SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 23, 2012

This publication was sponsored by **Merck Sharp & Dohme**

Ipskamp Drukkers BV, Enschede

ISBN 978-90-73675-20-9

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Founded at Leiden, The Netherlands, June 7, 1990

ISBN 978-90-73675-20-9

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Published by
Dutch Society for Sleep-Wake Research

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PREFACE

Dear colleagues,

The NSWO proudly presents its 2012 issue of our yearly proceedings.

On July 11th this year we lost our honorary member Rudi van de Hoofdakker, one of the founding members and first vice-president of our society. As a clinical psychiatrist he recognized the importance of basic sciences of chronobiology and used light as therapy for his patients. In this issue you will find an extensive In Memoriam.

Sleep in the public domain

This year NSWO was again successful by increasing awareness for sleep and sleep disorders in the Netherlands .
Our PR committee successfully performed an internet based survey which showed that 28 percent of the working force suffers from insomnia due to work. People responded that they do not have enough time to get rest and an astonishing 25% of the responders reported the use of wake promoting substances to be able to do their work. Again this NSWO survey received widespread media coverage.
Moreover, the Dutch National Sleep Week has become a major stimulant for many members to share their knowledge with the general public through activities organised in their sleep centres. Our attention for this subject has also prompted the public media to report on our "24/7 society" and its influences on sleep quality, sleep quantity and our performance in the daytime. Even in top-class sport sleep is on the agenda!

Sleep in the professional domain

All clinical specialties involved in sleep have currently started their own committees to study, discuss and promote the importance of sleep medicine within their own societies. At present NSWO is working on the integration of all sleep oriented societies of medical specialists and technicians to establish one umbrella organization in which all these societies can work together. NSWO is happy with its representation in the board of the Taskforce for Sleep and Wake disorders of the Dutch Society for Neurology and the Federation for accreditation of Sleep Medical Centres.
Moreover, NSWO is the Dutch representative in Europe at the level of ANSS and ESRS, which, amongst others, oversees the European accreditation of sleep medical centres. Furthermore, we are proud with the recent election of our board member Tom de Boer in the scientific committee of the ESRS.

Sleep and teaching

The teaching committee of NSWO has formed a taskforce for the organization of teaching courses. This resulted in a well attended course on all aspects of sleep apnoea, which was held in cooperation with SWS-neurology on 1st of June 2011 . We will organize yearly such trainings courses on specific topics in sleep medicine. Furthermore we are happy to announce that NSWO will organize in June 2014 the 3rd conference on "AGING and SLEEP" in cooperation with the French society for geriatrics and sleep medicine.

Future goal

The NSWO board will serve as a platform to promote scientific basic research, the spread of knowledge and its combination with sleep medicine. We also aim to increase the understanding of sleep disorders and to develop better treatment options for patients and to promote the spread of knowledge in the public domain.
NSWO will continue to participate in the process of accreditation of Sleep Medical Centres in all its aspects. Finally, we are working hard on the integration of the many players working in the field of sleep research and sleep medicine into one large scientific and clinical society under the umbrella of NSWO.

Hans Hamburger, president

Amsterdam, November 2012

EDITORIAL NOTE

In the 23rd edition of the proceedings of the Dutch Society for Sleep-Wake Research we reflect on the death of one of the founders of our society. Rudi van den Hoofdakker passed away this summer. Many of you will know him as a colleague, teacher, and friend.

Ghizlane Aarab and Ritsaert Lieverse present the summary of their PhD thesis. The comments on the thesis are written by Herman van Beek and Ybe Meesters. I want to thank both for their effort to contribute to this issue. I am also very happy that Ton Coenen was willing to write a mini-review about the relation between the sleep-wake cycle and cognitive-behavioral performance.

The mini-papers are kicked off by last years winner of the Piet Visser poster price, Jessica de Wild-Hartmann. In this issue you will find 7 mini-papers, followed by 33 abstracts. On behalf of the scientific committee I want to thank all NSWO members who contributed to this issue. In addition, I want to thank my co-editors for reviewing the mini-papers, ensuring that the papers achieve the highest quality possible.

Regular readers of the yearbook will notice that the number of mini-papers this year is low. In the last decade, until 2008, the yearbook contained 20-30 mini-papers each year, with a record of 36 papers in 2005. Since then, the numbers slowly decreased. The inclusion of the abstract section after 2008 (11 mini-papers) seemed to speed up this process. In 2010 and 2011 the number of mini-papers was approximately 15. This year is an all time low with only 7 mini-papers contributed by the members.

The decrease may indicate a shift in priority among the members. In 2005, Ge Ruigt, then acting Editor in Chief, made the remark that a wider access to the proceedings could result in a lower submission rate. Scientific journals may consider the manuscripts appearing in *Sleep-Wake Research in the Netherlands* as normal publications, making it harder to publish the results elsewhere. Nevertheless, I want to call upon the members to keep sending in their papers. The scientific committee will increase its efforts by extending the deadline into the vacation season, increasing the opportunity to contribute.

In the last part you will find the list of members of our society. Together with more information about sleep research and sleep medicine in the Netherlands, this list is also available on the NSWO website (www.nswo.nl).

Finally, the support of Merck Sharp and Dohme, for the publication of our yearbook, is gratefully acknowledged.

Leiden, October 2012

Tom de Boer
Chair Scientific Committee
Chief Editor NSWO Proceedings

Not the time passes by, but you and me

In memoriam Rutger H. van den Hoofdakker

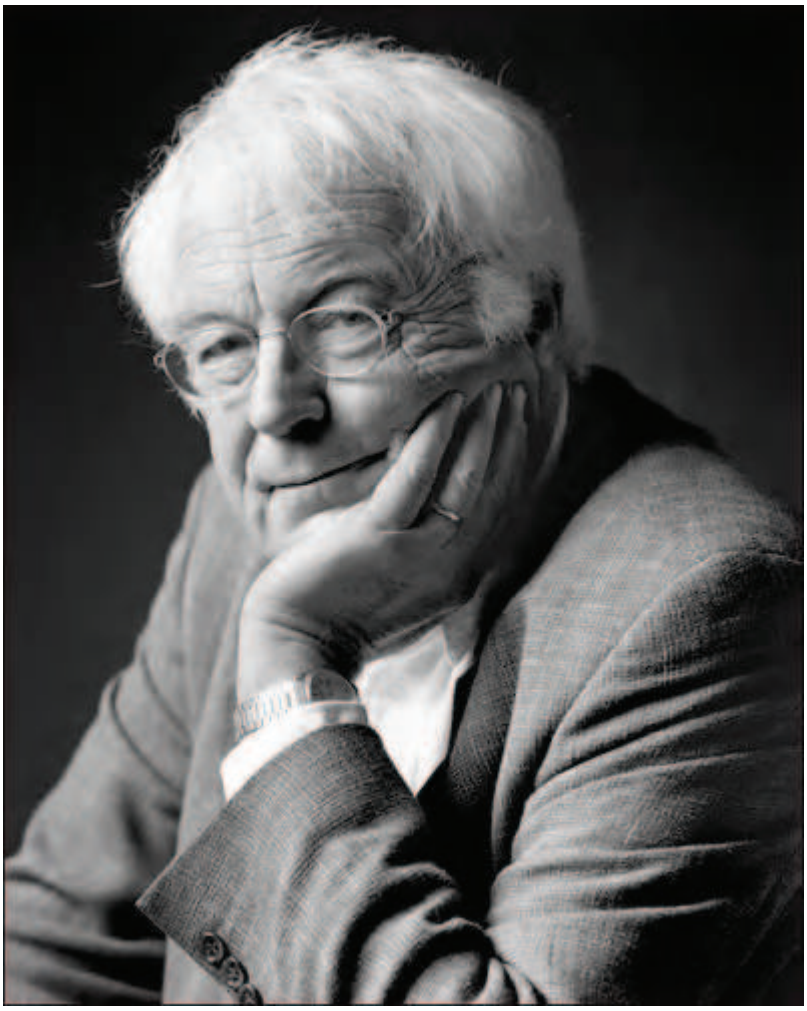
Domien G.M. Beersma, Marijke C.M. Gordijn, Serge Daan

Chronobiology, Centre for Life sciences, University of Groningen, The Netherlands.

On July 11th our friend and colleague Rudi van den Hoofdakker died in his home in Glimmen at the age of almost 78. Rudi was an honorary member of NSWO since his retirement because of his long term support of our society. He was one of the founders of NSWO back in 1990, and immediately became vice-chairman, which lasted for five years. Rudi was deeply convinced of the necessity of fundamental research for the development of treatment strategies for such complex affections as depression and other emotional disorders. He started in this field as a PhD student studying the EEG of sleeping cats. As head of the Department of Biological Psychiatry of the University Medical Centre in Groningen he broadly explored the therapeutic efficacy of sleep deprivation and light therapy. He was convinced that the patients deserved these chronotherapeutic interventions in combination with other means of treatment that had shown efficacy in well-designed experiments. Rudi was not only a fundamental researcher himself, he also was a psychiatrist who personally treated many patients, a teacher heavily involved in the education of general practitioners and psychiatrists, a concerned and inspiring PhD supervisor and an admired poet under the name of Rutger Kopland. Many of his poems are translated into a wide variety of languages.

In 2005 Rudi had a severe car accident from which he did not recover completely. He suffered from the scars to his mental performance, probably because of his persisting perfectionism that before had influenced his performance so much. Apart from the footprints that he left in his poems and his scientific publications we do have our own memories of long discussions at the kitchen table in Glimmen, of intensive scientific and political debates at various international locations, of searching mushrooms in the forests in Drenthe, of celebrating birthdays and other highlights, or just of receiving one of his very special postcards.

Rudi is no longer with us. On his coffin we could read the inscription ‘Niet de tijd gaat voorbij, maar jij en ik’ (Not the time passes by, but you and me). It is an example of the kind of comfort that Rudi gave us: the acceptance of what is unavoidable.



Prof. Dr. Rutger H. van den Hoofdakker (1934-2012)

ACCREDITATION OF SLEEP CENTERS IN THE NETHERLANDS

Al de Weerd
on behalf of the Federation of General SleepCenters (FSC)

Sleepcenter SEIN Zwolle-Groningen

Already for many years sleep specialists in The Netherlands wish to have a system of certification of individual specialists or accreditation of sleepcenters. The former was started by the NSWO in 2000, but proved to be not feasible. At that moment accreditation of centers was not accepted. Around 2006 the European Sleep Research Society published criteria for accreditation. Representatives of large general sleepcenters in The Netherlands used these criteria to start in the autumn of 2011 a system of accreditation by peer review of written reports and visitations.
Since that moment seven centers met the criteria and received their certificate as accredited general sleepcenter: Slotervaart, Amsterdam; SEIN, Zwolle; Kempenhaeghe, Heeze; Gelderse Vallei, Ede; Leids Universitair Sleepcenter; MCHaaglanden, The Hague; St Antonius, Nieuwegein. Two other centers are in the final stage of the process (Amphia, Breda and ZGT, Hengelo/Almelo). Three other centers will be visited in the autumn of 2012.
The goal of accreditation is to improve quality of work with as main parameters: quality of the staff, possibilities and quality of recording sleep and wake, quality and range of therapies and follow-up of patients, in- and out-patients logistic facilities, internal and external education in sleep and quality of scientific work.
Starting in the autumn of 2012 the FSC will welcome other general sleepcenters which aim at accreditation to join the process. Perhaps this will be possible as well for large centers dedicated only to treatment of sleep apnea in the near future. The final aim is to have 20-25 large accredited sleepcenters in our country, all members of the FSC.

For more information, contact the FSC via adweerd@sein.nl.

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PhD Theses

MANDIBULAR ADVANCEMENT DEVICE THERAPY IN OBSTRUCTIVE SLEEP APNEA

Ghizlane Aarab

University of Amsterdam, Amsterdam

Obstructive sleep apnea (OSA) is a condition characterized by repetitive complete or partial obstruction of the upper airway during sleep. There is evidence that links OSA to long-term cardiovascular morbidity, including hypertension, myocardial infarction and stroke, and to an increased risk of motor vehicle accidents. These cardiovascular co-morbidities and motor vehicle accidents result in an increased risk of mortality in OSA patients. Hence, untreated OSA is associated with serious medical consequences, which underlines the importance of timely recognition, accurate diagnosis, and effective treatment of this disorder.

Continuous positive airway pressure (CPAP) is generally considered the "gold standard" treatment for OSA. Although CPAP is a highly efficacious treatment, there is a need for other treatment options, because the effectiveness of CPAP is often limited by poor patient acceptance and tolerance, as well as by a suboptimal compliance. Nowadays, mandibular advancement devices (MADs) are widely prescribed for the treatment of mild-to-moderate OSA. These oral appliances are often considered by patients to be a more acceptable treatment modality compared to CPAP. In 2002, when we started with our placebo-controlled randomized clinical trial (RCT), especially case series were published on the therapeutic efficacy of mandibular advancement devices (MADs) in OSA patients. Consequently, there was not enough scientific evidence for the efficacy of MADs. Therefore, we decided to investigate three important aspects of MAD therapy in an RCT: (1) the time-variant nature of the apnea-hypopnea index (AHI) and its consequences for diagnosis and therapy evaluation in OSA patients; (2) the influence of mandibular protrusion on OSA signs and symptoms; and (3) the short-term and long-term effects of both MAD and continuous positive airway pressure (CPAP) in the treatment of OSA.

When using the AHI in the diagnosis and therapy evaluation of OSA, it is of importance that the AHI is stable over time. Therefore, the aim of the study in **chapter 2** of this thesis was to determine the variability of AHI during a follow-up of 10 weeks, and to describe a mathematical technique to asses its possible consequences for diagnostic and therapy evaluation purposes. From this study, it can be concluded that recordings can only confirm or deny the presence of OSA when the obtained AHI values lie outside a cut-off band surrounding the AHI cut-off point.

As a first step for the RCT described in this thesis, an adjustable MAD was developed with a constant vertical dimension at different mandibular positions. In **chapter 3** of this thesis, the initial efficacy of this MAD in the treatment of OSA was assessed in a pilot study. Further, it was aimed to evaluate the patients' compliance to the MAD therapy and to determine the feasibility of the procedures of this pilot trial for use in a future RCT. In **chapter 4** of this thesis, the influence of four mandibular protrusion positions, at a constant vertical dimension, on OSA signs and symptoms was assessed. On the basis of this study, it was recommended to start an MAD treatment in the 50% protrusion position as a result of a weighted compromise between efficacy and side-effects.

After the start of our RCT, several other RCTs have addressed the efficacy of MADs in the treatment of OSA. Their common control condition, CPAP, was usually found to be superior to MAD therapy. However, in these studies, only CPAP was titrated objectively. To enable an unbiased comparison between both treatment modalities, the MAD should be titrated objectively as well. The aim of the study in **chapter 5** of this thesis was to compare the effects of an MAD with those of nasal CPAP (nCPAP), following polysomnographically controlled titration of both treatment modalities. Further, in the study in **chapter 6**, both modalities were followed over a one-year period. Based on both studies, it was concluded that there is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA.

CONCLUSIONS

The following conclusions can be drawn from this thesis:

- It should be taken into account that in the diagnosis and therapy evaluation of OSA, there is considerable intra-individual variability between AHI recordings (**chapter 2**).
- It is recommended to start an MAD treatment in the 50% protrusion position in the treatment of mild-to-moderate OSA (**chapter 3** and **chapter 4**).
- There is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA, neither at the short-term (**chapter 5)** nor at the long-term (**chapter 6**).

Commentary on the dissertation by Ghizlane Aarab

MANDIBULAR ADVANCEMENT DEVICE THERAPY IN OBSTRUCTIVE SLEEP APNEA

Herman van Beek

Head dept. of Orthodontics, ACTA, Amsterdam

On October 5th Ghislaine Aarab defended her thesis: Mandibular advancement device therapy in obstructive sleep apnea.

From an interview: “I looked into the treatment of sleep apnea patients and compared the treatment with an oral snoring device with the positive air pressure treatment and a placebo treatment. The oral appliance was my topic of interest. The air pressure treatment is the proven golden standard, but rather testing for the patient. The oral device worked just as well in not too severe cases and showed less drop-outs long term. Therefore my conclusion would be that the oral snoring device would be the preferred choice in the treatment of sleep apnea.” (Source:www.acta.nl)

The research performed by mrs. Aarab led to a number of publications, compiled into her thesis.
The work was delivered with focus and thoroughness. First, the importance of multiple sleep centre investigations instead of one single investigation was demonstrated as the severity of sleep apnea apparently varies over time. Next, the efficacy of the mandibular advancement device was compared to the positive air pressure mask therapy, also after one year.

Comparable positive results were obtained in cases with mild to moderate sleep apnea and in view of the more limited number of drop-outs in the oral appliance group after one year, the oral device is considered first choice in the treatment of sleep apnea.

Attention was directed to the optimization of appliance construction, in particular to the amount of mandibular advancement at a given mouth opening. Too far forward would be uncomfortable and would perhaps increase the risk of dental movement and too little forward would perhaps not be effective. At an earlier stage, it was found that mouth opening without mandibular advancement would sometimes increase the risk of apnea. It seems likely that the individual optimum would depend on the peculiarities of the anatomy of the airway and the dentition, but the guideline of approximately 5 millimeters is useful and suitable for the start of treatment.

The research and the results described in this thesis are noteworthy and deserve a follow-up.

CHRONOBIOPSYCHOSOCIAL PERSPECTIVES OF OLD AGE MAJOR DEPRESSION, A RANDOMISED PLACEBO-CONTROLLED TRIAL WITH BRIGHT LIGHT

Ritsaert Lieverse

Free University of Amsterdam, Amsterdam

The research in my thesis focused on the effects of bright light treatment (BLT) in elderly patients with a major depressive disorder (MDD). We can conclude that we designed, performed and presented the largest Randomised Placebo Controlled Clinical Trial with BLT in nonseasonal MDD patients over age 60, and that our study yielded a reasonably clear outcome: bright light had a better antidepressant effect than placebo. Moreover, we found indirect support for the contention that therapeutic effects may in part be mediated by enhancements of circadian system functioning.

