement devices (MADs) in the treatment of obstructive sleep apnea (OSA). Their common control condition, (nasal) continuous positive airway pressure (nCPAP), was frequently found to be superior to MAD therapy. However, in most of these studies, only nCPAP was titrated objectively, but not MAD. To enable an unbiased comparison between both treatment modalities, the MAD should be titrated objectively as well.

\textbf{Objective:} The aim of the present study was to compare the treatment effects of a titrated MAD with those of nCPAP and an intra-oral placebo device.

\textbf{Methods:} Sixty-four mild/ moderate OSA patients (52.0 ± 9.6 years) were randomly assigned to three parallel groups: MAD, nCPAP, and placebo device. From all patients, two polysomnographic (PSG) recordings were obtained at the hospital: one before treatment and one after approximately six months of treatment.

\textbf{Results:} The change in the apnea-hypopnea index (ΔAHI) between baseline and therapy evaluation differed significantly between the three therapy groups (ANCOVA; \(P = 0.000\)). No differences in the ΔAHI were found between the MAD and nCPAP therapy (\(P = 0.092\)), whereas the changes in AHI in these groups were significantly larger than those in the placebo group (\(P = 0.000\) and 0.002, respectively).

\textbf{Conclusion:} There is no clinically relevant difference between MAD and nCPAP in the treatment of mild to moderate OSA when both treatment modalities are titrated objectively.

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LONG-TERM FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL OF ORAL APPLIANCE THERAPY IN OBSTRUCTIVE SLEEP APNEA

Ghizlane Aarab\textsuperscript{a}, Frank Lobbezoo\textsuperscript{a}, Martijn W. Heymans\textsuperscript{b}, Hans L. Hamburger\textsuperscript{c}, Machiel Naeije\textsuperscript{a}

\textsuperscript{a}Department of Oral Kinesiology, Academic Centre for Dentistry Amsterdam (ACTA), Research Institute MOVE, University of Amsterdam and VU University Amsterdam, 
\textsuperscript{b}Department of Epidemiology and Biostatistics, VU University Medical Center Amsterdam, and 
\textsuperscript{c}Department of Clinical Neurophysiology and Center for Sleep-Wake Disorders, Slotervaart Medical Center, Amsterdam, The Netherlands

\textbf{Background:} Long-term trials are needed to capture information regarding the persistence of efficacy and loss to follow-up of both mandibular advancement device (MAD) therapy and continuous positive airway pressure (CPAP) therapy.

\textbf{Objectives:} The aim of the study was to compare these treatment aspects between MAD and nasal CPAP (nCPAP) in a one-year follow-up.

\textbf{Methods:} 43 mild/moderate OSA patients (52.2 \pm 9.6 years) with a mean apnea-hypopnea index (AHI) of 20.8 \pm 9.9 events/hour were randomly assigned to two parallel groups: MAD (n = 21) and nCPAP (n = 22). Four polysomnographic (PSG) recordings were obtained: one before treatment, one for the short-term evaluation, and two recordings 6 and 12 months after the short-term evaluation. Excessive daytime sleepiness (EDS) was also evaluated at the PSG recordings.

\textbf{Results:} The initially achieved improvements in the AHI remained stable over time within both groups (P = 0.650). In the nCPAP group the AHI improved 4.1 events/hour more than in the MAD group (P = 0.000). The EDS values showed a gradual improvement over time (P = 0.000), and these improvements were similar for both groups (P = 0.367). In the nCPAP group more patients withdrew from treatment due to side-effects than in the MAD group.

\textbf{Conclusions:} The absence of significant long-term differences in EDS improvements between the MAD and the nCPAP groups with mild/moderate OSA may indicate that the larger improvements in AHI values in the nCPAP group are not clinically relevant. Moreover, nCPAP patients may show more problems in accepting their treatment modality than MAD patients.

\textit{Respiration 2011 in press}
MELATONIN DECREASES DAYTIME CHALLENGING BEHAVIOUR IN PERSONS WITH INTELECTUAL DISABILITY AND CHRONIC INSOMNIA.

W. Braam\textsuperscript{a,b,c}, R. Didden\textsuperscript{c,d,e}, A. Maas\textsuperscript{c,f}, H. Korzilius\textsuperscript{g}, M.G. Smits\textsuperscript{b,c} & L.M.G. Curfs\textsuperscript{c,h}

\textsuperscript{a} ‘s Heeren Loo Zuid-Veluwe, Wekerom, The Netherlands
\textsuperscript{b} Gelderse Vallei Hospital, Ede, The Netherlands
\textsuperscript{c} Governor Kremers Center, University Maastricht, Maastricht, The Netherlands
\textsuperscript{d} Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands
\textsuperscript{e} Trajectum, Zutphen, The Netherlands
\textsuperscript{f} GROW School for Oncology and Developmental Biology, University Maastricht, Maastricht, The Netherlands
\textsuperscript{g} Institute for Management Research, Radboud University Nijmegen, Nijmegen, The Netherlands
\textsuperscript{h} Department of Clinical Genetics, Academic Hospital Maastricht/University Maastricht, Maastricht, The Netherlands

Background: Persons with intellectual disability (ID) and sleep problems exhibit more daytime challenging behaviours than persons with ID without sleep problems. Several anecdotal reports suggest that melatonin is not only effective in the treatment of insomnia, but also decreases daytime challenging behaviour. However, the effect of melatonin treatment on daytime challenging behaviour in persons with ID has not been investigated in a randomised controlled trial.

Methods: We investigated the effects of melatonin on challenging behaviour using data from two randomised controlled trials on the efficacy of melatonin on sleep problems in 49 persons (25 men, 24 women; mean age 18.2 years, SD = 17.1) with ID and chronic insomnia. Participants received either melatonin 5 mg (<6 years 2.5 mg) or placebo during 4 weeks. Daytime challenging behaviour was measured by the Storend Gedragsschaal voor Zwakzinnigen – Maladaptive Behaviour Scale for the Mentally Retarded (SGZ; Kraijer & Kema, 1994) at baseline week and the end of the fourth treatment week. Salivary dim light melatonin onset (DLMO) was measured at baseline and the last day of the fourth treatment week. Sleep logs were used to gather information on sleep parameters.

Results: Melatonin treatment significantly reduced SGZ scores, sleep latency, and number and duration of night wakes, and treatment increased total sleep time and advanced DLMO. However, after 4 weeks of treatment, change in SGZ scores did not significantly correlate with change in sleep parameters, nor with change in DLMO. Relatively strong correlations were found between change in SGZ scores, change in DLMO and number of night wakes.

Conclusion: Melatonin treatment in persons with ID and chronic insomnia decreases daytime challenging behaviour, probably by improving sleep maintenance or by improving circadian melatonin rhythmicity.