That a relatively robust effect size was obtained in 3 weeks is of interest in itself. Antidepressant drugs often need more time to evolve into significant effects. The effect size was reasonably large as compared to what might be expected of pharmacotherapy, and it occurred irrespective of using concomitant antidepressants or not. Additionally, we assessed social rhythms and actigraphy in elderly patients with major depression and healthy controls. We found that these methods may have practical applications, since SRM-5 scores contribute to the prediction of response on bright light treatment in elderly patients with MDD, suggesting that low social rhythm regularity reflects the need for strong Zeitgebers to successfully entrain the circadian system.We further confirmed the feasibility of actigraphy in detecting psychomotor disturbances in patients with MDD and in providing objective sleep measures, which resulted in information that differed from that obtained by subjective questionnaires. Therefore, in the treatment of sleeping problems in MDD, actigraphy may be of help in a realistic assessment of sleeping problems. Our findings warrant further studies to assess the contribution of the biological clock to the pathogenesis and symptoms of MDD.

Our results might have immediate clinical relevance for a common disorder in the elderly. The results support inclusion of chronotherapeutic strategies in the treatment of elderly patients with nonseasonal MDD. BLT may provide a viable alternative for patients who refuse, resist or do not tolerate antidepressants.

Commentary on the dissertation by Ritsaert Lieverse

CHRONOBIOPSYCHOSOCIAL PERSPECTIVES OF OLD AGE MAJOR DEPRESSION, A RANDOMISED PLACEBO-CONTROLLED TRIAL WITH BRIGHT LIGHT

Ybe Meesters

University Center for Psychiatry, University Medical Center Groningen, The Netherlands

When the results of a Dutch study are mentioned in the *New York Times* and *Time Magazine*, these results have to be impressive, which is exactly what Ritsaert Lieverse's study is.

The last three decades, light therapy has been the treatment of first choice in treating seasonal affective disorders (winter depression). Rixt Riemersma-Van der Lek studied the effects of light in the care of patients with dementia, but the study of the effects of artificial light in the treatment of the elderly with a non-seasonal major depression had to wait for Lieverse.

In an ambitious research design and labour-intensive project he has realized a great study. In his thesis he has published the trial design and the trial itself separately. Although he has been unable to reach all the goals of the trial designed, he has managed to include 89 patients. In an experimental design he has compared the effects of exposure to high-intensity blue light with the effects of low-intensity red light (placebo condition) and has found that the first is superior in treating non-seasonally depressed elderly subjects. Depression ratings improve, together with sleep efficiency and steepness of the increase in melatonin levels in the evening. According to the author, the results of a treatment with light are comparable with results of treatment with antidepressants in patients with a major depression. Validation of this statement in a direct comparison in a research project would be interesting. Lieverse's findings that exposure to blue light can be very effective in the treatment of depression have been confirmed in a recent study by Royer et. al.

In addition to the intervention with light, Lieverse has studied the effects of social rhythm therapy and the social context. Social activity is important, but is not always related to circadian rhythms. These findings make this thesis of great interest to the clinician with an interest in chronobiology.

The final chapter in the thesis consists of a Dutch article (now published), presenting an extensive overview of possible chronotherapeutic interventions in the treatment of a number of mental problems.

The publicity around the presentation of the study results is encouraging and may be helpful in developing new chronobiological treatment modalities for mood and sleeping disorders in which biological aspects are accompanied by psychological and social factors.

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Mini review

SLEEP-WAKE REGIME AND COGNITIVE-BEHAVIORAL PERFORMANCE

Anton Coenen

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PROLOGUE

The Canadian psychologist Donald O. Hebb (1904-1985) was strongly interested in the brain-behavior relationship, trying to understand how the state of the brain was expressed in behavioral and cognitive processes. In 1955 Hebb [1] formulated his classic theory on the relation between behavioral arousal and performance, which theory is illustrated in Figure 1. This relation can be described by an inverted U-shaped function in which behavioral efficiency or performance is inadequate during both low and high levels of arousal, and best at intermediate levels. Situations of drowsiness and sleepiness impair performance, while emotions and anxiety, associated with a high level of arousal, reduces behavioral efficiency. An intermediate level of arousal is best to perform in an optimal way. Since the level of arousal, the physiological substrate of alertness and vigilance, fluctuates over day and night, the degree of behavioral performance will also vary, implying that there is a circadian modulation of behavioral efficiency.

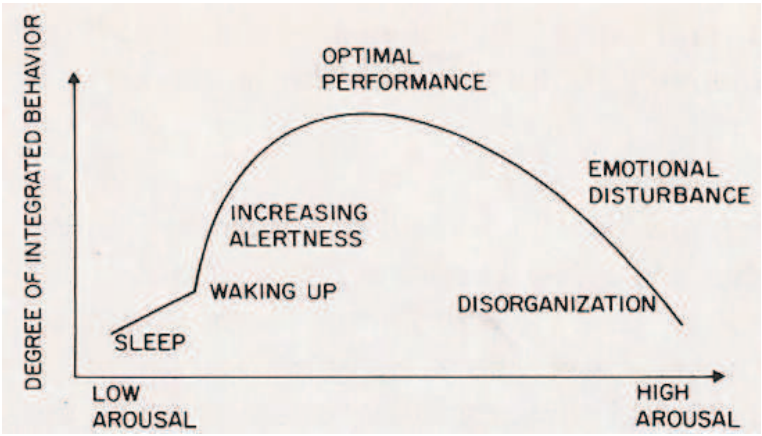

Figure 1. A representation of Hebb's theory on the relation between the level of arousal and performance, or degree of integrated behavior. Behavioral efficiency is optimal at intermediate levels of arousal, and lower at low and high levels. (After Hebb, 1955).

ALERTNESS: A HOMEOSTATIC-CIRCADIAN PROCESS

Cognitive and behavioral functions are regulated by a homeostatic process generating a pressure for sleep (process S), which depends on the prior amount of sleep and waking, and a circadian process responsible for the timing of sleep and waking (process C). Under normal conditions these two processes are aligned in such a way that an optimal performance during the day is provided, together with a strongly reduced responsiveness during sleep in the night.

The biological clock located in the suprachiasmatic nucleus contains the endogenous clock, entraining both the homeostatic and circadian processes to the daily rhythm of 24-hours. The two main biological rhythms are the sleep-wake rhythm, with a strong homeostatic component, and the core body temperature rhythm, with a strong circadian component [2] (Figure 2). All other physiological and cognitive brain and body rhythms are either coupled to the sleep-wake rhythm, or to the body temperature rhythm. The trigger for sleep forms the change from light to dark in the evening together with the decrease in body temperature, while the trigger for waking is the upcoming light in the morning, together with the increase in body temperature (Figure 2).

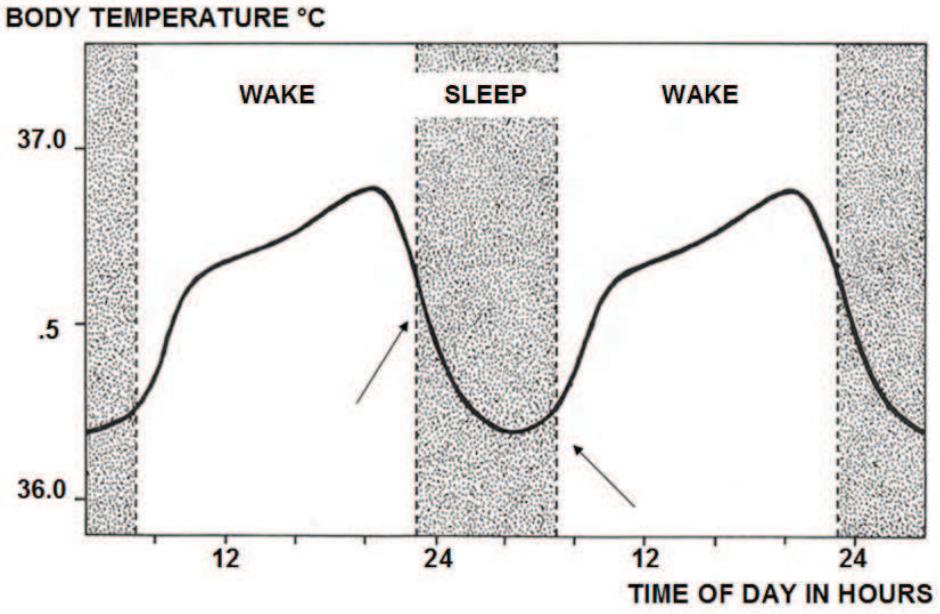

Figure 2. The two main body rhythms: the sleep-wake rhythm and the body temperature rhythm. The trigger for sleep (left arrow) is both the decrease in body temperature and the onset of darkness, while the trigger for waking (right arrow) is the rise in body temperature together with the morning light [3].

When dark comes in the evening the production of melatonin by the pineal gland starts. This 'dim-light melatonin onset', is a signal that prepares the brain for sleep. During deep sleep, dominating in the beginning of the night, the anabolic growth hormone (somatotropin) is released from the hypothalamus. Interruption of deep sleep abruptly stops the release of this hormone. On the phenomenon that the release of growth hormone is tightly coupled to the deep sleep, the 'restorative theory of sleep' is based [4]. Growth hormone promotes cell repair, necessary to restore the damages of the body following the efforts of a strenuous day. In this way somatotropin prepares the body for a new day. The release of the anabolic growth hormone is part of a complex process of the parasympathetic part of the autonomic system, influencing all bodily organs through the hypothalamic-pituitary axis, leading to rest and sleep.

Melatonin production is inhibited by light in the morning, indicating that it is time to wake up. The counter of the anabolic growth hormone is the catabolic hormone cortisol. The release of this hormone is part of the activity of the sympathetic wake system, influencing the body with epinephrine. During sleep the level of cortisol is low, but climbing slowly in the course of the night and reaching a top level in the early morning at awakening. This is the

'cortisol awakening response'. The pattern of this response to waking is relatively stable and has a strong diurnal variation, with generally a high level early in the morning and falling during the day [5]. The amount of cortisol reaches its lowest level at about midnight to 4 o'clock in the night. One of the primary functions of the sympathetic adrenal gland hormone cortisol is to increase blood sugar through gluconeogenesis, and so to provide the body with energy. The circadian modulations of the levels of growth hormone and cortisol are illustrated in Figure 3.

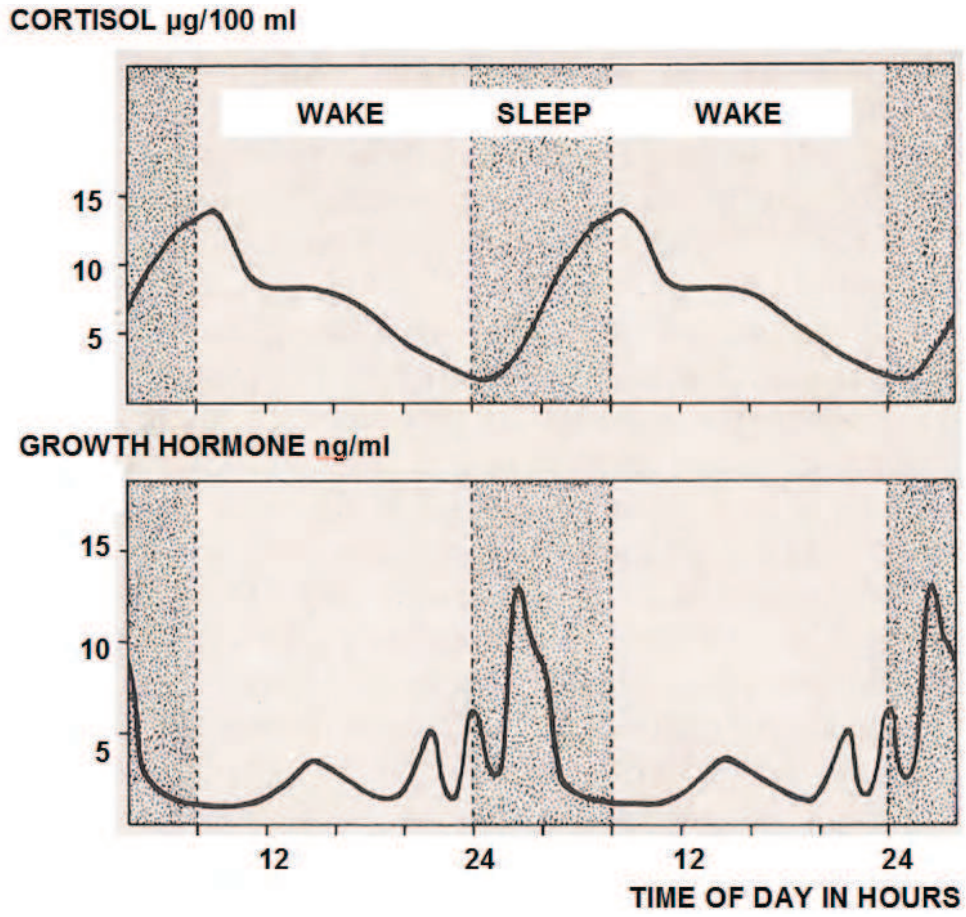

Figure 3. Circadian rhythms of two main sleep-wake hormones: the catabolic hormone cortisol and the anabolic growth hormone [3]. The concentration is measured in the blood of healthy, young adults. Note that the levels of these two hormones are each other's mirror image: when one is high, the other is low. Note also that growth hormone level increases after each meal, but that the top concentration is occurring during the first hours of sleep, where deep sleep dominates.

RHYTHMS OF BIOLOGICAL PROCESSES

In the early morning immediately after awakening behavioral performance is growing in a fast way. The phenomenon that it takes some time to get an optimal behavioral performance following awakening, is known as 'sleep inertia' [6]. This physiological state is characterized by a subjective feeling of grogginess. The impaired alertness may interfere with the ability to perform mental or physical tasks. A causal linkage between the recovery from sleep inertia and the dynamics of the cortisol awakening response is often suggested, but still

not completely proven [7, 8]. This should imply that sleep inertia is dissipated when the cortisol response is maximal. In line with this it is sometimes assumed that the cortisol level is related to performance, especially when it concerns physically demanding and strenuous behavioral performances. These should be best in periods with the highest cortisol amount. It appeared, however, that several physically demanding performances have an acrophase in the late afternoon.

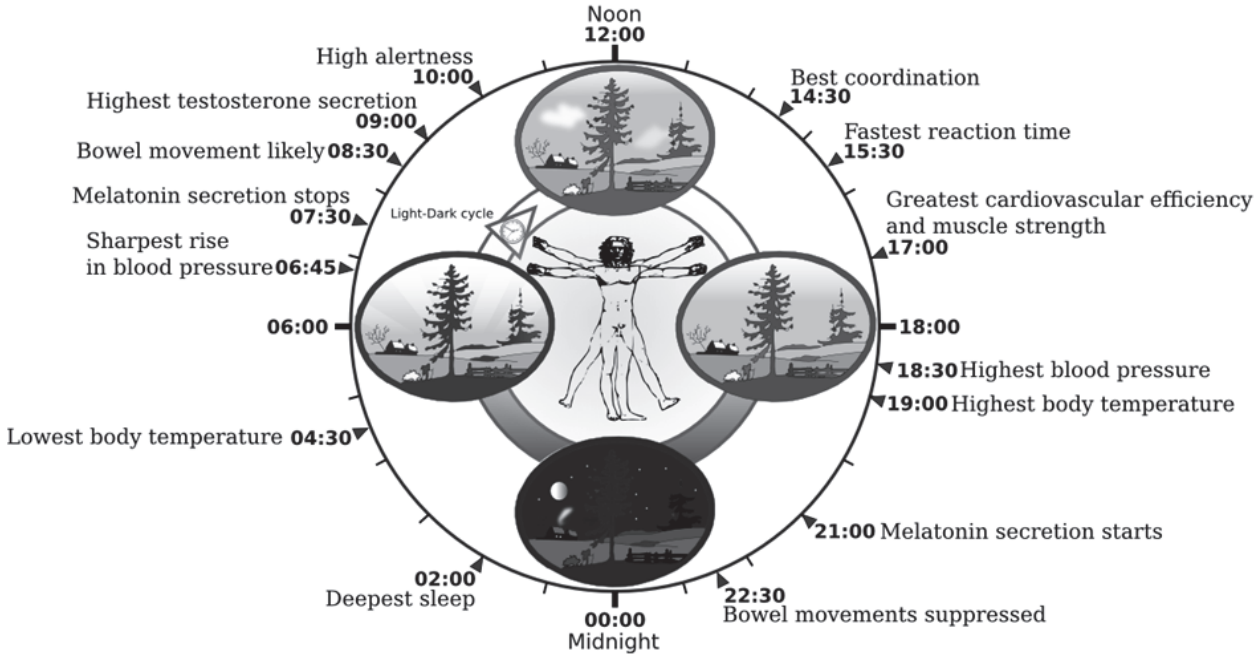

Figure 4. This diagram shows the acrophase of daily rhythms of a number of physiological and cognitive processes in humans with a normal sleep-wake pattern [9].

Especially those performances, with components focusing on muscle strength and high power efforts have peak values in the late afternoon, around 5 pm [10]. This is also the case for reaction times, which are fastest around this time [11]. The body shows the highest speed and the maximal power in the late afternoon and it seems that the rhythms of these physiological parameters are coupled to the rhythm of the core body temperature, having its acrophase around the same time. Also the efficiency for simple tasks, which can be performed in an almost automatic way, shows identical time-of-day effects [12]. A higher body temperature represents a physiological arousal that enhances human performance [13]. This provides strong support for the already classic hypothesis of Kleitman and colleagues [14] that body temperature is the underlying mechanism modulating neurobehavioral performance. This is consistent with the arousal hypothesis saying that within an optimal thermal zone a higher body temperature is associated with a higher performance.