\textit{This study was supported by a research grant by ‘s Heeren Loo Zorggroep Steunfonds and Governor Kremers Center.}

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LOSS OF RESPONSE TO MELATONIN TREATMENT IS ASSOCIATED WITH SLOW MELATONIN METABOLIZATION

W. Braam\textsuperscript{a,b,g}, H. Keijzer\textsuperscript{b}, I.M. van Geijlswijk\textsuperscript{c,d}, M.G. Smits\textsuperscript{b,g}, R. Didden\textsuperscript{e,g} & L.M.G. Curfs\textsuperscript{f,g}

\textsuperscript{a}‘s Heeren Loo Zuid-Veluwe, Wekerom, The Netherlands
\textsuperscript{b}Gelderse Vallei Hospital, Ede, The Netherlands
\textsuperscript{c}Department of Pharmacy, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands
\textsuperscript{d}Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Science, Utrecht University, The Netherlands
\textsuperscript{e}Radboud University, Nijmegen / Trajectum, Zutphen, The Netherlands
\textsuperscript{f}Department of Clinical Genetics, Academic Hospital Maastricht / University Maastricht, The Netherlands
\textsuperscript{g}Governor Kremers Center, University Maastricht, Maastricht, The Netherlands

Background. In some of our patients with intellectual disability (ID) and sleep problems, the initial good response to melatonin disappeared within a few weeks after starting treatment, while the good response returned only after considerable dose reduction. The cause for this disappearing effectiveness of melatonin is yet unknown. We hypothesize that this disappearing effectiveness is associated with slow metabolization of melatonin.

Methods. In this pilot study we measured metabolization of melatonin in two female (aged 61 and 6 yr.) and one male (aged 3 yr.) patients who had chronic insomnia, late melatonin onset and mild ID, and whose sleep quality worsened a few weeks after initial good response to melatonin treatment, suggesting melatonin tolerance. After a 3 week washout period, patients received melatonin 1.0, 0.5 or 0.1 mg respectively. Salivary melatonin level was measured just before melatonin administration, and 2 and 4 hours thereafter. After this melatonin metabolization test, melatonin treatment was resumed with a considerably lower dose.

Results. In all patients melatonin concentrations remained >50 pg/ml at 2, 4 and 6 hours after melatonin administration. After resuming melatonin treatment sleep problems disappeared. The same procedure was followed in 3 patients who did not show melatonin disappearing effectiveness after 6 months of melatonin treatment. In all patients in the control group melatonin concentrations decreased between 2 and 4 hours after melatonin administration with a mean decrease of 76%.

Conclusion. We hypothesize that disappearing effectiveness of melatonin can be caused by slow metabolization of exogenous melatonin. As melatonin is metabolized in the liver almost exclusively by cytochrome P450 enzyme CYP1A2, this slow metabolization of melatonin is probably due to decreased activity/inducibility of CYP1A2. In patients in which effectiveness of melatonin disappears, a melatonin metabolization test should be considered and a considerably dose reduction is advised.

This study was supported by a research grant by ‘s Heeren Loo Zorggroep Steunfonds and Governor Kremers Center.

EFFICACY OF INTERNET AND GROUP ADMINISTERED COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA IN ADOLESCENTS; A PILOT STUDY

Eduard J. de Bruin, Anne Marie Meijer, Frans J. Oort, Susan M. Bögels

Department of Education, University of Amsterdam

Introduction
Literature shows a high prevalence of insomnia in adolescents. Cognitive behavioral therapy for insomnia (CBT-i) is proven effective in adults. Adolescents however are not inclined to seek help for their sleep problems. Therefore we developed a CBT-i protocol for adolescents of 6 weekly consults administered through an internet-site (N=13) and compared results to CBT-i in a group setting (N=7). We expected shorter sleep onset latency (SOL), less wake after sleep onset (WASO), longer total sleep time (TST) and higher sleep efficiency (SE) after treatment for both groups.

Methods
Subjects were recruited through the media. After screening with online questionnaires and an interview for further diagnosis subjects without other primary psychological or medical disorders interfering with sleep were included in the trial. A baseline measurement with wrist-actigraphy for a 7 day period was obtained registering SOL, WASO, TST and SE, followed by the CBT-i treatment. Directly after the last consult follow up measurements were obtained for another 7 consecutive days.

Results
Mixed model analysis showed a significant decrease of SOL after treatment for both groups (F(1, 186.79) = 35.76, p<.01) although at baseline SOL in the internet condition was significantly lower compared to the group condition (F(1, 25.92) = 27.92, p<.01). There was also a significant improvement of SE for both groups (F(1, 178.85) = 24.89, p<.01) with a significant interaction for treatment and condition showing more improvement for the group condition (F(1, 180.27) = 6.84, p<.05). There was no significant effect on WASO and TST for either group.

Conclusion
Internet and group administered CBT-i is effective for improvement of sleep in adolescents. SOL decreased and SE improved. TST did not show an increase which we attribute to restriction of time in bed that still is applied after the last consult. Differences in SOL before treatment could be caused by holidays during baseline for the internet condition. Further studies with a larger sample, a waiting list control group and long term follow up are needed.

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CIRCADIAN MODULATION OF SLEEP IN RODENTS

Tom Deboer

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands

Sleep is regulated by circadian and homeostatic processes. The sleep homeostat keeps track of the duration of prior sleep and waking and determines the intensity of sleep. In mammals it is reflected by electroencephalogram (EEG) slow-wave activity (SWA, EEG power density between ~1-4 Hz) in non-rapid eye-movement (NREM) sleep. The circadian process is controlled by a pacemaker located in the suprachiasmatic nucleus (SCN) and provides the sleep homeostat with a circadian time frame.

These findings and ideas initiated questions about the interaction between the sleep homeostat and the circadian clock. Phase shifting experiments in humans and experiments with SCN lesioned rodents demonstrated that the two processes can function independently. Research in humans showed that the period of consolidated waking during the day is a logical consequence of the interaction between an increasing homeostatic sleep drive and a compensating circadian signal, which promotes waking during the day. In rodents it was shown that this interaction may be more intimate since sleep deprivation changed SCN neuronal firing and FOS expression and attenuated light induced phase shifts. Also several clock gene knock-out mouse models show a sleep phenotype.

More recently, we showed in the rat that under constant homeostatic sleep pressure still a circadian modulation of the amount of sleep and waking is observed. This seems to be the result of a circadian modulation of waking and NREM sleep episode duration where the circadian clock promotes longer waking episodes and shorter NREM sleep episodes during the active phase.

These data show that there is a circadian modulation of sleep in rodents, as in humans. However there are also distinct differences. In contrast to humans, rodent sleep has a strong ultradian component and a significant amount of sleep is observed during what is considered to be the active phase of the animal. Humans show a clear circadian modulation in REM sleep with high values shortly after the minimum in core body temperature. In rats a circadian modulation of REM sleep was not present in the protocol and also a wake maintenance zone, as is found in the evening in humans, was not observed in rodents.

The data suggest that sleep may have a profound influence on the functioning of the circadian clock, and that the influence of the circadian clock on sleep in the rat is probably weaker than in humans. Knowledge about the interaction between sleep and the circadian clock and the circadian modulation of sleep in other species than humans is important to be able to better understand the underlying regulatory mechanisms.