The time-of-day fluctuations in the domain of cognitive performance measures show a more complex picture. Circadian fluctuations are influenced by a number of parameters such as task complexity, ageing and chronotype of the person, as well as task motivation. The picture that emerges from this interplay of multiple factors is complicated and only some

main lines can be given here (see for review Schmidt et al., [15]). Memory retention often peaks in the morning, which is already described by Ebbinghaus [16] and by Jenkins and Dallenbach [17]. This is often explained by the positive effect of the quiet state of sleep on the consolidation on learned material. On the other hand, complex cognitive tasks, such as logical reasoning tasks, peak in the late morning, where alertness shows a maximum [18]. However, the performance on the 'psychomotor vigilance test', a widely used test for sustained attention, is fairly stable over the entire day [19]. A number of related cognitive tasks show such a performance rhythm, which is probably due to the rising circadian performance drive during the day, opposing and balancing the decreasing performance power caused by the declining homeostatic wake pressure [15]. The presumable fact that some tasks and modulating factors are more vulnerable to variations in the circadian system and others to changes in the homeostatic system, may explain the diversity in time-of-day fluctuations of cognitive processes [20]. Stated in a simplified way, it can be inferred that three major profiles of cognitive-behavioral time-of-day variations exist: those bound to the wake pressure with a peak in the morning; those linked to the circadian rhythm of body temperature with a peak in the late afternoon, and those coupled to both rhythms, with a relatively flat profile during the day. All three show an extended nadir in the night. Specific circadian rhythms of a large number of cognitive tasks can be found in the review paper of Schmidt and colleagues [15].

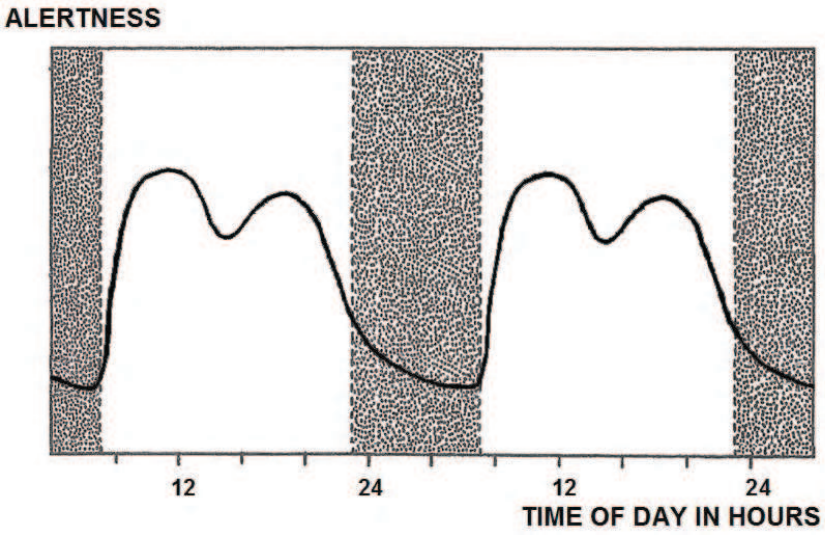

Figure 5. Circadian rhythm in alertness. In this double plot the degree of alertness is indicated in arbitrary units, showing peaks in the morning and afternoon, interspersed by the post-lunch dip. The figure is constructed on the basis of data from Åkerstedt and Folkard [21], Lavie [22], van Dongen and Dinges [20], Schmidt et al. [15] and Mongrain et al. [23].

POST-LUNCH DIP AND SIESTA

Figure 5 shows the circadian rhythm of alertness, as can be drawn from several literature data. Alertness, or vigilance, is a state with a fairly high physiological arousal in which continuous attention to events is paid, with the ability to react to them quick. This

multidimensional construct cannot be determined directly, but only indirectly with a measurable covariate, such as, for example, a subjective alertness scale, a psychomotor vigilance task, an electroencephalogram, or a sleep latency test. Alertness climbs up in a fast way after awakening, reaching a maximal plateau from about 8 am until 8 pm, which gradually slopes in time. Most often, but not always, a dip in this plateau around 3 pm can be noticed. The post-lunch dip is formed by the declining homeostatic morning component associated with a rising sleep propensity and an opponent compensation process taking care for a growing alertness in the afternoon [21]. The dip occurs in most people, even when the individual has taken no lunch. However, it is stronger after a heavy lunch, which is caused by the parasympathetic digestion process, starting directly after eating. This parasympathetic process is associated with an increased sleepiness. The existence of a post-lunch dip in performance is a genuine phenomenon, related to an innate human propensity for sleep [24]. The decrease in performance is expressed in a lower productivity of an averaged worker (Figure 6). It is striking how the profile of productivity over the day follows the circadian alertness profile. Both are slowly decreasing in the course of the day, and both show an extra dip in the early afternoon. An obvious conclusion is that productivity and the level of alertness and vigilance are strongly related.

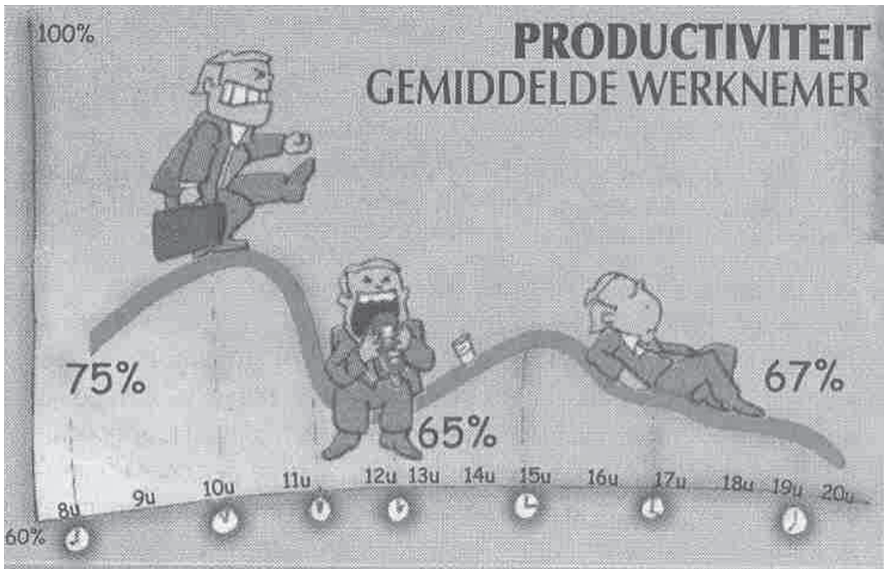

Figure 6. This graph, which recently appeared in the Dutch newspaper De Telegraaf, shows the productivity of an averaged employee over the day. Productivity is expressed in the number of products produced per hour worked.

In several countries with a hot climate a long afternoon nap, called siesta, is a common phenomenon. The siesta is a good way of passing in a pleasant way the hottest part of the day. This implies that the afternoon siesta is an integral part of many cultures throughout the world. Mostly this nap takes place from 2 pm to 4 pm. However, the post-lunch break represents a collision of biology and economics. In Spain the traditional siesta lasts almost three hours, which custom is almost regarded as a kind of a national right. But the country's economy feels that daytime napping is rather unproductive; reason that the long duration of the siesta is currently under discussion. Nevertheless, seen from a biological perspective an afternoon nap or siesta is rather refreshing. The importance of daytime naps has indeed been recognized for some time. A mid-afternoon nap has positive effects upon the maintenance of

the daytime vigilance level and enhances performance and self-confidence. Many reports also show an overall improvement in emotional state with naps. How long do the naps need to last to induce these positive effects? A nap which is shorter than 5 to 10 minutes has few benefits, whereas naps of between 30-60 minutes induce restorative effects on biological functions that last throughout the day. On the other hand, naps that last longer can actually cause the person to enter deep sleep stages, leading to sleep inertia upon awakening [25].

It seems reasonable to assume that napping at the work place should be possible and even encouraged, with the creation of facilities for employees for such a 'power nap'. Despite the fact that its implementation in industry raises practical issues, napping can be considered as a possible strategy to increase the vigilance level and productivity of workers. The optimal length for a power nap is about 40 to 60 minutes, which is long enough for restorative effects and short enough to prevent sleep inertia and also to jeopardize the nightly sleep [26].

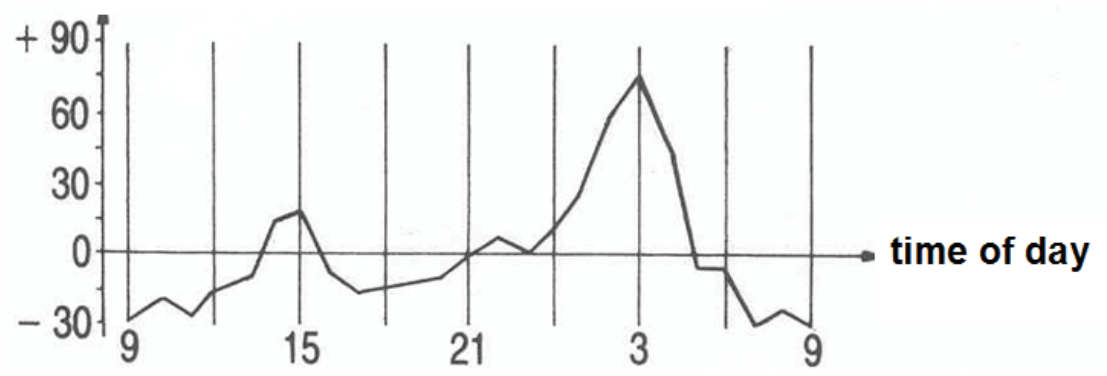

Figure 7. Temporal distribution of vehicular accidents displayed as a function of time of day. The mean number of daily accidents is expressed by the '0' line. Percentages higher and lower are indicated. The number of accidents is related to the traffic density. This graph represents the situation for Germany [27], but holds also for Israel [22], as well as for the United States [28].

TEMPORAL DISTRIBUTION OF ACCIDENTS

After 8 pm the level of alertness drops down to reach low values during the night. The diminished capacity to function is lowest in the period between 1 and 7 am. Sleepiness with low vigilance, low performance and long reaction times, is causing human failures. Most errors occur at times of day associated with a sleepy brain. Almost every automobile driver knows the treacherous brief periods of sleep, called 'microsleeps', causing falling asleep at the wheel [29]. Though most drivers have experienced a lucky escape from this frightening dangerous situation, several found death. Even the famous sleep expert, the American REM sleep discoverer Eugene Aserinsky, as well as the famous Dutch sport reporter Theo Koomen, were involved in fatal fatigue related car accidents. Figure 7 displays the number of sleepiness related vehicular accidents over day and night. Two zones of vulnerability within the 24-h cycle, corresponding with the two-peak rhythm in sleep tendency, can be identified: a major primary peak in the night and a smaller secondary one during the post-lunch period. Several immense industrial accidents, threatening public health, begun with human omissions in nightly hours. At Chernobyl the nuclear catastrophe started with a human error at 1.23 am, the Bhopal gas tragedy in 1984 began with an unnoticed leakage at 1 am, while at the same time of the night the oil tanker Exxon Valdez run aground in 1989, spilling huge amounts of

oil. The Three Mile Island nuclear plant accident in 1979 started with the overlooked loss of coolant water at 4 o'clock in the night [28].

THE OPTIMAL DAY-NIGHT REGIME FOR PERFORMANCE

There is strong evidence that sufficient shortening of the sleep process compromises performance and alertness. To avoid alertness and performance problems during the day, it is recommended that the average adult person requires 8 to 9 hours of sleep per night. This is longer than what is common; for example in The Netherlands the mean length of sleep is approximately 7.5 hours, which is even longer than most Europeans, who sleep on the average 7 hours. There are arguments to state that many people are continuously sleep deprived [30]. Research indicates that when nocturnal sleep periods are reduced by more than one hour per night compared to a decade ago, this results in an overall reduction of daytime alertness. It is estimated that a significant sleep loss exists in perhaps one-third of the population. Given the magnitude of this sleep debt, it is not surprising that sleepiness and fatigue are main factors in many vehicular accidents. A sleep extension study suggests that the average underlying sleep tendency in young adults is about 8.5 hours per night [31]. Thus, the average reported sleep length of 7 hours is probably too short, and a sleep length of less than 6.5 hours can even be disastrous. Given the alertness function of sleep and the increasing consequences of sleepiness, it is necessary that these processes given its major impact, must get more societal attention.

Studies are already underway to investigate the effects of the extension of sleep on measures of alertness, performance and daytime sleepiness. Young students reporting minimal daytime sleepiness were allowed to sleep as long as possible during a sleep extension period. All showed a significant increase in sleep during the extension period. Moreover, the extended sleep gave rise to a substantial improvement in daytime alertness, reaction time, and mood [32]. A specific study was performed in basketball players [33]. Subjects obtained, during a period of 5-7 weeks, as much nocturnal sleep as possible during a sleep extension period with a minimum time of 10 hours in bed each night. Improvements in basketball performance after that period indicated that optimal sleep is presumably beneficial in reaching peak performance. Replication and extension of these studies with more measures of performance is warranted.

The interest in learning fluctuations over the day is an old issue, and already early studies have focussed on the assessment of the most favourable time of day for teaching in schools. In the learning courses in school a number of aspects are coming together, and each aspect seem to have its own specific circadian variation, making it difficult to choose for a timetable optimal for all kinds of learning. Nevertheless, most researchers regard the morning as the most adequate time for learning, as expressed in the 'biorhythm model'. In this respect an interesting experiment was recently performed by Kvint and colleagues [34]. They used a sequence-learning task to assess whether the time-of-day is relevant for acquisition. Such sequence-learning task consists of a declarative, explicit component and a kinematic, implicit component. It turned out that the best time for fast and efficient acquisition of new declarative material is the morning, while the kinematic aspects of skill acquisition were not sensitive to the time of day. The finding that the acquisition of the declarative component of a motor skill is better in the morning, is in agreement with most studies on the acquisition of declarative and explicit material (see Schmidt et al. [15] for a review). The results showing that the time of training does not affect the acquisition of kinematic-related skills are in agreement with

studies on the speed optimization of motor sequence learning [19]. The decreased declarative learning in the afternoon and evening hours could be related to decreased attention at this time of day. Indeed, both circadian rhythms and homeostatic pressure influence resources necessary for attention and memory. The differential effects of time of the day on the acquisition of speed and motor related components, which are performed in a more automatic way, might be due to the fact that these require less control and thus alertness resources, while the increase in body temperature is positive for the execution of these motor components. Though a fruitful beginning has been made with these studies, a more detailed insight on the time-of-day effects of several types of learning more research is necessary.

EPILOGUE

Currently, knowledge of the variations over the day of neurobiological functions is scarcely exploited. Schools use many different time schedules and debates are going on which schedule is the best. Research is now pointing to time tables in which courses with a focus on declarative learning components can better be instructed in the morning, while the afternoon is better suited for courses with a focus on motor learning and sport performance. Moreover, a nap in between the two main parts of the day has advantages. Firstly, it provides the body with new energy, and secondly a nap is profitable for consolidating that what is learned. Also in sport, knowledge of circadian variations in achievements for the several, often quite diverging branches of sport, some with more accent on cognitive abilities and other on physical capacities, is worthwhile. For example, the insight that the body is fastest in the later afternoon is useful knowledge. An adequate use of the various time-of-day variations may have a major impact on human productivity, on school achievements, on sport performances, as well as on the reduction of traffic accidents.

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Annual Proceedings of the NSWO
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Jessica de Wild-Hartmann (l) receives the Piet Visser Poster price 2011 (picture by K. Schreuder)

SELF-REPORTED SLEEP AS PREDICTOR OF AFFECT IN DAILY LIFE AND FUTURE DEPRESSION

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INTRODUCTION

Sleep- and affect regulation are closely related. In major depression, disturbed sleep (predominantly insomnia) is conceptualized as key symptom as well as possible predictor[1]. In the general population, sleep loss has been associated with emotional dysregulation, e.g. increases in negative affect and decreases in positive affect [2, 3]. However, the directionality and dynamics of daily sleep- and affect regulations in natural circumstances have received little research attention.
The aim of the current study was twofold. First, to prospectively investigate the day-to-day associations between self-reported sleep and daily affect, the Experience Sampling Method (ESM) was used, allowing for the examination of (possible bi-)directionality of sleep-affect associations. Second, to examine the association between baseline sleep reports and future depression.

METHODS

621 women from a population based survey (originally recruited to study depression in females) underwent a five day ESM protocol[4] at baseline, assessing prospectively positive and negative affect ten times a day for five days, along with daily assessments of self-report sleep (sleep quality, sleep latency, sleep period and number of awakenings). Depressive symptoms (continuous; SCL-90[5]) and the presence of a DSM-IV diagnosis of depression (dichotomous; SCID-I[6]) were assessed at baseline and at four follow-up assessments (last assessment after approximately 1.2 years, see Figure 1). To establish directionality in the day-to-day associations between sleep and affect, sleep variables and affect measures were analyzed in turn as predictor and outcome measures in lagged analyses using mixed regression. Subsequently, the baseline sleep measurements were used as predictor of future depressive symptoms and the presence of depression.

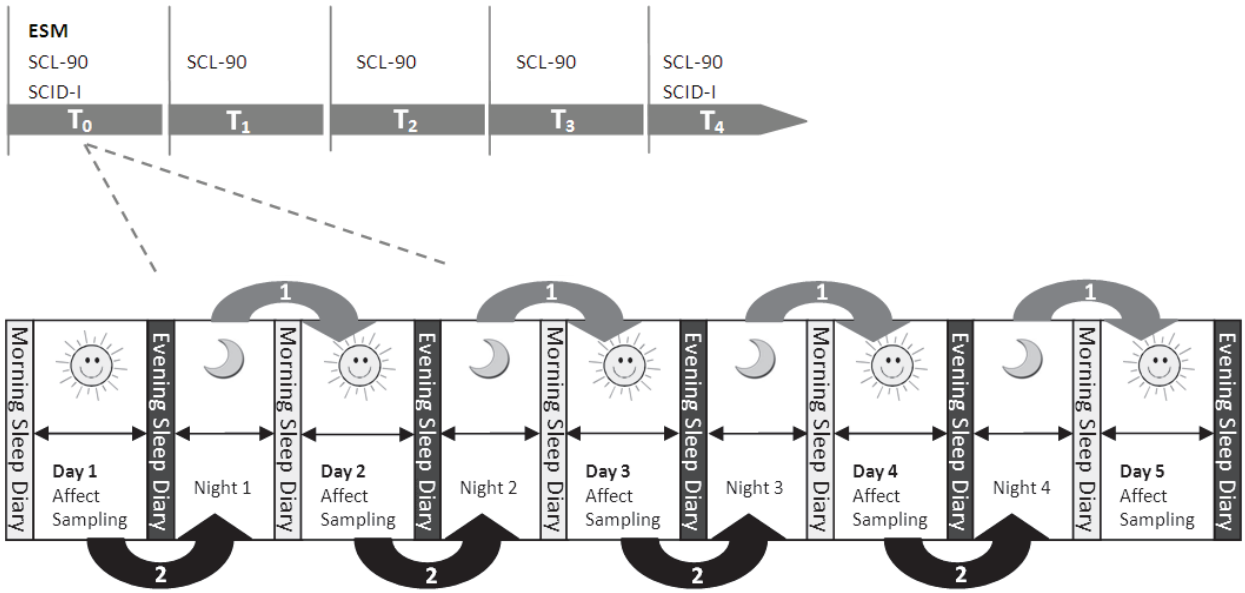

Figure 1. Upper part: Study procedure. The study consisted of five parts: A baseline part (T_0), in which the 5-day ESM study took place, and four follow-up assessments (T_1-T_4). T_4 occurred approximately 1.2 years after T_0.
Lower part: ESM study protocol. The ESM design allows for the investigation of the association between sleep and prior affect (arrow 1), as well as subsequent affect (arrow 2). ESM= Experience Sampling Method, SCL-90= Symptoms Checklist-90 (depressive symptoms); SCID-1= Structured Clinical Interview for DSM-IV Axis 1 (diagnosis of depression).