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XII Congress of the EBRS 20-26 Oxford, August 2011.
LONG-TERM ORAL APPLIANCE THERAPY IN OBSTRUCTIVE SLEEP APNEA SYNDROME; A CONTROLLED STUDY ON TEMPOROMANDIBULAR SIDE-EFFECTS

Michiel H.J. Doff, Steffanie K.B. Veldhuis, Aarnoud Hoekema, James J.R. Huddleston Slater, P.J. Wijkstra, Lambert G.M. de Bont, Boudewijn Stegenga

a University Medical Center Groningen, University of Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB, Groningen, The Netherlands.

Introduction: The objective of this study was to assess variations in the occurrence of temporomandibular disorders (TMDs) and the risk of developing pain and function impairment of the temporomandibular complex in obstructive sleep apnea syndrome (OSAS) patients treated with either an oral appliance (mandibular advancement device) or continuous positive airway pressure (CPAP) in a two-year follow-up study. In addition we assessed the relationship between the mean mandibular protrusion, and the frequency of wearing the appliance during follow-up with the occurrence of pain and function impairment of the temporomandibular complex.

Methods: Fifty-one patients were randomized to oral appliance therapy and fifty-two patients to CPAP therapy. TMDs (diagnosed according to the Axis I Research Diagnostic Criteria for TMD), pain intensity and disability, and mandibular function impairment were recorded at baseline, after 2 months, 1 year and 2 years of therapy.

Results: Only in the initial period of treatment the occurrence of pain-related TMDs was considerably higher (24%) in the oral appliance group compared to CPAP (6%). Oral appliance therapy furthermore resulted in more temporomandibular pain compared to CPAP (Odds ratio [OR] 2.33, 95% Confidence Interval [CI] (1.22 – 4.43). However, there were no limitations in mandibular function in both groups during the (entire) follow-up period.

Conclusion: Although generally not serious and of transient nature, oral appliance therapy results in more pain related TMDs in the initial period of use compared with CPAP therapy. Oral appliance therapy is associated with increased pain in the temporomandibular complex in the initial period of use. Because of the transient nature, this pain is not a reason to contra-indicate an oral appliance in OSAS patients. Moreover, TMDs and the risk of developing pain and function impairment of the temporomandibular complex appear limited with long-term oral appliance use.

ANXIETY AND MOOD DISORDERS IN NARCOLEPSY: A CASE-CONTROL STUDY

Hal DroogleeverFortuyn\textsuperscript{a}, Martijn Lappenschaar\textsuperscript{a}, Joop Furer\textsuperscript{b}, Paul Hodiamont\textsuperscript{a}, Cees Rijnders\textsuperscript{b}, Willy Renier\textsuperscript{c}, Jan Buitelaar\textsuperscript{a}, Sebastiaan Overeem\textsuperscript{c,d}

\textsuperscript{a} Dept. of Psychiatry, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{b} Dept. of Social Medicine, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{c} Dept. of Neurology, Donders Institute for Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{d} Sleep Medicine Centre Kempenhaeghe, Heeze

Introduction
Narcolepsy is a primary sleeping disorder with excessive daytime sleepiness and cataplexy as core symptoms. There is increasing interest in the psychiatric phenotype of narcolepsy. Although many authors suggest an overrepresentation of mood disorders, few systematic studies have been performed and conflicting results have been reported. Anxiety disorders in narcolepsy have only received little attention.

Methods
We performed a case-control study in 60 narcolepsy patients and 120 age-and sex-matched controls from a previous population study. The Schedules for Clinical Assessment in Neuropsychiatry were used to assess symptoms and diagnostic classifications of mood and anxiety disorders.

Results
Symptoms of mood disorders were reported by about one third of patients. However, the prevalence of formal mood disorder diagnoses - including major depression - was not increased. In contrast, more than half of the narcolepsy patients had anxiety or panic attacks. Thirty-five percent of the patients could be diagnosed with anxiety disorder (odds ratio=15.6), with social phobia being the most important diagnosis. There was no influence of age, sex, duration of illness or medication use on the prevalence of mood or anxiety symptoms and disorders.

Discussion
Anxiety disorders, especially panic attacks and social phobias, often affect patients with narcolepsy. Although symptoms of mood disorders are present in many patients, the prevalence of major depression is not increased. Anxiety and mood symptoms could be secondary complications of the chronic symptoms of narcolepsy. Recent studies have shown that narcolepsy is caused by defective hypocretin signaling. As hypocretin neurotransmission is also involved in stress regulation and addiction, this raises the possibility that mood and anxiety symptoms are primary disease phenomena in narcolepsy.

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ACTIGRAPHY VERSUS POLYSOMNOGRAPHY IN THE DIAGNOSIS OF PARADOXICAL INSOMNIA

E. Felix*, O.J.M. Vogels*, L.L. Teunissen*

*Sleep Wake Centre St. Antonius Hospital, Utrecht/Nieuwegein, the Netherlands.

Introduction: Insomnia can be divided in subtypes. An intriguing type of insomnia is paradoxical insomnia. This type of insomnia can be differentiated from other types of insomnia as there is a discrepancy between complaints and normal findings on polysomnography (PSG).
Since polysomnography is time consuming and costly, it is important to determine the applicability of other types of measurements of sleep quality. The aim of this study was to determine if sleep duration and sleep onset latency measured with 10 nights actigraphy (AG) are comparable to 1 night PSG in the determination of paradoxical insomnia.

Methods: Seventeen patients (11 men, 6 women, mean age: 45.6) with insomnia complaints were included. Sleep quality was measured with PSG and AG simultaneously. Patients continued to wear the actiwatches and kept a sleeplog for 9 subsequent nights. Exclusion criteria were depression, restless legs and excessive sleepiness during daytime. Total sleep time (TST), sleep onset latency (SOL) and wake time after sleep (WASO) were calculated from both PSG and AG first night and AG mean 10 night’s registrations.
Paradoxical insomnia was diagnosed if the TST measured with PSG or AG was >120 min, and/or the SOL >30 min compared to subjective TST and SOL.

Results: Intraclass Correlation Coefficient (ICC) between PSG and first night AG showed a significant correlation for TST (0.79(p<0.01)) and SOL (0.85 (p<0.01)), but not for WASO (0.46 (NS))
The mean TST measured with AG was 40 minutes longer compared to PSG TST. Mean SOL and WASO were 10 and 41 minutes shorter, respectively.
PSG compared to 10 nights AG showed disagreement on the diagnosis paradoxical insomnia in 4 of 17 patients, kappa 0.36, p 0.12. Five patients slept for a shorter amount of time during the first night, compared to the subsequent nights.

Conclusion: In this study Actigraphy and PSG are not comparable for diagnosing paradoxical insomnia. To diagnose paradoxical insomnia, patients should have normal sleep duration. Our study showed in five cases a shorter sleep duration during the first night, measured with PSG (the well known first night effect). PSG for two or more nights is however not common practice in patient care. AG for ten nights might be superior to PSG in representing the real sleep duration in patients with paradoxical insomnia.

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PHASE ADVANCING THE HUMAN CIRCADIAN SYSTEM WITH SHORT PULSES (30 MIN) OF BLUE LIGHT EXPOSURE

Moniek Geerdink\textsuperscript{a}, Domien G.M. Beersma\textsuperscript{a}, Vanja Hommes\textsuperscript{b}, Marijke C.M. Gordijn\textsuperscript{a}

\textsuperscript{a}Department of Chronobiology, Centre for Life Sciences, University of Groningen, The Netherlands
\textsuperscript{b}Philips Consumer Lifestyle, Drachten, The Netherlands

ABSTRACT

Introduction
Circadian rhythm sleep disorders (CRSD) are characterized by sleeping out of phase with the external light-dark cycle. In our society this often results in sleep deficits and a mismatch between endogenous and external rhythms, leading to health problems and daytime performance decrements. Light in the morning is able to induce phase advances of the endogenous clock, but optimal treatment parameters have not been identified. In fact, the most complete PRC for single light pulses is obtained with light pulses of 6.5h-duration. 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 CRSD patients.

Methods
In our study 13 relatively late chronotypes (aged 23-27y, 6f/7m) participated in three conditions: (1) 3 consecutive days of 30 min morning-light exposure, (2) 3 consecutive days of 60 min light exposure and (3) a control week. The blue light pulse was applied by the use of the Philips GoLite BLU (HF3320, blue leds, intensity at the cornea $\approx 3.6E+14$ photons/cm\textsuperscript{2} 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 (SD 79) min was observed over three days, which was clearly significantly different from both light conditions (F(2,11)=5.0, p<0.05). Sleep inertia, as measured by the change in subjective ratings of sleepiness (Karolinska Sleepiness Scale, KSS) during the first 30/60 min after waking up was significantly reduced during both the days with 30 min light pulses (mean ± sem: -2.5 ± 0.3) and during the days with 60 min light pulses (-2.2 ± 0.4) compared to the control week (-1.3 ± 0.3; F(2,11)=6.3, p<0.05).

Conclusion
It is concluded that 30 min of high intensity blue light in the morning is capable of inducing a phase advance of the rhythm of melatonin of almost 1 hour within three days which is accompanied by a more rapid reduction of sleepiness after waking up.

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SLEEP DEPRIVATION IMPAIRS CONTEXTUAL FEAR CONDITIONING AND ATTENUATES SUBSEQUENT BEHAVIORAL, ENDOCRINE AND NEURONAL RESPONSES

Roelina Hagewoud, Lillian J. Bultsma, R. Paulien Barf, Jaap M. Koolhaas, Peter Meerlo

Center for Behavior and Neurosciences, University of Groningen, The Netherlands

Sleep deprivation (SD) affects hippocampus-dependent memory formation. Several studies in rodents have shown that brief SD immediately following a mild footshock impairs consolidation of contextual fear memory as reflected in a reduced behavioral freezing response during reexposure to the shock context later on.

In the first part of this study, we examined whether this reduced freezing response is accompanied by an attenuated fear-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis. In the second part, we established whether the attenuated freezing response in SD animals is associated with reduced activation of relevant brain areas known to be involved in the retrieval and expression of fear memory.

Results show that 6 h of SD immediately following the initial shock results in a diminished adrenal corticosterone (CORT) response upon re-exposure to the shock context the next day. Immunohistochemical analysis of brain slices showed that the normal increase in phosphorylation of the transcription factor cAMP response-element binding protein (CREB) upon reexposure to the shock context was reduced in SD animals in the CA1 region of the hippocampus and in the amygdala.

In conclusion, brief SD impairs the consolidation of contextual fear memory. Upon re-exposure to the context, this is reflected in a diminished behavioral freezing response, an attenuated HPA axis response, and a reduction of the normal increase of pCREB expression in hippocampus and amygdala.

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MEASUREMENT OF SLEEP

Bob Kemp

Sleep Centre, MCH hospital, Den Haag

Introduction. A recent book on sleep and cognition also presents a chapter on basic sleep recording and analysis techniques for researchers and practitioners entering the field.

Methods. Electrode and skin preparation, EXG derivations, amplifiers, digitization and archival are discussed. Manual sleep stage scoring is contrasted to automatic analysis of sleep spindles, slow waves and submental EMG.

Conclusion. Many details need to be optimized in order to obtain good recording quality. When compared to manual scoring, computer analysis is more accurate and can distinguish separate physiological entities but it is less adaptive to individual EXG characteristics and artifacts. Automatic analyses must be supervised by a human expert.

Figure. Sleep electrode positions and computer-monitored physiological entities of sleep.

BODY TEMPERATURES, SLEEP, AND HIBERNATION

Kurt Kräuchi\textsuperscript{a} and Tom Deboer\textsuperscript{b}

\textsuperscript{a}Thermophysiological Chronobiology, Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Basel, Switzerland.

\textsuperscript{b}Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

The human sleep-wake cycle is usually tightly coupled to the circadian time course of core body temperature. The circadian regulation of heat loss in the evening, via distal skin regions, is intimately associated with sleepiness and the ease to fall asleep, whereas the homeostatic increase in sleep pressure does not influence the thermoregulatory system. The rise in heat loss and reduction in heat production during lying down and relaxing behavior before sleep is hypothesized to be part of the role of sleep as a mechanism for energy conservation and may be a remnant of our evolutionary past. After sleep initiation non-rapid-eye-movement-sleep (NREMS) to REMS cycle fluctuations seem to have minor thermoregulatory functions, especially in humans.

From experimental data obtained in humans and rodents, it can be concluded that warming can increase sleep propensity, sleep consolidation and the duration of SWS (slow wave sleep). In contrast, the effects of cooling on sleep are not yet sufficiently studied. More systematic investigations applying different temperature levels particularly in the range where thermoregulation is achieved solely by vasomotor responses (the thermo-neutral zone) are needed to develop applicable thermal therapeutic strategies for sleep disturbances.

From anatomical and neurophysiological studies it has become clear that the pre-optic-anterior-hypothalamus (POAH) is the main integrator of sleep and thermoregulatory information. It receives input from brain areas involved in circadian and sleep-wake regulation, and skin and brain areas recording body and environmental temperature. The POAH integrates this information and influences vigilance states and body temperature in response to that input.

The torpid state, particularly of those animals that display daily torpor, may be a valuable model to investigate the relationship between thermoregulation and sleep. During daily torpor, the animals seem to apply similar physiological processes as occur in humans during normal entrance into sleep, but in a more extreme way, providing an excellent opportunity to investigate these processes in detail.