RESULTS AND DISCUSSION

Directionality of sleep-affect associations in daily life (see Figure 2).

Daily self-report sleep variables and subsequent positive affect were consistently associated, particularly sleep quality and positive affect (β=.06, p<.001). There was one significant association between sleep quality and subsequent negative affect (β=-.03, p<.001). Generally, the associations between sleep and subsequent affect were stronger than between sleep and prior affect. There were no significant associations between any sleep variable and prior affect. There was only one significant association between sleep and positive affect: positive affect predicted subsequent sleep quality (β=-.04, p=.019).

Baseline sleep as a predictor for depression (see Figure 3).

Baseline sleep variables, with the exception of sleep latency, predicted depressive symptoms over the follow-up period (ranging from β= -.08, p=.004 to β=-.07, p=.017).Sleep quality and number of awakenings predicted a diagnosis of depression (according to DSM-IV) after 1.2 years (OR = 0.27, p <.001 and OR =1.68, p =.032, respectively).

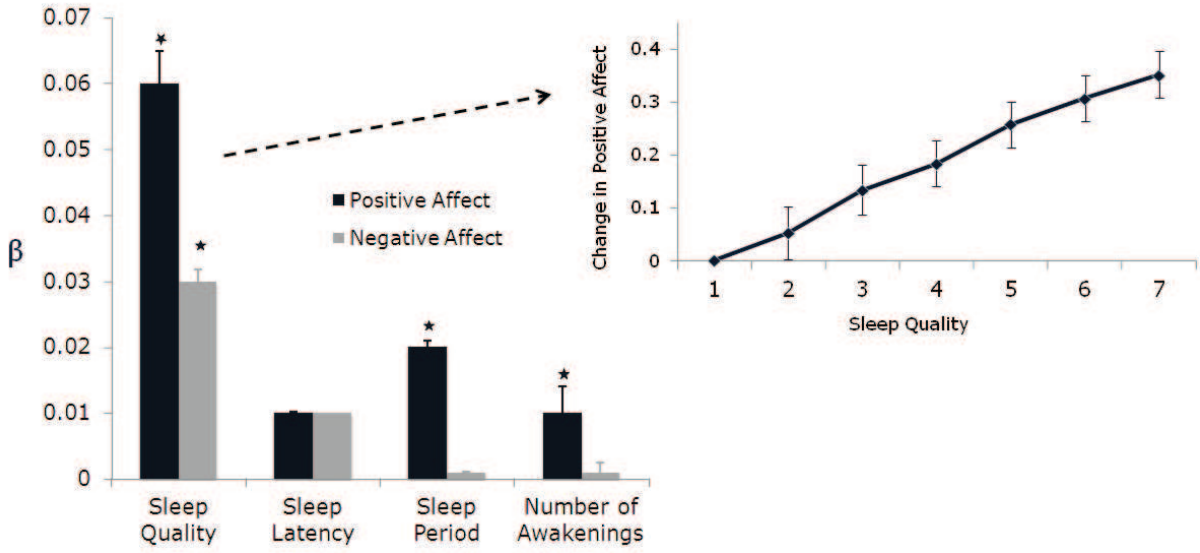

Figure 2. Standardized effect sizes for the association between sleep variables and subsequent positive and negative affect.

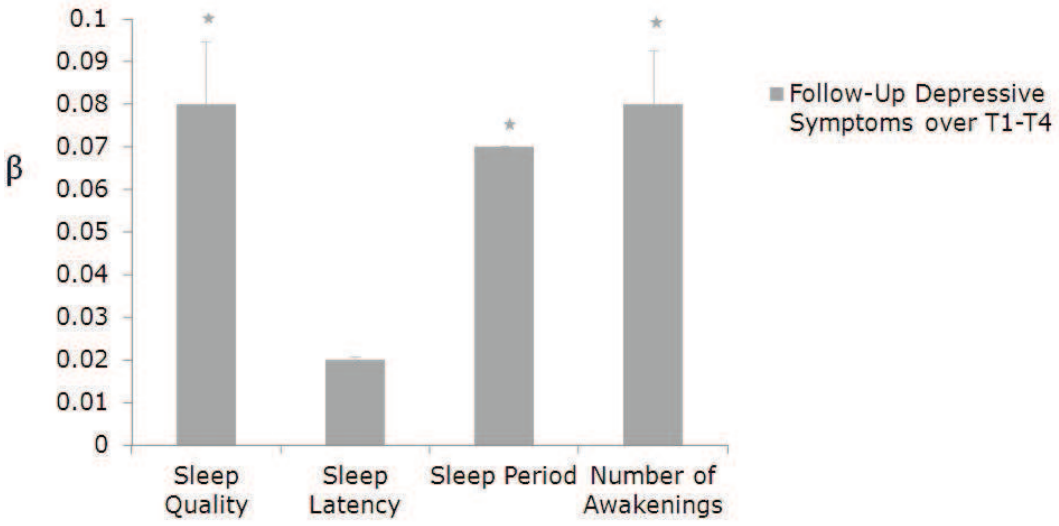

Figure 3. Standardized effect sizes for the association between baseline sleep and follow-up depressive symptomatology measured over T_1-T_4 (SCL-90).

CONCLUSIONS

The results of the present study demonstrate a strong association between subjective sleep and affect in women from the general population, both during subsequent days as well as longitudinally. Low sleep quality, increased nightly awakenings and a longer sleep period were associated with reduced positive affect during the following day. In contrast with our expectation, the association between sleep and momentary affect appeared not bidirectional: subjective sleep was associated with subsequent rather than with prior affect. Furthermore, sleep predicted the appearance of depressive symptoms as well as depression. This confirms earlier findings[1] that disturbed sleep is apparently a risk in the onset of depression.

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Annual Proceedings of the NSWO
Volume 23, 2012

Research papers

EEG BASED PERSONALIZED MEDICINE IN ADHD: REFLECTING DIFFERENT ETIOLOGIES?

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INTRODUCTION

The objective of this series of studies was to investigate the value of EEG markers for predicting treatment outcome to stimulant medication in ADHD and investigate if such EEG markers can be used to improve treatment outcome to neurofeedback. Furthermore, we attempted to interpret and integrate these findings into a conceptual framework in line with recent research and recent insights into the pathophysiology of ADHD.

The use of EEG in predicting treatment outcome in ADHD has a long history, where in 1973 Satterfield[1] already described EEG features associated with favorable treatment outcome. More recently, since the term Personalized Medicine was coined and the adoption of Personalized Medicine by the FDA, this approach is receiving further interest and this approach appears very promising for psychiatry, given the suspected heterogeneity of neurophysiological abnormalities within psychiatric disorders.

METHODS

The EEG of 49 children with ADHD (6-17 yrs.) and 49 healthy controls (7-18 yrs.) was assessed before treatment. Treatment consisted of prescription of stimulant medication to ADHD children, and these ADHD children were re-assessed after at least 4-weeks on medication and performance on a CPT-test was used as a measure of treatment response. For the neurofeedback study, 21 ADHD patients were treated with personalized neurofeedback protocols, based on their individual EEG. Improvements on behavior (ADHD rating scale), sleep (PSQI) and neurophysiology (EEG and ERP) were assessed.

RESULTS

Responders to stimulant medication were characterized by excess frontal alpha ($p=.018$) and frontal theta waves ($p=.025$)[2]. A slowed individual alpha peak frequency (iAPF) predicted non-response to stimulant medication, but both frontal theta and slow-iAPF subgroups are reflected in an increased theta/beta ratio[3]. Children with ADHD demonstrated a lower EEG vigilance as compared to controls, and there was a trend for lower EEG vigilance to be associated with better treatment response[4]. Personalized neurofeedback treatment resulted in a response rate of 76%, normalized sleep ($p=.001$), increased ERP N200 amplitude ($p=.014$) and P300 amplitude ($p=.004$) and decreased SMR EEG power ($p=.009$)[5]. No correlation between neurofeedback response and iAPF was found for ADHD symptoms.

CONCLUSIONS

In ADHD, several EEG sub-groups were found to be associated with treatment outcome to stimulant medication. The sub-group with a slow iAPF was found to be associated with non-response to stimulant medication[2]. It was further found that the often-reported Theta/Beta ratio in ADHD reflects both the excess theta group and slowed iAPF group, and given their differential response to treatment, this warrants future studies to dissociate these 2 EEG subtypes[3]. The slowed iAPF likely reflects a generic predictor for non-response since it is also associated with non-response to antidepressants, rTMS in depression and antipsychotics (for overview see [6]). This endophenotype deserves further study and can be used to more specifically develop new treatments for this group of non-responders, most likely focusing on interventions that increase cerebral blood-flow.

Another sub-group reflective of impaired vigilance regulation (excess frontal theta and frontal alpha) was found to be associated with favorable treatment outcome to stimulant medication[2,4], in line with earlier studies. Personalizing neurofeedback treatment based on these pre-treatment EEG sub-types resulted in larger effect sizes for inattention as compared to previous studies, however these findings require replication in a larger controlled study.

The core-pathophysiology of the specific 'impaired vigilance regulation' sub-type is hypothesized to result from a circadian phase delay resulting in sleep onset insomnia (SOI), in line with studies demonstrating that 70-80% of children and adults with ADHD are characterized by circadian phase delay and subsequent SOI[7,8]. In this view the effects of stimulant medication are hypothesized to result in symptom suppression, by increasing vigilance during the day, not directly affecting the core pathophysiology. This might explain the limited long-term effects of stimulant medication as reported in the NIMH-MTA trial, but might also shed more light on the causes of ADHD symptoms and thus new treatments with better long-term outcomes. Circadian advancing treatments (such as melatonin and bright light) have been found effective in ADHD and these treatments affect the suprachiasmatic nucleus, which has been shown to project to the noradrenergic locus coeruleus (LC), thereby explaining the vigilance stabilizing effects of such treatments in ADHD. Another treatment alternative for the treatment of ADHD is neurofeedback. Neurofeedback has been demonstrated to impact on the sleep spindle circuitry, resulting in increased sleep spindle density during sleep and improvements on sleep such as shorter sleep latencies and increased total sleep time (for review see [9]), and it is hypothesized that this results in normalization of SOI and subsequently affects the noradrenergic LC, resulting in vigilance stabilization (for review see [9]).

Thus, EEG holds promise in identifying subjects who might be responsive and unresponsive to stimulant medication and neurofeedback, though these findings should be replicated in larger studies, such as the iSPOT-A study currently underway, recruiting more than 500 patients with ADHD who are prescribed with methylphenidate, and the study designed by the Collaborative Neurofeedback group. Furthermore, a better understanding of these EEG subtypes can improve our understanding of the core pathophysiology and result in specific new treatments for ADHD and testable hypothesis.

ACKNOWLEDGEMENT
Presented at the 59th American Academy for Child and Adolescent Psychiatry (AACAP) meeting, October 23-28 2012, San Francisco, USA.

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SLEEP DIAGNOSES IN ELDERLY PATIENTS AND YOUNGER CONTROLS VISITING AN OUTPATIENT CLINIC FOR EPILEPSY

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INTRODUCTION

Sleep disorders are common in the general population, and are a frequently observed co-morbidity in people with epilepsy.[1] [2] Besides their seizure related problems, patients with epilepsy could present specific complaints indicating a sleep disorder, e.g. snoring combined with excessive daytime sleepiness. With these complaints, a breathing related sleep disorder will be investigated and is likely to be found. In prospective screening of people with refractory epilepsy and clinical suspicion of OSAS, this diagnosis was confirmed in 46-80%.[3] [4] However, sometimes the clinical signs are not that obvious. For example, when sleep-related paroxysmal motor symptoms are present, it is a significant challenge for the clinician to make a diagnosis, especially in patients with epilepsy. A distinction has to be made between nocturnal epilepsy and non-epileptic sleep disorders. Since the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale is found to be insufficiently sensitive and specific, polysomnography (PSG) with video monitoring remains a necessity in those cases. [5] When symptoms are non-specific, for example fatigue or sleepiness, which are frequently reported by patients with epilepsy [6], the clinician should be suspicious of a sleep disorder, and also be alert on side-effects of anti-epileptic drugs (AEDs). It is worthwhile to identify sleep disorders. Sleep disorders have a proven negative effect on the quality of life in patients with epilepsy. Moreover, the observation of better seizure control, up till 30%, after identification and treatment of obstructive sleep apnea syndrome (OSAS) emphasizes the importance of considering a polysomnography in patients with epilepsy.[7]

The exact rate of co-occurrence of sleep disorders and epilepsy is unknown. There is no significant difference in occurrence of restless legs syndrome (RLS) between people with epilepsy (18-35%) versus controls (12-29%).[4] [8] There are no systematic PSG studies about non-REM sleep parasomnias in patients with epilepsy. One prospective trial demonstrated a remarkable high prevalence of REM sleep behavior disorder (RBD) in 12.5% of elderly patients with epilepsy (≥ 60 years old).[8] Because of their pathophysiology, some sleep disorders (e.g. RBD or RLS) are simply more frequently observed and thereby co-occur with increasing age. It remains unknown if the outcome of sleep investigation is significantly different between younger or elderly patients with epilepsy, who present complains indicating a sleep disorder.

The aim of this study is to compare, in patients visiting an epilepsy outpatient clinic, the diagnosis at referral to the sleep clinic with the final diagnosis. Furthermore, the frequency of a final diagnosis will be compared between younger and elderly patients.

METHODS

Young and elderly patients, who are respectively between 30 and 40 years old or at least 60 years old during one of their visits at the sleep clinic, and who visited the epilepsy clinic as well, were retrospectively included. Data from the period January 2005 up till December 2011 was collected. This population consisted of patients with epilepsy and patients suspected for epilepsy but who were finally diagnosed with a non-epileptic disorder, for example syncope or psychogenic seizures. Results of validated questionnaires on sleep disorders, PSG and actigraphy were studied. The final sleep diagnosis was made according to the International Classification of Sleep Disorders-2. The Pearson Chi-square test or the Fischer's Exact test, the latter in case of a small sample size and 2 x 2 contingency table, was used to compare groups. $P<=0.05$ was taken as the level of significance. The statistical analysis was performed using the Statistical Package of Social Sciences (SPSS version 17.0, Baltimore).

RESULTS

Ninety subjects out of our patient-database met the inclusion criteria. Forty-six were previously diagnosed with epilepsy, 44 others had paroxysmal complaints with another etiology. Of the 46 patients with epilepsy, 17 patients were young (mean age at time of PSG 35yr, range 29-41yr) and 29 were older subjects (mean age at time of PSG 66yr, range 59-75yr). The type of epilepsy was in 67% localization-related epilepsy (cryptogenic or symptomatic). Nine percent had a diffuse epileptic encephalopathy, four percent had idiopathic generalized epilepsy, and in twenty percent the type of epilepsy could not be defined.

In the 90 subjects, the reason of referral to the sleep clinic was not different between patients with epilepsy or patients with another paroxysmal disorder. Out of all patients, a sleep disorder was found in 89% (n=80). In the 46 patients with epilepsy, and in the subcategory of older patients with epilepsy, respectively 91% and 97% were diagnosed with a sleep disorder. Of the 90 patients, 64 had one sleep disorder, 25 had two disorders, and 4 had three. The prevalence of more than one diagnosis did not differ between younger or elderly patients. In the 46 patients with epilepsy, 35 had one sleep disorder and eleven had two disorders. Having more than one sleep diagnosis was more common in younger patients when compared with the elderly, 41% versus 14%, however this difference did not reach statistical significance ($p = 0.07$).

Of the whole study population, in 29 subjects the final diagnosis was OSAS and in two cases OSAS was found as a comorbidity. There was no difference in the prevalence of this disorder between younger and elderly. If we compare the prevalence of OSAS between the age-categories in patients with epilepsy (n=46), also no difference was found.

Out of the 90 subjects, in eight isolated RLS was found, in six RLS with PLMS and in 12 cases PLMS was found without RLS. In the whole population, RLS with/or PLMS was significantly more frequently found in 42% of the elderly and in 14% of the younger patients ($p = 0,004$). In patients with epilepsy, this difference between the age categories was not found.

The reason of referral and the final diagnoses of the patients with epilepsy are found in Table 1. Out of the 17 younger patients with epilepsy, six had complained about disturbing movements when sleeping. In those six patients a parasomnia was frequently suspected but was only diagnosed in one patient. In two of these six patients another sleep disorder was found, and in none of them the complaints could be explained by epilepsy. Out of the 29 elderly patients with epilepsy, five patients had complaints on paroxysmal motor symptoms at

night. All five patients had a sleep disorder, again in none the symptoms were based on epilepsy.

DISCUSSION

In our selected population of patients with epilepsy and complaints indicating a sleep disorder, the presence of a sleep disorder was frequently confirmed. The prevalence of a sleep disorder did not differ between patients with epilepsy and patients with another paroxysmal disorder, respectively 91% and 89%.