EXPANDING SELF-HELP IMAGERY REHEARSAL THERAPY FOR NIGHTMARES WITH SLEEP HYGIENE AND LUCID DREAMING: A WAITING-LIST CONTROLLED TRIAL

Jaap Lancee; Jan van den Bout; Victor Spoormaker*

Utrecht University
* Present affiliation: Max Planck Institute of Psychiatry

ABSTRACT

Introduction
Nightmares are a common disorder with serious consequences. Recently, the cognitive-behavioral interventions Imagery Rehearsal Therapy (IRT) and exposure proved effective in a self-help format. The aim of the current study was to compare the following self-help formats to a waiting-list: IRT; IRT with sleep hygiene; and IRT with sleep hygiene and a lucid dreaming section.

Methods
Two-hundred-seventy-eight participants were included and randomized into a condition. Follow-up measurements were 4, 16, and 42 weeks after treatment completion. Seventy-three participants completed all questionnaires and 49 returned the nightmare diaries.

Results
Contrary to our expectations, the original IRT was more effective than the 2 other intervention conditions. Moreover, IRT was the only intervention that convincingly proved itself compared to the waiting-list condition.

Discussion
However, these data should be interpreted with caution due to the low power and high dropout. Yet it seems that in a self-help format, IRT and exposure (which was validated previously) are the treatments of choice for nightmares.

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NIGHTMARE FREQUENCY IS ASSOCIATED WITH SUBJECTIVE SLEEP QUALITY BUT NOT WITH PSYCHOPATHOLOGY

Jaap Lancee; Victor Spoormaker*; Jan van den Bout

Utrecht University
* Present affiliation: Max Planck Institute of Psychiatry

ABSTRACT

Introduction
This study aimed to evaluate all known and hypothesized predictors for nightmare frequency measures in a population with frequent nightmares.

Methods
A total of 666 Internet recruited participants completed questionnaires on nightmares, sleep, and psychopathology, 146 of whom further completed a subsequent 7-day diary.

Results
In contrast to previous research, comparison of questionnaire and diary measured nightmare frequency revealed a significantly higher log-transformed nightmare frequency on the questionnaire: \( t(127) = 4.43; p < .001 \). No differences were found regarding the number of nights with nightmares, \( t(127) = 0.61; p = .54 \). Regression analyses showed that subjective sleep quality was the only variable significantly associated with nightmare frequency variables in the whole sample (\( R^2 \text{adj} \) between 10.5% - 11.5%; \( p < .01 \)).

Discussion
These results support the notion that nightmares are independent from other mental complaints in a population of nightmare sufferers and should therefore be viewed from a sleep medicine perspective: As a sleep disorder that can and should receive specific attention and treatment.

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Lancee, J., Spoormaker, V. I., & van den Bout, J. (2010). Nightmare frequency is associated with subjective sleep quality but not with psychopathology. Sleep and Biological Rhythms, 8, 187-193.
LONG-TERM EFFECTIVENESS OF COGNITIVE-BEHAVIORAL SELF-HELP INTERVENTION FOR NIGHTMARES

Jaap Lancee; Victor Spoormaker*; Jan van den Bout

Utrecht University
* Present affiliation: Max Planck Institute of Psychiatry

ABSTRACT

Introduction
Nightmares are a prevalent disorder leading to daily impairments. Two cognitive-behavioral self-help interventions – imagery rehearsal and exposure – recently showed short-term efficacy compared to a waiting-list and a group that recorded their nightmares.

Methods
This article reports the long-term results of the imagery rehearsal (n = 103) and exposure (n = 95) interventions. Participants were assigned randomly to a condition after completing baseline measurements; they received a 6-week self-help intervention and completed questionnaires 4, 16, and 42 weeks after end of treatment.

Results
Initial effects on nightmare measures were almost completely sustained after 42 weeks (d = 0.50 - 0.70); no differences were found between exposure and Imagery Rehearsal Therapy.

Discussion
These results suggest that nightmares should be targeted specifically and that an Internet delivered self-help intervention seems to be a good first option in a stepped care model.

In press as:
RAPID CHANGES IN THE LIGHT/DARK CYCLE DISRUPT MEMORY OF CONDITIONED FEAR IN MICE

Dawn Hsiao-Wei Loh, Juliana Navarro, Arkady Hagopian, Louisa M. Wang, Tom Deboer and Christopher S. Colwell

Department of Psychiatry and Biobehavioural Sciences, University of California, Los Angeles, USA
Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands

Introduction. Circadian rhythms govern many aspects of physiology and behavior including cognitive processes. Components of neural circuits involved in learning and memory, e.g., the amygdala and the hippocampus, exhibit circadian rhythms in gene expression and signaling pathways. The functional significance of these rhythms is still not understood. In the present study, we sought to determine the impact of transiently disrupting the circadian system by shifting the light/dark (LD) cycle. Such "jet lag" treatments alter daily rhythms of gene expression that underlie circadian oscillations as well as disrupt the synchrony between the multiple oscillators found within the body.

Methods. We subjected adult male C57Bl/6 mice to a contextual fear conditioning protocol either before or after acute phase shifts of the LD cycle. As part of this study, we examined the impact of phase advances and phase delays, and the effects of different magnitudes of phase shifts.

Results. Under all conditions tested, we found that recall of fear conditioned behavior was specifically affected by the jet lag. We found that phase shifts potentiated the stress-evoked corticosterone response without altering baseline levels of this hormone. The jet lag treatment did not result in overall sleep deprivation, but altered the temporal distribution of sleep. Finally, we found that prior experience of jet lag helps to compensate for the reduced recall due to acute phase shifts.

Conclusions. Acute changes to the LD cycle affect the recall of fear-conditioned behavior. This suggests that a synchronized circadian system may be broadly important for normal cognition and that the consolidation of memories may be particularly sensitive to disruptions of circadian timing.

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MELATONIN AND SLEEP EFFECTS ON HEALTH, BEHAVIOR PROBLEMS AND PARENTING STRESS

Annette van Maanen\textsuperscript{a}, Anne Marie Meijer\textsuperscript{a}, Marcel G. Smits\textsuperscript{b}, Frans J. Oort\textsuperscript{a}

\textsuperscript{a}Research Institute Child Development and Education, University of Amsterdam  
\textsuperscript{b}Centre for Sleep-Wake Disorders and Chronobiology, Hospital Gelderse Vallei, Ede

ABSTRACT

Introduction In children with sleep onset insomnia and delayed Dim Light Melatonin Onset, melatonin treatment not only improves sleep but also health, behavior and parenting stress. The aim of the present study was to see whether the latter effects are dependent on the direct effects on sleep.

Methods Data come from 41 children (24 boys, 17 girls; mean age = 9.43 years). They entered melatonin treatment (1 – maximum 5 mg) for three weeks, then discontinued treatment by first taking a half dose for one week, and then stopped completely for another week. Sleep was measured with sleep diaries filled in by parents and with actometers.

Results We found a positive effect of sleep duration on health but this disappeared after discontinuing treatment. We also found that melatonin treatment decreased behavior problems, which effect appeared to be stronger for children with an earlier Dim Light Melatonin Onset.

Conclusion These results show that the melatonin effects on health and behavior problems may partly be dependent on sleep.

Figure 1 Expected scores on health for children with average, short, and long sleep durations, immediately after melatonin treatment and at the end of the stop week.

Figure 2 Expected scores on behavior problems for children with average, early, and late DLMO, before melatonin treatment and at the end of the stop week.

Van Maanen A, Meijer AM, Smits MG, Oort FJ. Melatonin and sleep effects on health, behavior problems and parenting stress. Sleep Biol. Rhythms 2011, accepted for publication.
CHRONIC PARTIAL SLEEP DEPRIVATION REDUCES BRAIN SENSITIVITY TO GLUTAMATE N-METHYL-D-ASPARTATE RECEPTOR MEDIATED NEUROTOXICITY

Arianna Novati, Henriëtte J Hulshof, Ivica Granic, Peter Meerlo

Center for Behavior and Neurosciences, University of Groningen, The Netherlands

It has been hypothesized that insufficient sleep may compromise neuronal function and contribute to neurodegenerative processes. While sleep loss by itself may not lead to cell death directly, it may affect the sensitivity to a subsequent neurodegenerative insult. Here we examined the effects of chronic sleep restriction (SR) on the vulnerability of the brain to N-Methyl-D-Aspartate (NMDA)-induced excitotoxicity.

Animals were kept awake 20 h per day and were only allowed to rest during the first 4 h of the light phase, i.e., their normal circadian resting phase. After 30 days of SR all rats received a unilateral injection with a neurotoxic dose of NMDA into the nucleus basalis magnocellularis (NBM). Brains were collected for assessment of damage.

In the intact non-injected hemisphere, the number of cholinergic cells in the NBM and the density of their projections in the cortex were not affected by SR. In the injected hemisphere, NMDA caused a significant loss of cholinergic NBM cells and cortical fibers in all animals. However, the loss of cholinergic cells was attenuated in the SR group as compared to the controls.

In conclusion, these data suggest that SR reduces the sensitivity to a subsequent excitotoxic insult. Chronic SR may constitute a mild threat to the brain that does not lead to neurodegeneration by itself but prepares the brain for subsequent neurotoxic challenges. These results clearly do not support the hypothesis that sleep loss increases the sensitivity to neurodegenerative processes.

This work was supported by The Netherlands Organization for Scientific Research (NWO Vidi grant 84.04.002 to PM).

THE CLINICAL FEATURES OF CATAPLEXY: A QUESTIONNAIRE
STUDY IN NARCOLEPSY PATIENTS WITH AND WITHOUT
HYPOCRETIN-1 DEFICIENCY

Sebastiaan Overeem\textsuperscript{a,b}, Sofie van Nues\textsuperscript{c}, Wendy van der Zande\textsuperscript{c}, Claire Donjacour\textsuperscript{c}, Petra van Mierlo\textsuperscript{b}, Gert Jan Lammers\textsuperscript{c}

\textsuperscript{a} Dept. of Neurology, Donders Institute for Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{b} Sleep Medicine Centre Kempenhaeghe, Heeze
\textsuperscript{c} Dept. of Neurology, Leiden University Medical Centre, Leiden

Introduction
Narcolepsy is often not recognized or accurately diagnosed. This may be due to the fact that cataplexy, a core symptom which is virtually 100% specific, can be diagnosed based on the patient's history. However, the current definition of cataplexy is not very precise and the common distinction between "typical" and "atypical" cataplexy is not well codified.

Methods
We aimed to provide a detailed description of the phenotypic variability of cataplexy. We included 109 patients with a definite history of cataplexy and a proven hypocretin-1 deficiency. The questionnaire contained 37 items to broadly cover the clinical aspects of cataplexy, including triggers, pattern and duration of muscle weakness, associated aspects such as sensory phenomena, and limitations in daily life due to cataplexy.

Results
"Laughing" only listed in place 11th of most frequent triggers. "Laughing excitedly" was much more potent, showing that a certain intensity of the emotion is important for a "cataplectogenic" effect. Anger was the highest ranking "non-humorous" trigger, followed by "unexpectedly meeting someone well known." About 60% of patients also had spontaneous cataplectic attacks. Forty-five percent of patients experienced both partial and complete attacks and 30% only partial cataplexy. Fifteen percent of complete attacks were reported to last longer than 2 min. An abrupt return of muscle function was an important feature. The jaw and the face were most often involved in partial attacks, even more than the knee or the leg.

Conclusion
Cataplexy presents with a large phenotypical diversity, so the current "typical" versus "atypical" distinction may be difficult to hold. We propose that grading cataplexy with different levels of diagnostic confidence may be more useful.

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SLEEP DEPRIVATION IMPAIRS EFFECTIVE CONNECTIVITY DURING RESTING STATE

Giovanni Piantoni\textsuperscript{a}, Bing Leung P. Cheung\textsuperscript{b}, Barry D. Van Veen\textsuperscript{b}, Nico Romeijn\textsuperscript{a}, Brady A. Riedner\textsuperscript{c}, Giulio Tononi\textsuperscript{c}, Ysbrand D. Van Der Werf\textsuperscript{a,d}, Eus J. W. Van Someren\textsuperscript{a,e}

\textsuperscript{a} Dept. Sleep and Cognition, Netherlands Institute for Neuroscience, Amsterdam
\textsuperscript{b} Dept. of Electrical and Computer Engineering, University of Wisconsin, Madison, WI
\textsuperscript{c} Dept. of Psychiatry, University of Wisconsin, Madison, WI
\textsuperscript{d} Dept. of Anatomy and Neurosciences, VUmc University Medical Center, Amsterdam
\textsuperscript{e} Dept. of Integrative Neurophysiology, VU University, Amsterdam

Introduction

Slow waves are a landmark of deep sleep and are thought to play a key role in preparing our brain to process new information. Slow waves are thought to travel over the cortex mostly in an anterior-to-posterior direction and a recent study has identified the cingulate cortex as one of their favorite routes. During wakefulness, cingulate cortices are also major hubs of information exchange in the brain. Therefore, we hypothesize that, without the beneficial effect of slow wave activity (SWA), the transfer of information along the cingulate cortex during the following day is reduced and, because of the directionality in SWA, the reduction is more pronounced in one direction than the other.

Methods

As a measure of effective connectivity, we used Granger Causality (GC) on high-density EEG between preselected sources during wakefulness, after normal sleep and sleep deprivation. The information flow of the brain was manipulated by asking 8 participants to keep their eyes open or closed for two minutes, while EEG signal was recorded from 64 electrodes. GC was assessed between three regions along the cingulate cortex for both directions: anterior-to-posterior and posterior-to-anterior.

Results

After normal sleep, GC from the posterior to the anterior cingulate cortex was higher during eyes-open than during eyes-closed, in agreement with enhanced flow of sensory information from the visual cortex to more frontal cortical areas. This increased posterior-to-anterior connectivity during eyes-open no longer occurred after sleep deprivation. In the opposite direction, anterior-to-posterior, GC was not different between eyes-open and eyes-closed during waking after normal sleep or sleep deprivation.