In the patients with epilepsy who were suspected of a breathing related sleep disorder, this was confirmed in eleven out of twelve elderly, and in three out of five younger patients. This outcome is comparable with earlier studies, which found in cases with clinical suspicion of OSAS a prevalence of this disorder of 70-73%.[4 9]

In some cases the outcome of the work-up at the sleep clinic was different than expected. For example, in eleven patients (six young and five elderly), who reported on paroxysmal motor symptoms at night, the explanation of their nocturnal symptoms was not epilepsy and also the diagnoses non-REM related parasomnia or RBD were scarce. In only one of these eleven patients, a 62-year old male with idiopathic generalized epilepsy since childhood, RBD was found. In another case sleepwalking was diagnosed

Our study in patients with epilepsy puts forward that when a specific sleep diagnosis was suspected by the referring clinician (breathing related sleep disorder, RLS with/or PLMS or possible parasomnia) this was confirmed in 21 out of 34 patients (62%). Furthermore the diagnostic work-up revealed in eight of these 34 patients (24%) a second sleep disorder. Due to the small sample size of this study firm conclusions on differences in diagnoses between younger and older patients could not be made. In patients with epilepsy only a tendency was found in the number of diagnoses, younger patients have more frequently multiple sleep diagnosis compared to elderly ($p = 0.07$). OSAS and RLS did not occur more often in younger compared to older patients with epilepsy.

CONCLUSIONS

This retrospective study proved that sleep disorders occur frequently in older and younger patients with epilepsy and sleep related complaints, which is congruent with previous research results. No significant differences in final sleep diagnoses based on PSG results could be found between younger and older patients with epilepsy. Surprisingly, no epilepsy related etiology was found when the reason of referral to the sleep clinical was related to paroxysmal motor symptoms during sleep. Since identification and treatment of sleep disorders in patients with epilepsy leads to better seizure control, it is useful to do a complete diagnostic work-up, including PSG, when such a disorder is suspected.

Table 1. The reason of referral to the sleep clinic and the final main diagnoses in 17 younger and 29 elderly patients with epilepsy. In 11 subjects a second sleep disorder was found, these diagnoses are not shown here. (No SD = no sleep disorder, OSAS = obstructive sleep apnea syndrome, CSAS = central sleep apnea syndrome, PS = primary snoring, RLS = restless legs syndrome, PLMS = periodic limb movement syndrome, SW = sleepwalking, non- REM sleep related parasomnia, RBD = REM-sleep behavior disorder, Narco = Narcolepsy, PPI = psychophysiologic insomnia, IMC = insomnia due to medical condition, PI = paradoxical insomnia, ISH = inadequate sleep hygiene.)

	Reason of referral											
	Non-specified sleep-related complaints		*Breathing related complaints*		*Possible RLS with/or PLMS*		*Motor symptoms, possible parasomnia*		*Excessive daytime sleepiness*		*Total*	
Diagnosis	*young*	*elderly*	*young*	*elderly*	*young*	*elderly*	*young*	*elderly*	*young*	*elderly*	*young*	*elderly*
No SD	0	0	0	0	0	0	3	0	0	1	3	1
OSAS	1	0	3	10	0	0	1	0	1	1	6	11
CSAS	0	1	0	1	0	0	0	0	0	0	0	2
PS	0	0	1	0	0	0	0	0	0	0	1	0
RLS	0	0	0	0	1	3	0	2	0	0	1	5
PLMS	1	1	0	1	0	1	0	1	0	0	1	4
SW	0	0	0	0	0	0	1	0	0	0	1	0
RBD	0	0	0	0	0	0	0	1	0	0	0	1
Narco	0	0	0	0	0	0	0	0	0	1	0	1
PPI	0	0	0	0	0	1	0	0	0	0	0	1
IMC	0	1	0	0	0	0	0	0	0	0	0	1
PI	0	0	1	0	0	0	0	0	0	0	1	0
ISH	2	1	0	0	0	0	1	1	0	0	3	2
Total	4	4	5	12	1	5	6	5	1	3	17	29

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A COMPARISON OF THE DISTRIBUTION OF CHRONOTYPES IN TWO GEOGRAPHICAL LOCATIONS

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INTRODUCTION

Chronotype is a term used to categorize people by their preferred sleep/wake and activity times; those favoring early times are called morning-types and those favoring late times are called evening-types.[1] Chronotype, or morningness/eveningness, has been experimentally shown to have a neurobiological basis. Specifically, morningness/eveningness has a basis in inter-individual differences in the phase of the circadian pacemaker.[2] The involvement of the circadian pacemaker implies a potential role for light exposure patterns, as light is a dominant Zeitgeber (circadian time synchronizer) in humans.[3]

The effect of light on the phase of the circadian pacemaker varies as a function of the timing, duration and intensity of the light exposure.[4,5] A mathematical function called a phase response curve (PRC) describes the relationship between the timing of light and its effect on circadian phase.[4] It shows that light exposure in the morning leads to a phase advance (placing the circadian rhythm earlier in time), whereas light exposure in the evening leads to a phase delay (placing the circadian rhythm later in time).

Sleep/wake timing preferences may influence light exposure patterns, and vice versa. Evening-types have been found by some investigators to sleep relatively early in their endogenous circadian cycle compared to morning-types.[6,7] They should therefore be exposed to (day)light across a greater part of the phase *advance* portion of their PRC for light.[7] Paradoxically, this would be expected to advance the preferred timing of sleep, which seems inconsistent with being an evening-type person.

If light exposure patterns are nonetheless causally involved in determining morningness/eveningness, then it is reasonable to assume that geographical locations with different daylight patterns may differentially influence the morningness/eveningness distribution of the population. Indeed, questionnaire-based research has revealed variation in the distribution of morning- and evening-types as a function of location.[8] It has been theorized that this reflects uncoupling of circadian phase from entrainment to natural daylight ("sun time") in larger cities, leading to dominance of behavioral cycles over environmental light-dark cycles and resulting in a wider morningness/eveningness distribution with more delayed chronotypes.[8,9]

In the context of this idea, we employed a morningness/eveningness questionnaire to compare chronotype distributions between two geographical locations in the U.S.A.: Philadelphia, Pennsylvania and Spokane, Washington. Although these cities are both located on the eastern edge of their respective time zones, they differ in latitude, daily daylight exposure, and population density. In summer, Philadelphia has up to 58 minutes less sunlight per day, with the sun rising up to 40 minutes later than in Spokane. In winter, Spokane has up to 55 minutes less sunlight per day, with the sun rising up to 16 minutes later than in Philadelphia. Philadelphia's population is roughly seven times greater than that of Spokane, with approximately 3.4 times as many people per km^2. See Table 1.

METHODS

Data were taken from 543 telephone-screened, healthy, non-smoking subjects with regular sleep schedules, who had not engaged in shift work for at least three months and had not traveled across time zones in the month prior to screening. Subjects were between the ages of 18 and 40 (M=28.3, SD=5.9) and 62.7% of the sample was male. The data set included 150 subjects from Philadelphia and 393 subjects from Spokane.

In order to assess chronotype, subjects completed the Composite Scale of Morningness (CSM)[10] as part of an on-site screening process to determine eligibility for various laboratory studies.

The means of the CSM scores were compared between locations, using an independent t-test. The variances of the CSM scores were also compared between locations, using Levene's test for equality of variance. Both tests employed a type I error threshold of 0.05.

Table 1. Population and sunlight by location.

	Philadelphia, PA	*Spokane, WA*
Geographical Location	40°00'N, 75°09'W	47°40'N, 117°25'W
Population Density	4,405/km^2	1,308/km^2
Total Population	~1.5 million	~200,000
Summer Sunrise Time	05:32	04:52
Winter Sunrise Time	07:19	07:36
Summer Daily Sunlight	15h 1min	15h 59min
Winter Daily Sunlight	9h 20min	8h 25min

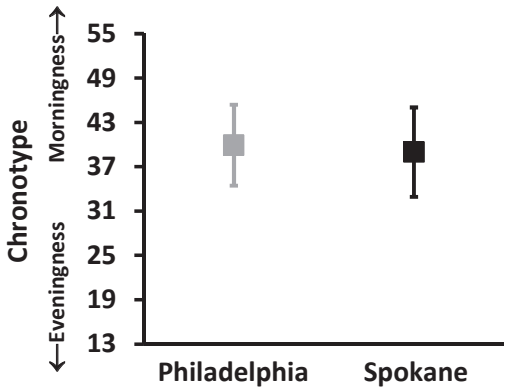

Figure 1. Means ± SD for CSM scores by location.

RESULTS AND DISCUSSION

CSM scores in Philadelphia (M=39.9, SD=5.5) were not significantly different from those in Spokane (M=38.9, SD=6.1), although there was a trend for slightly more eveningness in Spokane (t_{541}=1.67, P=0.096). The variance in CSM scores did not differ significantly between the two locations ($F_{1, 541}$=2.2, P=0.139). See Figure 1.

Our results showed no significant differences in chronotype distribution between Philadelphia and Spokane, despite differences in daylight patterns and population size and density. Notably, our results did not conform to the idea of greater uncoupling of circadian phase from

entrainment to natural daylight in larger cities resulting in a wider morningness/eveningness distribution with more delayed chronotypes.

The dose of light required to substantively affect circadian phase has long been debated.[11] Recent studies have shown that even common indoor lighting has the potential to entrain circadian rhythms[5,12,13] (and possibly offset seasonal change as well[13–15]). Furthermore, mathematical modeling research has shown remarkable robustness of the circadian pacemaker to variable day-to-day light exposure patterns.[16] These findings suggest that light exposure patterns are only part of the story, if causally relevant here at all. Other factors such as genetic make-up[17] and social desirability and constraints[18–21] may also determine sleep/wake timing preference and thus chronotype.

CONCLUSIONS

Our findings are not in line with the theory of greater uncoupling of circadian phase from entrainment to natural daylight in larger cities.[8] This theory is based in analyses of a wider range of geographical locations and thus cannot be dismissed on the basis of a single location pair. That said, the purported effects of population density, through altered sunlight exposure, on circadian entrainment may be significantly moderated by exposure to artificial light and/or social Zeitgebers. This may actually be advantageous in research on circadian rhythms and sleep, in that it would lessen concerns about systematic circadian confounds when combining samples from multi-site investigations.

ACKNOWLEDGMENTS

This research was supported by the NIH (HL70154), NASA (NAG9-1161), FMCSA (DTMC75-07-D-00006) and DoD (W81XWH-05-1-0099).

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EFFECTIVENESS OF COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA: INFLUENCE OF DEPRESSIVE SYMPTOM SEVERITY AND WORRYING

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INTRODUCTION

Insomnia is characterised by difficulties initiating sleep, maintaining sleep, or non-restorative sleep that is poor in quality during at least one month. These problems have to be accompanied by a form of impaired daytime functioning.[1] It is a pervasive problem for many people; ten to fifteen per cent of the general population reports sleep difficulties.[2]
The majority of sleeping problems occur in the presence of another disorder, particularly psychiatric co morbidities are very common. For instance, the co-occurrence of insomnia with depression is well known.[3] Insomnia can have a negative impact on patients after remission of depression because there is an increased risk of relapse of the condition.[4] Sleep disturbance can also be a risk factor for suicide in depressive patients.[5] Other disorders that frequently accompany sleeping problems are anxiety disorders. Especially Generalised Anxiety Disorder (GAD) is associated with insomnia.[4] Excessive, generalised and uncontrollable worry is the main feature of GAD.[6] Like with depression, anxiety can be negatively influenced by insomnia.[4]
Cognitive Behavioural Therapy for Insomnia (CBT-I) is a proven effective treatment for primary as well as co morbid insomnia.[7,8] The effectiveness of CBT-I for depressed patients is documented by several authors. [9,10] In these studies, depressed and non-depressed subjects benefitted equally from the treatment. Research of CBT-I for patients suffering excessive worrying or GAD is much less documented.
Current knowledge about the effect of CBT for co morbid insomnia is still insufficient, especially for patients with GAD. Therefore, the aim of this study is to shed some light on this issue and to evaluate whether depressive symptoms or worrying influences the effectiveness of CBT-I.

METHODS

The 122 patients who were included in this study (74,4% female) ranged in age from 17 to 85, with a mean age of 45,57. All patients had an examination of their sleep with 2x24 hour polysomnography and one or two weeks actigraphy. They were referred to a psychologist at the sleep centre for psychophysiological insomnia, insomnia due to a mental disorder, idiopathic insomnia, paradoxical insomnia, inadequate sleep hygiene or a combination of two or more of the mentioned conditions. All participants received CBT-I, consisting of psycho-education, sleep hygiene, stimulus control, sleep restriction, relaxation exercises and cognitive restructuring.
Patients completed a sleep evaluation list (developed by SEIN, division psychology in 2007) before treatment, after treatment and six months later. The sleep evaluation list aims to measure the subjective approval of various aspects of sleep. In the first part, patients are asked to give a score (0-10) on the following items: their sleep in general, the sleep onset, the continuity of their sleep, the total amount of sleep during the night, how calm their sleep is,

how invigorating their sleep is and how rested they feel during daytime. A total score is calculated by summing up all the individual scores above, with higher scores reflecting more satisfaction with sleep. In the second part, they are asked to indicate their total amount of hours sleep per night, their sleep onset latency in minutes and the amount of minutes spent awake after sleep onset.
Before treatment, patients completed the Beck Depression Inventory (BDI-II-NL), a self-report inventory list to assess the severity of depressive symptoms.[11] To create a high and a low BDI group, a cut-off score of 14 was used.[11] To measure the trait of worry, we used the Penn State Worry Questionnaire (PSWQ).[12] To create a high and a low PSWQ group, a cut-off score of 49 was used.[13]

RESULTS AND DISCUSSION

Complete data were obtained for patients who completed the BDI (92) and/or the PSWQ (119). The BDI and PSWQ scores were related; the correlation between the two measures was 0,31 (p=0,003).

Effects of CBT-I for high and low BDI patients

Figure 1A describes the change in mean sleep evaluation scores in the two groups. Sleep evaluation scores changed in time ($F(2,172)=63,62$, $p<0,001$), due to less satisfaction with sleep at pre-treatment in comparison to the satisfaction at post treatment and the 6 month follow up. This positive effect on sleep evaluation scores did not differ between the two groups ($F(1,86)=0,07$, $p=0,79$).
The subjective total sleep time changed in time ($F(2,178)=13,68$, $p<0,001$), due to an augmentation of estimated sleep hours at post treatment and the six month follow up in comparison to hours of sleep at pre-treatment. This effect was the same for both groups ($F(1,89)=0,31$, $p=0,58$).
The subjective sleep onset latency also changed in time ($F(2,178)=10,97$, $p<0,001$), due to longer sleep onset latencies at pre-treatment in comparison to post treatment and 6 month follow up onset latencies. This effect was the same for both groups ($F(1,89)=0,67$, $p=0,42$).
The estimated minutes spent awake after sleep onset also changed in time ($F(2,170)=26,44$, $p<0,001$), due to a greater amount of minutes at pre-treatment in comparison with post treatment and the 6 month follow up. Again, the groups did not differ ($F(1,85)=0,001$, $p=0,99$).

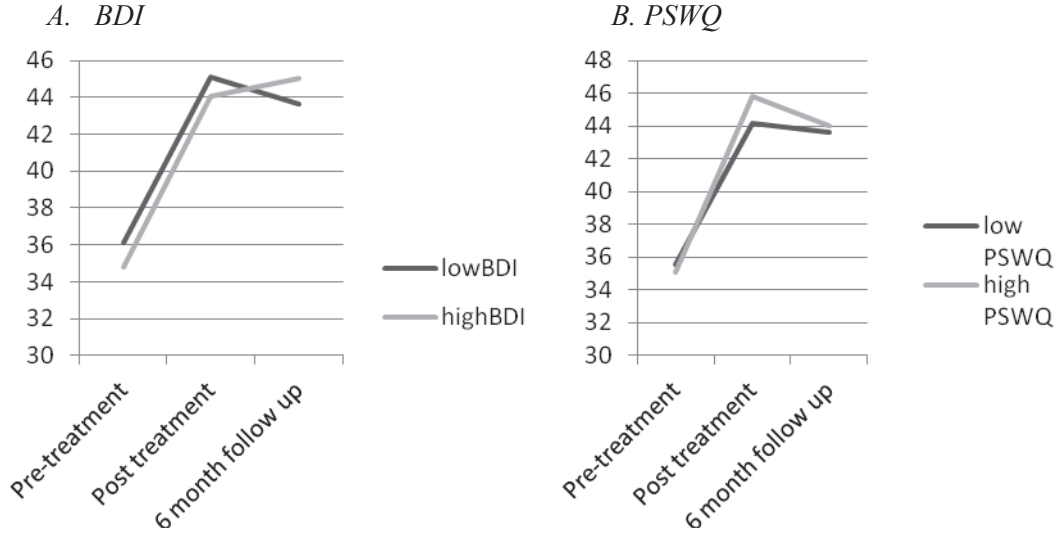

Figure 1: Change in mean sleep evaluation scores at pre-treatment, post treatment and at the 6 month follow up for A. lowBDI and highBDI patients and B. low PSWQ and high PSWQ patients.

Effects of CBT-I for high and low PSWQ patients

Figure 1B describes the change in mean sleep evaluation scores in the two groups. Sleep evaluation scores changed in time ($F(2,226)=92,98$, $p<0,001$), due to lower satisfaction with sleep at pre-treatment in comparison to the satisfaction at post treatment and the 6 month follow up. This effect was the same for high and low PSWQ patients ($F(1,113)=0,11$, $p=0,75$). The subjective total sleep time also changed in time ($F(2,232)=17,04$, $p<0,001$), due to an augmentation of hours of sleep at post treatment and the six month follow up in comparison to hours of sleep at pre-treatment. This effect was the same for both groups ($F(1,116)=2,15$, $p=0,15$).

The estimated sleep onset latency changed in time ($F(2,230)=15,44$, $p<0,001$), due to longer sleep onset latencies at pre-treatment in comparison to post treatment and 6 month follow up onset latencies. This positive effect on perceived sleep onset latencies did not differ between the two groups ($F(1,115)=0,07$, $p=0,79$).

The estimated amount of minutes spent awake after sleep onset also changed after treatment ($F(2,220)=26,74$, $p<0,001$). In the pre-treatment condition the amount of minutes awake was higher in comparison with these minutes at post treatment and the 6 month follow up. Again, the groups did not differ ($F(1,110)=2,27$, $p=0,14$).

These findings are consistent with findings from earlier studies, where CBT-I is found to be effective for insomnia with and without co morbid conditions.[9-12]

Some remarks should be made about interpretation of the results. In our study, we found a high correlation between BDI and PSWQ scores, which makes it harder to separate the two groups and to speak of an effective treatment for two isolated groups. Apparently, depressive symptoms and worrying overlap and possibly influence each other. Another remark that should be made is the absence of a clinical diagnosis of depression or GAD. Effects of treatment could be different in diagnosed patients, an interesting focus for future research.

Several limitations of this study should be noted. Our population consisted of patients who completed all of three measurements. A large portion of patients referred to treatment did not return all evaluation lists. Because of this, there is a possibility that patients who did return their lists are also the ones who benefitted most from CBT-I. Further research can give more information about benefits for patients not included in our analysis. Furthermore, our dependent variables (sleep measures after CBT-I) are subjective assessments. Therefore, we do not know whether characteristics of sleep changed after CBT-I. Future studies may compare objective sleep measures before and after CBT-I in addition to subjective measures.

CONCLUSIONS

In this study, insomnia patients with high and low depression severity benefited equally from CBT-I. This was also true for insomnia patients soring high and low on the trait of worry. This suggests that CBT-I is equally effective in improving subjective sleep experiences in insomnia patients, regardless of depressive symptom severity or worrying.

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EFFECT OF CPAP ON BLOOD PRESSURE AND CARDIAC OUTPUT DURING THE APNEA CYCLE IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is strongly related to cardiovascular disorders (atrial fibrillation, chronic heart failure) and arterial hypertension[1]. Continuous positive airway pressure (CPAP) treatment stabilises the upper airway during sleep preventing upper airway collapse. CPAP has a direct positive effect on night-time hypertension[2]. However, the immediate effects of apnea on cardiac output (CO), stroke volume (SV), heart rate and systemic blood pressure during sleep apnea are not well known.

OBJECTIVE

Measurement of beat-to-beat heart rate, stroke volume (SV) and systemic blood pressure during episodes of apnea in baseline conditions and during CPAP therapy.

METHODS

The cardiovascular effects of apnea in baseline conditions and the effect of CPAP were evaluated in 5 severe OSAS patients by continuous blood pressure measurement and SV estimation by the model flow method[3] during full polysomnography. Blood pressure was measured from the finger arteries by means of two finger cuffs which were alternatively inflated. (Portapress)
Blood pressures were registered during wake (A) and in the first hours of sleep to evaluate OSAS in untreated condition (B), followed by CPAP titration until optimal pressure was reached (C).
An apnea cycle was defined by the beginning of an obstructive apnea, including the arousal response (apnea time till the start of the ventilatory period). The individual apnea cycles (range 40- 70 seconds) in the 5 patients were normalised to mean apnea cycles. During wake and CPAP treatment 2 epochs (60 seconds) measurement were taken for comparison with samples of the apnea cycles

RESULTS

Patients characteristics before and after treatment are given in Table 1 and 2. The AHI range was between 50 and 88. The (apnea) normalised beat to beat cardiovascular measurements are given in Figure 1-4. Only the apnea cycles demonstrated significant changes. Heart rate (HR) decreased statistically significantly ($p<.05$) from 20% up to 80% of the apnea cycle (Fig. 1B) with a mean max decrease of 24% at 67% of the apnea. Marked decreases ($p<.05$) in systolic and diastolic blood pressures were present during apnea from 10% up to 70% of the apnea

cycle (Fig. 2B). SV (fig 3B) showed a tendency for decrease during apnea, however without any statistical significance, whereas cardiac output (CO, fig 4B) was decreased ($p<.05$) between 20% up to 80% of the apnea cycle.
With adequate CPAP (C), HR, arterial blood pressures and CO were stable throughout the recording episodes and its values were not statistically different compared to baseline values measured during wake (A).

Figure 1: Changes in heart rate during the apnea cycle in Wake (A), NREM 1,2 sleep (B), and during CPAP therapy (C)
(mean values solid lines, SD dotted Lines;
↓ = sign decrease, P<0.5).

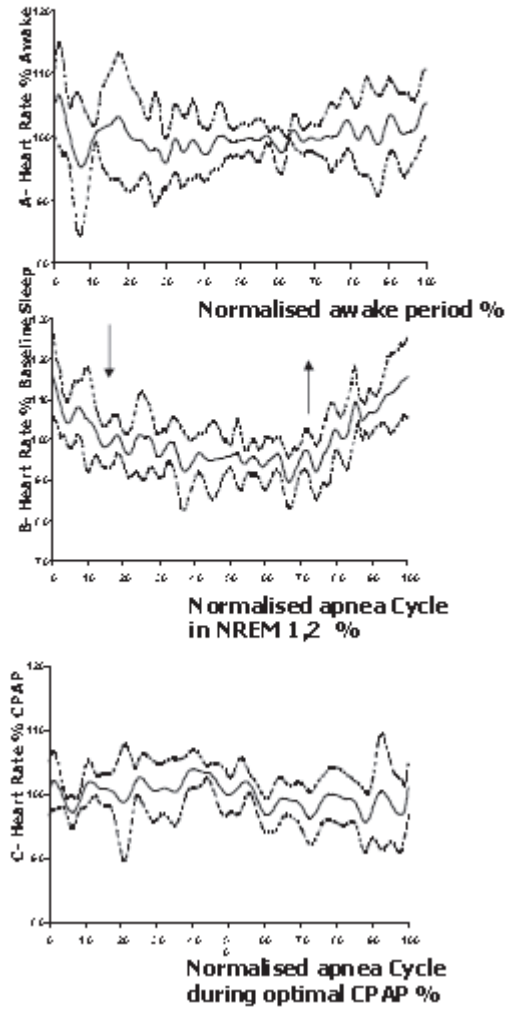


Figure 3: Changes in stroke volume during the apnea cycle in Wake (A), NREM 1,2 sleep (B), and during CPAP therapy (C)
(mean values solid lines, SD dotted Lines).

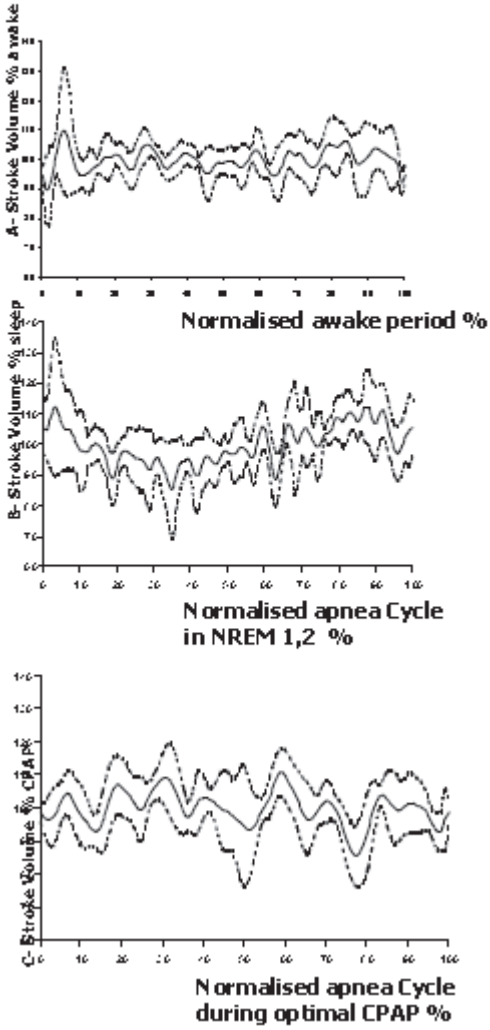


Table 1. patient characteristics during baseline conditions

Variables	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5
Age (years)	**54**	**51**	**59**	**50**	**46**
Medical history	**Arterial Hypertension**	**Arterial Hypertension**	**Arterial Hypertension**	**Arterial Hypertension**	**Arterial Hypertension DM, CARA**
Medication report only the generic names of the drugs	**lisinopril Chlorothiazide**	**acebutolol Chlorothiazide**	**Atenolol**	**None**	**Amlodipine**
BMI (kg/m^2)	**31.8**	**37.8**	**27.1**	**31.7**	**34**
Major symptom	**EDS**	**EDS**	**EDS**	**EDS**	**EDS**
Systolic blood pressure	**160**	**150**	**150**	**150**	**160**
Diastolic blood pressure	**108**	**90**	**90**	**100**	**90**
Alcohol (/day)	**2-4**	**3-4**	**<1**	**3-4**	**0**
Smoking (cigarettes/d)	**1**	**10**	**3**	**20**	**0**
***Daytime sleepiness*:**					
ESS	**14**	**14**	**10**	**12**	**13**
MSLT SL NREM1, path. <10	**8**			**10.5**	**4**
***Sleep* (min/%TIB)**					
Total Sleep Time, TST	**237 (74%)**	**409 (96%)**	**365 (94%)**	**365 (90%)**	**348 (84%)**
Stage NREM 1	**17 (5%)**	**25 (6%)**	**17 (4%)**	**41 (10%)**	**36 (9%)**
Stage NREM 2	**220 (60%)**	**290 (68%)**	**254 (65%)**	**263 (65%)**	**243 (59%)**
Stage Deep sleep, NREM 3	**8 (2%)**	**0**	**7 (2%)**	**0**	**20 (5%)**
Stage Deep sleep, NREM 4	**0**	**0**	**0**	**0**	**6 (1%)**
REM	**29 (8%)**	**94 (22%)**	**87 (22%)**	**58 (14%)**	**39 (9%)**
Sleep stage shifts/hr	**4.1**		**3.9**	**4.4**	**9.1**
Awakenings/hr	**1.8**		**1**	**4**	**4.8**
Respiration					
Apnea index, AI (#/hr)	**47.2**	**60**	**38**	**35**	**46**
Hypopnea index, HI (#/hr)	**26.3**	**22**	**12**	**35**	**35**
Oxygen desaturation index (#/hr)	**43.2**	**55**	**50**	**66**	**78**
Total time SaO_2< 90% (min)	**-**	**195**	**-**	**280**	**290**

Table 2: Polysomnographic data during CPAP titration

Variables	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5
Sleep **(min/%TIB)**					
Total Sleep Time, TST	**237 (64%)**	**302 (99%)**	**201 (89%)**	**368 (86%)**	**284 (79%)**
Stage NREM 1	**23 (3%)**	**31 (10%)**	**15 (7%)**	**(8%)**	**21 (6%)**
Stage NREM 2	**121 (33%)**	**79 (26%)**	**87 (38%)**	**(34%)**	**132 (37%)**
Stage NREM 3	**18 (5%)**	**22 (7%)**	**41 (18%)**		**21 (6%)**
Stage NREM 4	**28 (8%)**	**87 (29%)**	**23 (10%)**	**(26%)**	**43 (12%)**
REM	**59 (16%)**	**83 (27%)**	**36 (16%)**	**(18%)**	**68 (19%)**
Sleep stage shifts/hr	**6.5**	**8**	**8**		**5.3**
Awakenings/hr	**4**	**0**	**2**		**2.7**
Applied CPAP pressure**s**	**Cm H_2O**	**Cm H_2O**	**Cm H_2O**	**Cm H_2O**	**Cm H_2O**
Stage , NREM 1		**5**	**4**		**5**
Stage NREM 2		**6**	**5**		**7**
Stage NREM 3		**7**	**6**		**8**
Stage NREM 4		**8**	**7**		**9**
Stage REM		**9**	**7**		**10**
Final CPAP pressure	**10**	**9**	**7**	**8**	**10**

Figure 2: Changes in systolic and diastolic blood pressure in Wake (A), NREM 1,2 sleep (B), and during CPAP therapy (C) (mean values solid lines, SD dotted Lines; | = sign decrease, P<0.5).

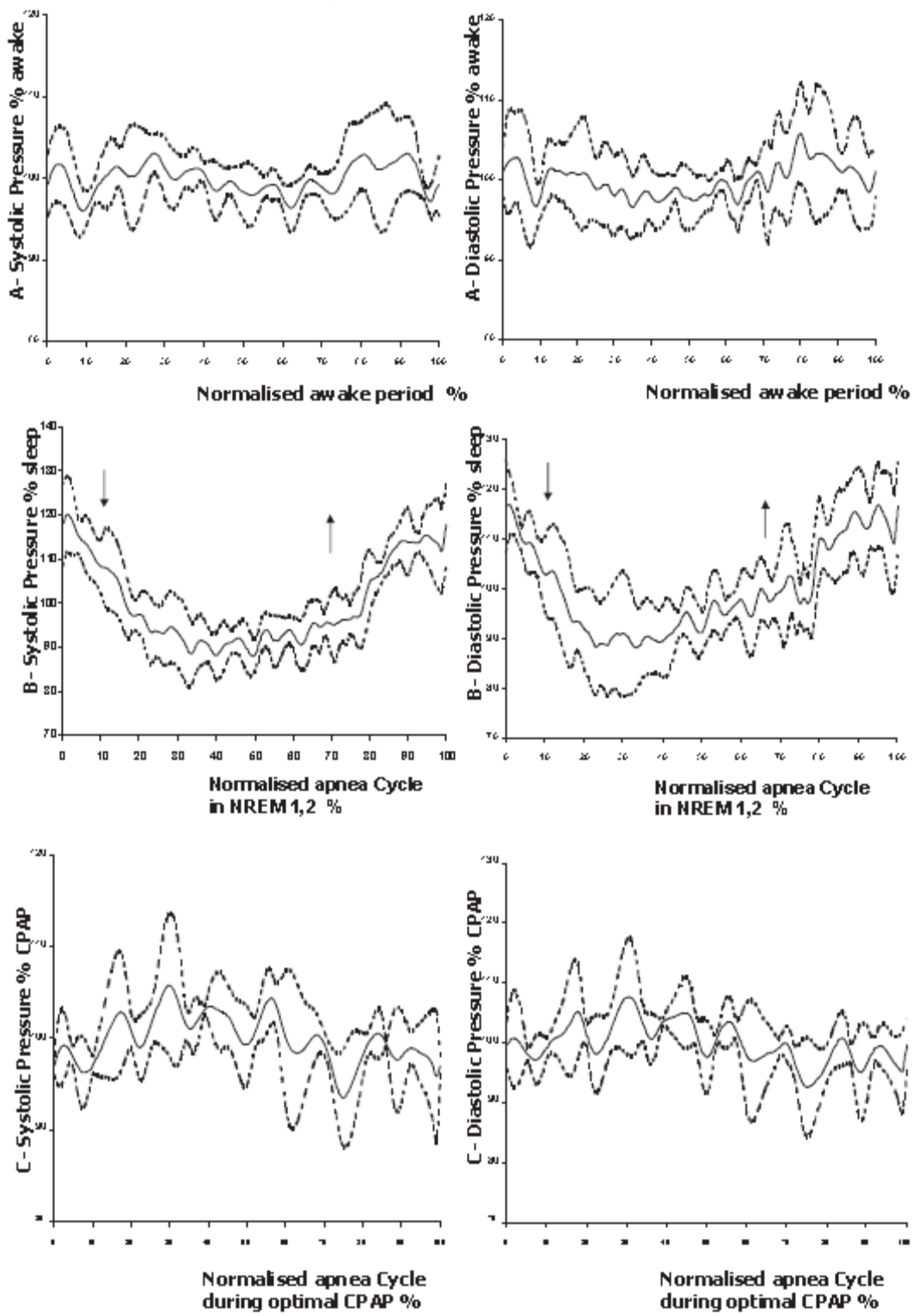
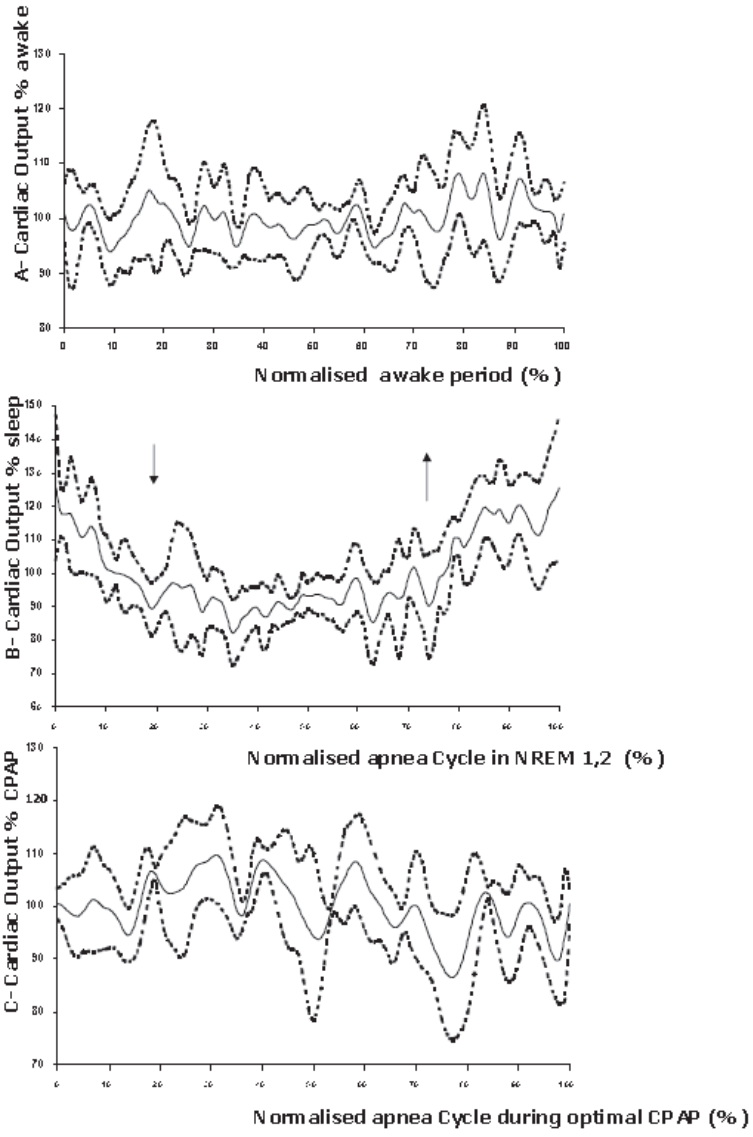


Figure 4: Changes in cardiac output in Wake (A), NREM 1,2 sleep (B), and during CPAP therapy (C)

(mean values solid lines, SD dotted Lines; ↓ = sign decrease over period ↑, P<0.5



DISCUSSION

The beat-to-beat measurements in our severe OSAS patients show marked cardiovascular disturbances during apnea. Negative intrathoracic pressures swings from the apnea start on may induce the significant decreases in HR, CO and blood pressures. These marked changes will also affect cardiac afterload and in combination with hypoxic and hypercapnia episodes may induce heart failure on the long-term. CPAP effected immediately a stabilisation of HR, CO and blood pressure.