Conclusion

Sleep deprivation impairs the increased posterior-to-anterior information flow that is normally present during eyes-open wakefulness. This effect was limited to the posterior-to-anterior direction, which is involved in the transfer of sensory information to the frontal cortex. These findings suggest that slow wave activity has a preferential directionality in its restorative action, which is necessary to maintain the next day’s efficient transmission of sensory information to higher order cortical areas.

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TASK-INDUCED NEURONAL NETWORK CONNECTIVITY REAPPEARS DURING SLEEP IN HUMANS

Giovanni Piantoni\textsuperscript{a}, Ysbrand D. Van Der Werf\textsuperscript{a,b}, Ole Jensen\textsuperscript{c}, Cornelis J. Stam\textsuperscript{d}, Eus J. W. Van Someren\textsuperscript{a,e}

\textsuperscript{a} Dept. Sleep and Cognition, Netherlands Institute for Neuroscience, Amsterdam
\textsuperscript{b} Dept. of Anatomy and Neurosciences, VUmc University Medical Center, Amsterdam
\textsuperscript{c} Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen
\textsuperscript{d} Dept Clinical Neurophysiology, VUmc University Medical Centre, Amsterdam
\textsuperscript{e} Dept. of Integrative Neurophysiology, VU University, Amsterdam

Introduction
Research has shown that sleep helps consolidate recently acquired memory. One hypothesis suggests that neuronal connections that have been activated during a task are reactivated during subsequent sleep. In humans, local reactivation during sleep of recently activated cortical areas has been demonstrated, but until now there is no evidence of reappearance of connections between previously coupled distant cortical areas. The aim of the present experiment was to test whether task-induced oscillatory behavior of long-range cortico-cortical connections selectively reappears during subsequent sleep.

Methods
Magnetoencephalographic (MEG) data were acquired from eight participants during performance of two tasks, each on a separate day in balanced order. A mirror tracing task and a face-name association task were chosen because they engage different neuronal networks as they involve procedural and declarative learning, respectively. After each task, participants were invited to take a 90 minute nap, equivalent to the duration of a sleep cycle. Connectivity was assessed by correlating fluctuations in power between sensors in the beta frequency band for the tasks and in the slow oscillation band, delta band and spindle frequency band for sleep. We used the nonparametric permutation statistics to test whether sensor pairs that were more correlated in one task than in the other were also more correlated during the corresponding sleep periods.

Results
Sensor pairs that showed high beta-power correlations selectively during the procedural learning task were found to pair again, above chance level, in the delta band during subsequent sleep (p = .004). This reactivation of connectivity was not found in the slow-oscillation or spindle band. Recoupling could not be demonstrated for the task-induced beta-power correlations in the declarative learning task (p = .60). The connections that reappeared during sleep following the procedural learning task are located over the pre-motor and the parietal cortices, indicating process-specificity.

Conclusion
Connectivity between brain regions induced by a motor learning task, as identified by beta-power correlations between sensors, reappeared during subsequent sleep in the delta band. The reconnected areas are implicated in motor control and visuospatial processing. To our knowledge, our findings are the first to indicate that reappearance of oscillatory coupling in task-relevant neuronal networks occurs in humans.

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ALTERNATIVE METHOD FOR NON-INVASIVE AUTOMATIC POSITIVE AIRWAY PRESSURE THERAPY IN OSAS PATIENTS

L. C. Rohling\textsuperscript{a}; M. M. M. Eijsvogel\textsuperscript{a}; M. Wagenaar\textsuperscript{a}; F. H. C. de Jongh\textsuperscript{a,b}

\textsuperscript{a} Department of Pulmonary Medicine & Sleep, Medisch Spectrum Twente, Enschede, The Netherlands
\textsuperscript{b} Engineering Fluid Dynamics group, University of Twente, Enschede, The Netherlands

Introduction The mainstay of medical treatment of Obstructive sleep apnea syndrome (OSAS) is administration of non-invasive positive airway pressure (PAP) therapy during sleep while delivering continuous PAP (CPAP) or auto-adjusted PAP (APAP). APAP has generally been accepted as an alternative to CPAP in the treatment of OSAS. Meta-analysis has shown that APAP can control OSAS as effectively as CPAP, with the use of lower mean pressures. Although, this advantage is often outbalanced by higher peak pressures which occur due to artifacts confusing the algorithm. The intention of researchers is to determine and deliver the ‘right’ pressure to the individual patient within one night, but also from night to night. It remains to be examined whether optimization of the applied pressure can be attained by using the lowest possible minimum level and by limiting the maximum pressure to a different extent. The aim of this study was to investigate whether a new adjusted mode of APAP can improve patient adherence in comparison to fixed CPAP in present-day PAP therapy of OSAS patients.

Methods New diagnosed OSAS patients were selected for a single blind randomized crossover trial. During 12 weeks patients received two different PAP therapies, CPAP and restricted APAP (RAPAP). Prior to starting up PAP therapy patients received a manual CPAP PSG titration. The titration night was used to set the CPAP and RAPAP. The RAPAP pressure sets the pressure level 2 cmH\textsubscript{2}O around the titrated pressure. After 6 weeks there was a transition to the other PAP therapy. The REMstar Auto M-series (Philips Respironics Inc., USA) was used during this study. Data were collected by objective and subjective measurements. Objective: polygraphy during both PAP treatment modes, and by downloading the data of the PAP device. Subjective: sleepiness (Epworth Sleepiness Score (ESS)), quality of life (disease specific: Quebec Sleep Questionnaire (QSQ), and generic: SF-36), preference for treatment mode, and tolerance.

Results Thirty-nine OSAS patients were recruited of which 33 completed the study. After 6 weeks with RAPAP, the median AHI decreased (2.4 [0.2 – 27.6]/hour, \(p < 0.01\)) but did not differ compared to CPAP (\(p = 0.20\)). The compliance was similar between the treatment groups (CPAP: 6.6 [2.2 – 8.7] vs. RAPAP: 6.7 [3.7 – 8.9] hours/night, \(p = 0.33\)). The median of the mean applied pressure over 6 weeks RAPAP therapy was 8.0 [5.1 – 12.1] cmH\textsubscript{2}O and for CPAP 9.0 [5.5 – 13.0] cmH\textsubscript{2}O (\(p < 0.01\)). At the end of the study, patients expressed no significant preference for one or the other treatment. The subjective measurements ESS, SF-36 and QSQ showed improvement compared to baseline but no difference between treatment modes.

Conclusion Analysis of 33 patients demonstrated that RAPAP and CPAP therapy have equivalent improvement in major outcomes of sleep apnea, including daytime sleepiness, impaired quality of life, respiratory disturbance index, compliance, and preference. RAPAP showed the advantage of delivering lower pressures during the therapy period. The new alternative RAPAP therapy seems to fit within the conventional CPAP treatment.