CONCLUSIONS

CPAP is mandatory for severe OSAS patients to avoid marked cardiovascular stress and consequent chronic heart failure.

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CREATING A SLEEP PERMISSIVE STATE USING MILD BED WARMING

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INTRODUCTION

Up to 65% of the general adult population report that they are dissatisfied with their sleep at least a few nights a week.[1] Morin and coworkers showed that alternative self-help strategies and products to promote sleep (like herbal tea or acupuncture), are used by 32.5% of the general population.[2] However, many of the self-help strategies and off-the-shelf products are not evidence based. Mild skin warming can be regarded as a relatively new and proven non-pharmacological method to improve sleep. Recent studies showed that mild skin warming, without affecting the core body temperature decline, improved sleep onset[3,4] and promoted slow wave sleep and sleep maintenance.[5] In the aforementioned studies, the skin warming was induced using a water-perfused thermo suit, which is not a very comfortable, cost-effective and home applicable solution. We were challenged to translate these findings from experimental laboratory studies into a prototype of a home-applicable, sleep promoting solution. As a suitable solution we came up with a low power heating blanket. However, sleep disruptive effects had been reported in an earlier study that used a convenient, conventional electric heating blanket without a temperature feedback mechanism. These negative effects on sleep were most likely caused by an elevation in the overnight core body temperature, next to a mildly warmer skin temperature.[6] As pointed out by Romeijn and coworkers, efforts to improve sleep by external warming should obtain feedback to create a closed loop manipulation.[7] Our prototype, a low powered heating blanket, was equipped with such a feedback system.

Last year we reported on the use of a first generation feedback-controlled electric heating blanket where we failed to show both consistent elevation of the skin temperature and improvement of sleep maintenance. We observed that the intervention resulted in a heat overload and this was most likely due to the rather slow temperature feedback settings.[8] As a consequence, we changed the prototype and investigated whether a mild increase in skin temperature could be achieved with this second generation temperature feedback-controlled electric heating blanket, with faster feedback settings and less feedback zones. It was hypothesized that mild bed warming would result in an increase in skin temperature - not core body temperature - and subsequent sleep improvement.

METHODS

Eight participants without sleep complaints (4 males and 4 females, mean age ± SD: 23.3 ± 2.9) visited the sleep lab for two non-consecutive nights. Participants were randomly assigned

to one out of two treatment sequences: a neutral, no bed warming condition (N) followed by a bed warming condition (W), or vice versa. In the bed warming condition, the bed was preheated (30 minutes prior to bedtime) and kept at a minimum temperature of 34°C for the remainder of the night. Bed warming was achieved with a second generation feedback-controlled electric heating blanket with 3 heating zones and a fast feedback control, developed at our technical department. In the neutral condition, the electric heating blanket was switched off. Bedroom temperature in both conditions was set at 18°C.

Polysomnographic sleep recordings (PSG) were obtained with a digital recorder (Vitaport-3; TEMEC Instruments B.V., Kerkrade, The Netherlands) and included EEG (F3, F4, C3, C4, O1, O2) using the Sleep BraiNet system (Jordan NeuroScience, San Bernardino, USA), EOG and submental EMG. PSG recordings were scored by the Siesta group (Vienna, Austria)[9] according to the standard Rechtschaffen and Kales criteria.[10] Subjective sleep was measured using the Pittsburg Sleep Diary[11] with an additional question that examined bed temperature perception[12] on a 7-point Likert scale (ranging from -3: 'cool' to 0: 'neutral', and to 3: 'warm'). Skin temperature was measured at nine places: both infra-clavicular areas, both hands, abdomen, both mid-thighs and both feet using 9 Thermochron iButtons (DS1922L; Maxim/Dallas Semiconductor Corp, Sunnyvale, USA) shielded with thermal probe covers (#M-80150; Major Medical Products Inc., Batavia, USA). Skin Temperature was sampled every 30 seconds with a precision of 0.0625°C. A weighted average skin temperature was calculated. Core body temperature was measured with the Jonah temperature pill (Vitalsense; Philips Respironics, Murrysville, USA) and digitally stored using the Equivital System (Hidalgo Ltd, Swavesey, UK). Core body Temperature was sampled every 15 seconds with a precision of 0.01°C. Bed temperature was measured with 18 temperature sensors (RTD-3-F3105; Omega, Stamford, USA) integrated in the electric heating blanket. Bed temperature was sampled every minute, with a precision of 0.01°C and a grand average over all 18 temperature sensors was calculated. All temperature data were aligned on "lights off" time. Paired samples t-tests ($\alpha = 0.05$, 1-sided) were performed using SPSS 16.0, to test the effects of bed warming on sleep, temperature and temperature perception.

RESULTS

Sleep. Several aspects of sleep, as measured using PSG, were significantly improved in the bed warming condition as compared to the neutral condition (Fig. 1). The relative amount of Wake in the warmed bed was 0.9% (4 min.) as compared to 2.7% (14 min.) in the non-warmed bed ($p = 0.009$). The relative amount of S1 in the warmed bed was 2.5% (11 min.) as compared to 3.7% (18 min.) in the non-warmed bed ($p = 0.036$). Sleep efficiency was 2.2% higher in the bed warming condition ($p = 0.004$) as compared to the neutral condition and the total number of awakenings decreased from 10 awakenings per night in the neutral condition to 5 in the bed warming condition ($p = 0.020$). In line with the PSG results, subjective reports on sleep showed that the nocturnal time spent awake was significantly lower in the bed warming condition (mean ± SEM, N: 16.8 ± 7.6 min. vs. W: 7.1 min. ± 4.1; $p = 0.033$), as compared to the neutral condition.

Temperature. The overnight skin temperature (Fig. 2, *middle panel*) did not significantly differ between the bed warming condition and the neutral condition (N: 35.00 ± 0.17°C vs. W: 34.88 ± 0.13°C; $p = 0.150$), despite the average overnight bed temperature (Fig. 2, *left panel*) being significantly higher in the bed warming condition (N: 32.33 ± 0.32°C vs. W: 34.34 ± 0.03°C, $p < 0.001$). The bed warming significantly affected the subjective temperature perception: the warmed bed was experienced as warmer (N: 0.5 ± 0.2 vs. W: 1.1 ± 0.3, $p = 0.023$). As aimed for, core body temperature (Fig. 2, *right panel*) was not affected by the applied intervention (N: 36.66 ± 0.11°C vs. W: 36.58 ± 0.07°C; $p = 0.474$).

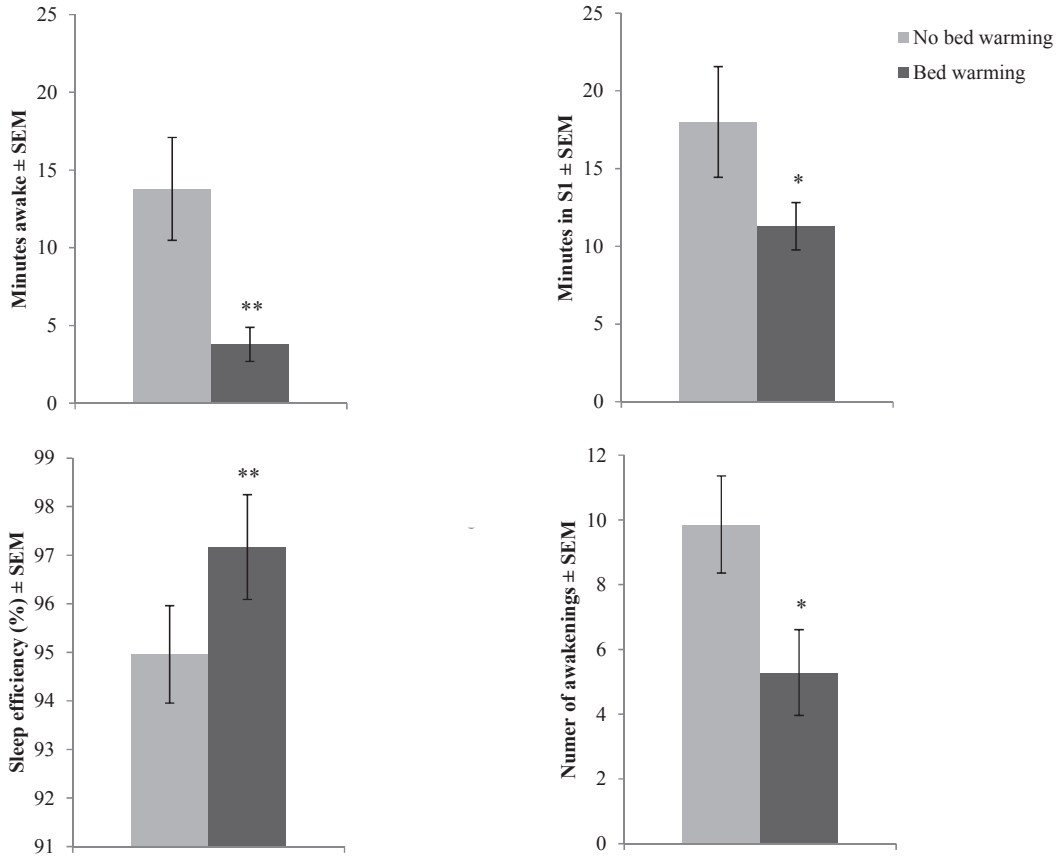

Figure 1. Time awake (*top left panel)*, time in S1 (*top right panel*), sleep efficiency (*bottom left panel*) and number of awakenings (*bottom right panel*), in the neutral condition (*light grey*) and the bed warming condition (*dark grey*). Values are presented as means ± SEM, * $p < 0.05$, ** $p < 0.01$.

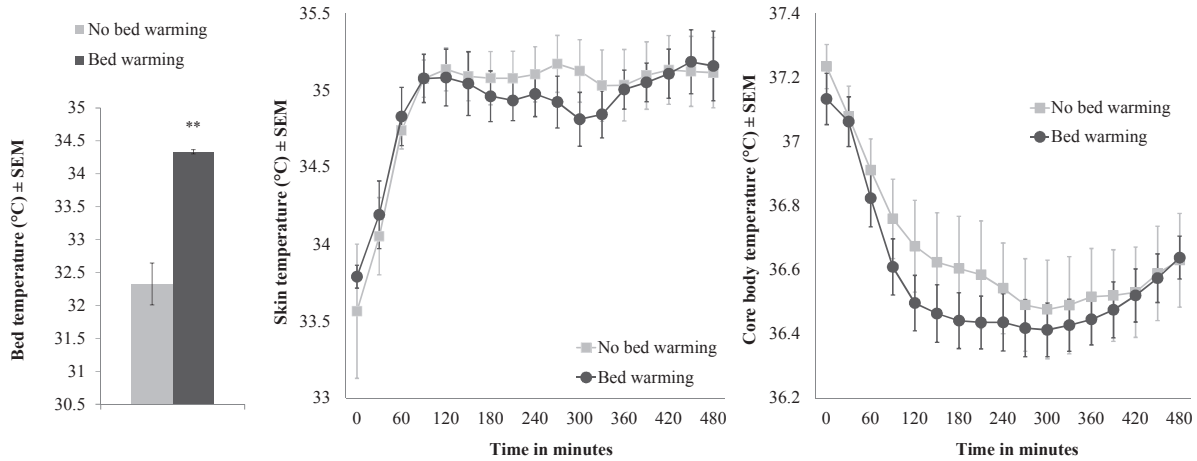

Figure 2. Average bed temperature (*left panel*), average skin temperature (*middle panel*) and average core body temperature (*right panel*) in the neutral condition (*dark grey*) and the bed warming condition (*light grey*). Values are presented as means ± SEM, data in graphs aligned on lights off (0 on x-axis), ** $p < 0.01$.

DISCUSSION

The present study shows that both Wake and S1 during the nocturnal sleep period can be suppressed in healthy young adults using mild bed warming. The application of a heating blanket with three separate feedback-controlled heating zones (instead of 9 zones as reported in 2011)[8] and a faster feedback successfully prevented the heat overload and subsequent wake promoting effects observed in our earlier study.

In contrast to studies that warmed the skin using water-perfused thermo suits with full body contact,[3-5] we failed to find an effect of bed warming on skin temperature and on the relative overnight proportion of light and deep sleep (S2 and SWS). Raymann and coworkers showed in young adults that the water-perfused pajama intervention resulted in mild skin warming and subsequently in more time spent in S2 and SWS at the cost of Wake and S1.[5] Our bed warming intervention did not result in warmed skin and subsequently resulted in suppression of Wake and S1 only.

The failure to find skin warming using our blanket protocol might be related to the contact surface of the intervention. Since our heating blanket only provides contact warming of one side of the body (as opposed to full body contact warming when using pajamas), the optimal direct contact warming surface is smaller. One might also argue that the setup of the temperature measurement, with most skin temperature sensors located at a side of the body that was not in contact with the warming blanket, resulted in an underestimation of the effect of the skin warming.

Based on these data we might extend the framework of temperature manipulations during the night as a sleep permissive factor[7]. When the bedding is warmed, without affecting the skin temperature, we might speak of a *sleep permissive situation* (and hence suppressing wake),

whereas the situation in which warming results in mild skin warming can be regarded as *sleep promoting* (and hence inducing deeper sleep). Of note, in the situation that warming results in heat overload and thermal discomfort, the thermal situation can be judged as *sleep prohibiting*.

Based on our results, mild bed warming can be regarded a sleep-permissive condition that can be easily achieved using a feedback controlled electric blanket.

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SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 23, 2012

Abstracts

METHYLPHENIDATE MODIFIES THE MOTION OF THE CIRCADIAN CLOCK

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People with attention-deficit/hyperactivity disorder (ADHD) often experience sleep problems, and these are frequently exacerbated by the methylphenidate they take to manage their ADHD symptoms. Many of the changes to sleep are consistent with a change in the underlying circadian clock. The present study was designed to determine if methylphenidate alone could alter properties of the circadian clock. Young male mice were examined in light-dark cycles and in constant darkness and recordings were performed on behavioral activity, sleep, and electrical activity in the suprachiasmatic nucleus (SCN) of freely moving mice. Methylphenidate in the drinking water (0.08%) significantly increased activity in the mid-to-late night, and led to a delay in the onset of activity and sleep relative to the light-dark cycle. While locomotor levels returned to baseline after treatment ended, the phase angle of entrainment required at least a week to return to baseline levels. In constant darkness, the free-running period of both wheel-running and general locomotor rhythms was lengthened by methylphenidate. When the treatment ended, the free-running period either remained stable or only partially reverted to baseline levels. Methylphenidate also altered the electrical firing rate rhythms in the SCN. It induced a delay in the trough of the rhythm, an increment in rhythm amplitude, and a reduction in rhythm variability. These observations suggest that methylphenidate alters the underlying circadian clock. The observed changes are consistent with clock alterations that would promote sleep-onset insomnia.

MCA's research is supported by a Discovery grant from the Natural Sciences and Engineering Research Council of Canada. JHM's research is supported by Technology Foundation STW, P10-18. TD's research was supported by the Netherlands Organization for Scientific Research (NWO, grant 818.02.016).

Neuropsychopharmacology (2012) 37: 2446-2455.

DISTRIBUTION AND PERIODICITY OF LEG MOVEMENTS DURING SLEEP IN CHILDREN WITH RESTLESS LEGS SYNDROME.

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Introduction: In patients with Restless Legs Syndrome (RLS), polysomnography (PSG) reveals excessive (periodic or at random) leg movements (LMs). In adult patients, studies have shown characteristic values in parameters of limb movements during sleep. These measures are the periodicity index (PI), the duration of the inter limb movements intervals and the time distribution over the night. The aim of the study is to describe the same parameters in children with RLS and to compare the results to those in adults.

Methods: N= 11 patients (3 females; median age: 8 years, range 2-16) were included if they showed limb movements with an index of at least 5/hour of sleep. Limb movements were measured and assessed according to the AASM rules (2007); recording and scoring of the accompanying video PSG was done using the same rules. For the PI, the duration of the inter limb movement intervals and the time distribution of LMs the methods described by Ferri et al and ourselves were used.

Results: In contrast to the mean interval duration of 24.3 s, which we found previously in adults, no clear peak value was detected in children. The distribution of these intervals is mainly in the range of 10-20 seconds. During the night periodic limb movements in sleep (PLMS) have their highest prevalence in the beginning of the night with a peak in the 2^{e} hour of NREM sleep (fig 1). Isolated limb movements in sleep (LMS) are more evenly spread over the whole night, with a small peak during NonREM sleep in the 7th hour of sleep (fig 2). The periodicity index (PI) had a value of 0.64 in REM sleep and of 0.69 when REM and NonREM sleep are taken together. The distribution over time and the PI values are approximately similar to those found in adults.

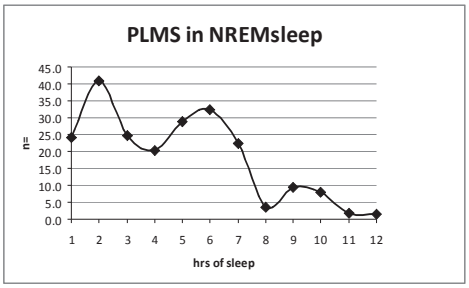

Fig 1.