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POOR SLEEP QUALITY AND FATIGUE BUT NO EXCESSIVE DAYTIME SLEEPINESS IN MYOTONIC DYSTROPHY TYPE 2

Alide Tieleman\textsuperscript{a}, Hans Knoop\textsuperscript{b}, Anton van de Logt\textsuperscript{b}, Gijs Bleijenberg\textsuperscript{b}, Baziel van Engelen\textsuperscript{a}, Sebastiaan Overeem\textsuperscript{a,c}

\textsuperscript{a} Dept. of Neurology, Donders Institute for Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{b} Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen
\textsuperscript{c} Sleep Medicine Centre Kempenhaeghe, Heeze

Introduction
In myotonic dystrophy type 1 (DM1), sleep disorders are common, with excessive daytime sleepiness (EDS) as a predominant feature. In myotonic dystrophy type 2 (DM2), the presence of sleep disturbances is unknown.

Methods
29 genetically proven DM2 patients were surveyed using the Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index (PSQI) and Checklist Individual Strength. The results were compared with 29 adult onset DM1 patients and 65 population controls, both matched for age and sex.

Results
Only 6.9\% of DM2 patients had EDS compared with 44.8\% of DM1 patients and 6.2\% of population controls (DM2-DM1: \(p=0.001\); DM2-controls: \(p=0.51\)). Sleep quality was poor (PSQI >5) in both DM2 and DM1 groups, and differed significantly from population controls (DM2 6.5+-3.0; DM1 6.2+-3.7; controls 4.3+-3.0; DM2-controls: \(p=0.002\)). Poor sleep quality was not explained by depression or other comorbidity but was mainly due to sleep disturbances as a result of nocturnal pain. Comparable with the DM1 group, DM2 patients experienced severe fatigue (DM2 38.7+-13.1; DM1 42.9+-8.5; controls 21.1+-11.1; DM2-controls: \(p<0.001\)). Results were not confounded by abnormal thyroid function or medication use.

Conclusion
These results provide new insight into the phenotype of DM2 and have consequences for clinical treatment. In addition, the absence of EDS in DM2 is a new discriminative feature with adult onset DM1.

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EFFICACY OF THE ‘TENNIS BALL TECHNIQUE’ IN PATIENTS WITH POSITIONAL OBSTRUCTIVE SLEEP APNEA SYNDROME

G.E. de Vries\textsuperscript{d}, P.M. Meijer\textsuperscript{d}, J.H. van der Hoeven\textsuperscript{a}, R.A. Feijen\textsuperscript{b}, B. Stegenga\textsuperscript{c}, and P.J. Wijkstra\textsuperscript{d}

\textsuperscript{a}Clinical Neurophysiology;
\textsuperscript{b}Ear, Nose and Throat Surgery;
\textsuperscript{c}Oral and Maxillofacial Surgery;
\textsuperscript{d}Pulmonary Medicine and Tuberculosis,
University Medical Center Groningen (UMCG), University of Groningen, Groningen, Netherlands.

Introduction
In obstructive sleep apnea syndrome (OSAS) collapsibility of the upper airway is increased in the supine sleeping position, resulting in an increase of apnea-hypopnea index (AHI) and severity of the respiratory events.

Aim
To assess whether the 'tennis ball technique' (TBT) prevents positional OSAS-patients (i.e. AHI minimally twice as high in supine position as in other positions) from lying on their back and whether this therapy is effective in reducing AHI, severity of events and excessive daytime sleepiness (EDS).

Methods
Thirty three patients with positional OSAS at baseline (14 mild, 17 moderate, 2 severe) were treated with TBT (Table 1). After at least 4 weeks a second sleep study under treatment was performed to assess differences between baseline and follow-up percentage in supine position, AHI, minimal oxygen saturation, maximal duration of respiratory events and EDS. EDS was measured with the Epworth Sleepiness Scale. Treatment was considered successful when AHI reduced below 5/hour or reduced at least 50%.

Results
The percentage of supine sleeping position reduced from a median (interquartile range (IQR)) of 33.2 (23.6-43.7) \% to 6.6 (0.0-13.4) \%, p<.001. AHI decreased from a median (IQR) of 15.4 (12.1-19.9) /hour to 6.0 (3.4-10.0) /hour, p<.001. Minimal oxygen saturation improved from a median (IQR) of 86 (83-88) \% to 87 (84-89) \%, p=.047. Maximal duration of respiratory events reduced from a mean (SD) of 60.3 (20.7) seconds to 49.8 (25.0) seconds, p=.046. Mean (SD) score on the Epworth Sleepiness Scale decreased from 11.2 (5.3) to 9.2 (5.3), p=.002. TBT treatment was successful in 23 of the 33 patients.

Conclusion
TBT is effective in reducing time spent in supine sleeping position and in reducing AHI, severity of respiratory events and EDS, at least on the short-term.

Abstract presented at the Netherlands Respiratory Society
INTERRELATIONS AND CIRCADIAN CHANGES OF EEG FREQUENCIES UNDER BASELINE CONDITIONS AND CONSTANT SLEEP PRESSURE IN THE RAT

Roman Yasenkov and Tom Deboer

Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands

Introduction. Similar to the nap-protocols applied in humans, the repeated short-sleep deprivation protocol in rats stabilizes slow-wave activity (SWA, 0.5-4 Hz) in the non-rapid eye movement (NREM) sleep electroencephalogram (EEG), thus reflecting a constant sleep pressure or sleep homeostatic level, whereas higher frequencies (7-25 Hz) in these conditions preserve their daily rhythm, therefore demonstrating a strong input from an endogenous circadian clock. How different EEG frequencies in rapid eye movement (REM) sleep and waking respond to these constant conditions, how they interrelate to each other within the different vigilance states, and which component of sleep regulation (homeostatic or circadian) is involved, remains unknown.

Methods. To answer these questions, we applied power spectral analysis and correlation analysis to 1 Hz bin EEG frequency data for different vigilance states in freely moving rats in constant darkness, under baseline conditions and during the repeated short-sleep deprivation protocol.

Results. Our analysis suggests that 1) 0.5-5 Hz frequencies in NREM sleep and higher frequencies in REM sleep (above 19 Hz) and waking (above 10 Hz) are sleep-dependent, and thus seem to be under control of the sleep homeostat, while 2) faster frequencies in the NREM sleep EEG (7-25 Hz) and 3-7 Hz activity in the REM sleep EEG are under strong influence of the endogenous circadian clock. Theta activity in waking (5-7 Hz) seems to reflect both circadian and behaviour dependent influences. NREM sleep EEG frequencies between 9-14 Hz showed both homeostatic and circadian components in their behaviour.

Conclusions. Thus, frequencies in the EEG of the different vigilance states seem to represent circadian and homeostatic components of sleep regulatory mechanisms, where REM sleep and waking frequency ranges behave similarly to each other and differently from NREM sleep frequencies.

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Yasenkov R and Deboer T. Interrelations and circadian changes of EEG frequencies under baseline conditions and constant sleep pressure in the rat. Neurosci 2011; 180: 212-221.
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