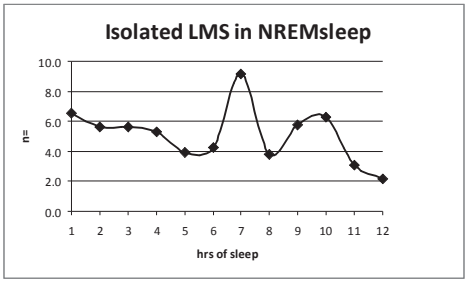

Fig 2.

Conclusion: In a small group of patients with RLS in childhood we only partly found the characteristics in limb movements during sleep as can be seen in adult patients with RLS.

References: 1. Ferri et al, J Clinical Neurophysiology 2009; 120: 257-263
2. Arends et al, J SLEEP Research 2010: supp 1:283

Presented at the poster session of the 21st Meeting of the European Sleep Research Society Paris, France, 04-08 September 2012

A DECADE OF EEG THETA/BETA RATIO RESEARCH IN ADHD: A META-ANALYSIS

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Objective: Many EEG studies have reported that ADHD is characterized by an elevated Theta/Beta ratio (TBR). In this study we conducted a meta-analysis on the TBR in ADHD.

Method: TBR data during Eyes Open from location Cz were analyzed from children/adolescents 6-18 years of age with and without ADHD.

Results: Nine studies were identified with a total of 1253 children/adolescents with and 517 without ADHD. The grand-mean effect size (ES) for the 6-13 year-olds was 0.75 and for the 6-18 year-olds was 0.62. However the test for heterogeneity remained significant; therefore these ESs are misleading. Post-hoc analysis found a decreasing difference in TBR across years, explained by an increasing TBR for the non-ADHD groups.

Conclusion: Excessive TBR cannot be considered a reliable diagnostic measure of ADHD. However, a substantial sub-group of ADHD patients do deviate on this measure and TBR has prognostic value, warranting its use as a prognostic measure rather than a diagnostic measure.

Acknowledgements
We hereby would like to acknowledge all authors who supplied us with additional information making this meta-analysis possible and people who provided us with feedback and comments related to this meta-analysis, Sandra Loo, Lea Williams, Michelle Wang, Ali Nazari, Hartmut Heinrich, Gene Arnold, Roger DeBeus, David Kaiser, Jaeseung Jeong, Juliana Yordanova, Karin Gomarus, Fred Coolidge, Gene Arnold and Daniel Brandeis. Furthermore, we acknowledge the Collaborative Neurofeedback Group and its members for feedback and support at the different stages of this manuscript.

This is the abstract from a manuscript submitted to the Journal of Attention Disorders

INCREASED FOOD INTAKE AND CHANGES IN METABOLIC HORMONES IN RESPONSE TO CHRONIC SLEEP RESTRICTION ALTERNATED WITH SHORT PERIODS OF SLEEP ALLOWANCE

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Rodent models for sleep restriction have good face validity when examining food intake and related regulatory metabolic hormones. However, in contrast to epidemiological studies where sleep restriction is associated with body weight gain, sleep restricted rats show a decrease in body weight. This difference with the human situation might be caused by the alternation between periods of sleep restriction and sleep allowance that often occurs in real life. Therefore we assessed the metabolic consequences of a chronic sleep restriction protocol that modeled working weeks with restricted sleep time alternated by weekends with sleep allowance. We hypothesized that this protocol could lead to body weight gain.

Male Wistar rats were divided over three groups: sleep restriction (SR), forced activity control (FA) and home cage control (HC). SR rats were subjected to chronic sleep restriction by keeping them awake for 20h per day in slowly rotating drums. To model the human condition, rats were subjected to a 4-week protocol with each week consisting of a 5-day period of sleep restriction followed by a 2-day period of sleep allowance.

During the first experimental week, SR caused a clear attenuation of growth. In subsequent weeks, two important processes occurred: 1) a remarkable increase in food intake during SR days, 2) an increase in weight gain during the weekends of sleep allowance, even though food intake during those days was comparable to controls.

In conclusion, our data revealed that the alternation between periods of sleep restriction and sleep allowance lead to complex changes in food intake and body weight, that prevented the weight loss normally seen in a continuous sleep restriction protocol. Therefore this “week-weekend” protocol is an improvement in comparison to our previous sleep restriction model and may be a better model to study the metabolic consequences of restricted sleep.

Barf RP, Desprez T, Meerlo P, Scheurink AJW. Increased food intake and changes in metabolic hormones in response to chronic sleep restriction alternated with short periods of sleep allowance. American Journal of Physiology 302: R112-R117, 2012.

TELEMETRIC STUDY OF SLEEP ARCHITECTURE AND SLEEP HOMEOSTASIS IN THE DAY-ACTIVE TREE SHREW *TUPAIA BELANGERI*

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In this study we characterized sleep architecture and sleep homeostasis in the tree shrew, *Tupaia belangeri*, a small, omnivorous, day-active mammal, closely related to primates.

Adult tree shrews were individually housed under a 12h light / 12h dark cycle in large cages containing tree branches and a nest box. The animals were equipped with radio transmitters to allow continuous recording of electroencephalogram (EEG), electromyogram (EMG) and body temperature without restricting their movements. Recordings were performed under baseline conditions and after sleep deprivation (SD) for 6h or 12h during the dark phase.

Under baseline conditions, the tree shrews spent a total of 62.4 ± 1.4% of the 24h cycle asleep, with 91.2 ± 0.7% of sleep during the dark phase and 33.7 ± 2.8% sleep during the light phase. During the dark phase, all sleep occurred in the nest box; 79.6% of it was non-rapid eye movement (NREM) sleep and 20.4% was rapid eye movement (REM) sleep. In contrast, during the light phase, sleep occurred almost exclusively on the top branches of the cage and only consisted of NREM sleep. Sleep deprivation was followed by an immediate increase in NREM sleep time and an increase in NREM sleep EEG slow-wave activity (SWA) indicating increased sleep intensity. The cumulative increase in NREM sleep time and intensity almost made up for the NREM sleep that had been lost during 6h SD, but did not fully make up for the NREM sleep lost during 12h SD. Also, only a small fraction of the REM sleep that was lost was recovered, which mainly occurred on the second recovery night.

The day-active tree shrew shares most of the characteristics of sleep structure and sleep homeostasis that have been reported for other mammalian species, with some peculiarities. Because the tree shrew is an established laboratory animal in neurobiological research, it may be a valuable model species for studies of sleep regulation and sleep function, with the added advantage that it is a day-active species closely related to primates.

Coolen A, Hoffman K, Barf P, Fuchs E, Meerlo P. Telemetric study of sleep architecture and sleep homeostasis in the day-active tree shrew Tupaia belangeri. Sleep 35: 879-888, 2012.

CIRCADIAN AND HOMEOSTATIC REGULATION OF SLEEP AND ELECTROENCEPHALOGRAM PATTERNS IN THE RAT

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Objective. 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 the homeostatic process is reflected by slow-wave activity (SWA; ~1-4 Hz) in the non-rapid eye-movement (NREM) sleep electroencephalogram (EEG). The circadian process is controlled by a pacemaker located in the suprachiasmatic nucleus of the hypothalamus and provides the sleep homeostat with a circadian framework. Many different experimental manipulations and sleep deprivation protocols have been applied in humans to investigate the interaction between the two processes. They show that in humans the period of consolidated waking during the light period of the day is a consequence of the interaction between an increasing homeostatic sleep drive and a circadian signal, which promotes waking during the day and sleep during the night. In particular, in humans a clear increase in REM sleep was found in the early morning, and a short period of increased waking was observed in the evening, shortly before habitual bedtime.

Results. In the rat we have shown that under constant homeostatic sleep pressure (constant SWA levels), in a nap protocol in constant dark conditions, still a small circadian modulation of the amount of NREM sleep and waking is observed. This modulation was the result of a circadian modulation of waking and NREM sleep episode duration. However, a significant circadian modulation in REM sleep was absent. Also a short period of increased waking was not found in the rat. Spectral analysis of EEG frequency activity showed clear frequency dependent circadian and homeostatic changes in the different vigilance states.

Conclusion. The data show that circadian and homeostatic changes in EEG frequencies, particular in NREM sleep, are similar between rats and humans. In contrast, the influence of the circadian clock on sleep-wake distribution is small in the rat, compared to humans. In the rat, the sleep homeostatic modulation, in phase with the circadian clock, seems to amplify the relatively weak clock induced circadian changes in NREM sleep and waking, and is probably the main cause of a circadian modulation in REM sleep in the rat.

This research was supported by the Netherlands Organization for Scientific Research (NWO) grant 818.02.016.

ESRS 2012 J Sleep Res (2012) 21 suppl 1. 13.

REDUCED SLEEP AND LOW ADENOSINERGIC SENSITIVITY IN *CACNA1A* R192Q MUTANT MICE

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Study objectives: Adenosine modulates sleep via A_1 and A_{2A} receptors. As the A_1 receptor influences $Ca_V2.1$ channel functioning via G-protein inhibition, there is a possible role of the $Ca_V2.1$ channel in sleep regulation. To this end we investigated transgenic *Cacna1a* R192Q mutant mice that express mutant $Ca_V2.1$ channels that are less susceptible to inhibition by G-proteins. We hypothesized that *Cacna1a* R192Q mice could show reduced susceptibility to adenosine which may result in a sleep phenotype characterized by decreased sleep.

Design: R192Q mutant and littermate wildtype mice were subjected to a 6-h sleep deprivation, treatment with caffeine (a non-specific adenosine receptor antagonist which induces waking), or cyclopentyladenosine (CPA, an A_1 receptor specific agonist which induces sleep).

Measurements and Results: Under baseline conditions, *Cacna1a* R192Q mice showed more waking with longer waking episodes in the dark period and less non-rapid eye-movement (NREM) sleep, but equal amounts of REM sleep compared to wildtype. After treatment with caffeine R192Q mice initiated sleep 30 min earlier than wildtype, whereas after CPA treatment, R192Q mice woke up 260 min earlier than wildtype. Both results indicate that *Cacna1a* R192Q mice are less susceptible to adenosinergic input, which may explain the larger amount of waking under undisturbed baseline conditions.

Conclusion: We here show that adenosinergic sleep induction, and responses to caffeine and CPA, are modified in the R192Q mutant in a manner consistent with decreased susceptibility to inhibition by adenosine. The data suggest that the A_1 receptor modulates sleep via the $Ca_V2.1$ channel.

This was not an industry supported study. This research was supported by the Netherlands Organization for Scientific Research [NWO, grant 818.02.016 (T.D.); Vici 918.56.602 (M.D.F)], and the Center of Medical System Biology (CMSB) established by the Netherlands Genomics Initiative/Netherlands Organization for Scientific Research (NGI/NWO) and Community (M.D.F., A.M.J.M.v.d.M.).

Sleep in press.

ADOLESCENTS' SLEEP IN LOW- STRESS AND HIGH-STRESS (EXAM) TIMES: A PROSPECTIVE QUASI-EXPERIMENT

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Introduction
This prospective quasi-experiment (N=175; mean age: 15.14 years) investigates changes in adolescents' sleep from low-stress (regular school week) to high-stress times (exam week) and examines the (moderating) role of chronic sleep reduction, baseline stress, and gender.

Method
Sleep was monitored over three consecutive weeks using actigraphy.

Results
Adolescents' sleep was more fragmented during the high-stress time than during the low-stress time, meaning that individuals slept more restless during stressful times. However, sleep efficiency, total sleep time, and sleep onset latency remained stable throughout the three consecutive weeks. High chronic sleep reduction was related to later bedtimes, later sleep start times, later sleep end times, later getting up times, and more time spent in bed. Furthermore, low chronic sleep reduction and high baseline stress were related to more fragmented sleep during stressful times.

Conclusion
This study shows that stressful times can have negative effects on adolescents' sleep fragmentation, especially for adolescents with low chronic sleep reduction or high baseline stress.

Behavioral Sleep Medicine, in press

THE CHRONIC SLEEP REDUCTION QUESTIONNAIRE (CSRQ): A CROSS-CULTURAL COMPARISON AND VALIDATION IN DUTCH AND AUSTRALIAN ADOLESCENTS

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Introduction
Although adolescents often experience insufficient and/ or poor sleep, sleep variables such as total sleep time do not account for individuals' sleep need and sleep debt and may therefore be an inadequate representation of adolescents' sleep problems and its daytime consequences. This problem can be overcome by using the Chronic Sleep Reduction Questionnaire (CSRQ), an assessment tool that measures symptoms of chronic sleep reduction and therefore accounting for sleep need and sleep debt. The present study aims at developing an English version of the CSRQ and assesses the reliability and validity of the Dutch and the English CSRQ version.

Method
The CSRQ was administered in large Dutch (n = 166, age = 15.2 ± 0.57 years, 28% male) and Australian (n = 236, age = 15.5 ± 0.99 years, 65% male) samples. Subjective sleep variables were measured with surveys and sleep diaries of five= school nights. Additionally, sleep of the same five nights was monitored with actigraphy.

Results
Both CSRQ versions showed good psychometric properties concerning their reliability (Dutch: $\alpha = 0.85$; English: $\alpha = 0.87$) and validity as the same overall structure of the two CSRQ versions and significant correlations with subjective and objective sleep variables were found. School grades were related to chronic sleep reduction, whereas the relationship between grades and other sleep variables was weak or absent.

Conclusion
These results highlight the idea that chronic sleep reduction may be a better indicator of adolescents' insufficient and/ or poor sleep than other sleep variables such as total sleep time.

Journal of Sleep Research, in press

SLEEP POSITION TRAINER VS. TENNIS BALL TECHNIQUE IN POSITIONAL OSA

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Late-breaking abstract consideration: Positional OSA is a clinical problem. 49% of mild, 20% of moderate and in 6% of severe OSA are positional depended, defined as a combination of AHItot>5 + AHI supine > 2x AHInon-supine and AHI< 5 in non-supine position (Mador). The group with mild OSA do have complaints, tolerate CPAP poor or reimbursement with low AHI of CPAP is not possible. Also around 30% of OSAS patients cannot be treated with MRA because of (paro)dental problems. So there can be a place in the therapeutic field for positional therapy. Positional therapy has been shown to be as effective as CPAP when used (Permut). However the few studies done show poor compliance rates. We investigated in a RCT standard position therapy versus a new easy to wear and use position therapy device, with very hopeful results.
M.Mador. Chest 2005 128 2130-2137
I. Permut J Clin Sleep med 2010 6 (3) 238-243
Introduction: standard tennis ball techniques like the positional band (PB) can be as effective as CPAP in positional OSA (POSA) but compliance is low.
Objectives: can compliance of positional therapy in POSA be improved with a new device, the sleep position trainer (SPT) and have the same effectiveness as PB?
Therapies: The SPT is a small in supine position vibrating device, placed on the ventral thorax. Body position and temperature sensors are built in; data can be stored and read out giving hours of use and supine position time. The PB is a belt with three inflatable airbags worn on the back preventing supine position.
Methods: 55 new patients with POSA were randomized to SPT (29) or PB (26). Standard home-PSG was done at baseline and after 1-month therapy. Quebec Sleep Questionnaire (QSQ), ESS and VAS scores were taken. The SPT device was, in a non-vibrating mode, also build in the PB to measure daily compliance in both groups.
Results: comparing PSG: AHItot, AHIsup, %supTST was respectively 11.4, 30.7, 27.9% for SPT and 13.2, 37.3, 31.1% for PB. After 1 month the same parameters were respectively reduced to 3.9, 0.0, 0.0 for SPT and 5.8, 0.0, 0.0 for PB. After 1 month therapy also no differences in QSQ, ESS, PSG sleep parameters were observed, however perceived therapeutic effectiveness by means of VAS was 74,5 for SPT and 55,2 for PB (P 0.02). Compliance decreased in both groups with time. At 1 month compliance was 70% for SPT, 42% for PB. Compliance expressed as use >4 hours/night for > 5 days/week was 76% for SPT, 42% for PB (P 0.01). Dropouts were 7% in SPT, 28% in PB.
Conclusions: SPT and PB effectively treat POSA when used. Only the SPT does have an acceptable compliance after 1 month.
General Conflicts of Interests: *The Presenting Author has no, real or perceived conflicts of interest that relate to this abstract.*
Tobacco-Industry related conflict of interests: *No*
Submitted Late Braking Abstract ERS 2012 Vienna

SLEEP SCREENING PROJECT FOR OSA IN COMPANY WORKERS: A PILOT STUDY

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Late-breaking abstract consideration: There is a huge interest in screening for obstructive sleep apnea (OSA) in populations like primary care, workers /employees and in more specific populations, like commercial drivers and in patients at increased cardiovascular risk (diabetes, hypertension, obesity). Screening for OSA in healthy employees can be worthwhile, since OSA is a prevalent disease with daily symptoms, increased cardiovascular risk, and more traffic-related accidents, while effective therapy is available. The authors were engaged by Philips to advise about screening their Dutch employees (13.000). In a systematic review Abrishami (1) et al. found surprisingly few properly performed studies on screening. Hence, it was decided to develop a valid screening strategy in a pilot setting.

(1) A. Abrishami. A systematic review of screening questionnaires for obstructive sleep apnea J Can Anesth 2010;57:423–38

Introduction: Philips-Netherlands has intended to screen its Dutch employees (13.000) for OSA.

Objectives: due to the large number of employees and the small amount of studies on screening for OSA, an optimal screening strategy had to be developed in a pilot study.

Methods: 1861 Philips employees where invited by e-mail. Six sleep questionnaires (Q), type IV portable monitoring (PM), and a standard home-polysomnography were done. Uni-variate analysis and logistic regression analysis was performed to determine the optimal screening strategy. OSA was defined as AHI>15, or AHI>5 with symptoms but without overt insomnia.

Results: 249 Persons gave informed consent, 235 returned all Q, 190 did both sleep studies and from 176 (9,5%) all data were available. The StopQ, StopBangQ, BerlinQ, Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and Athens Insomnia Scale were positive in 45%, 57%, 36%, 9%, 34%, and 7%, respectively. Using PM a RDI>15 was found in 61 persons (35%). Finally, OSA was diagnosed in 65 persons (37%). Age, presence of heart failure or arrhythmias, absence of insomnia, BerlinQ- Question 5 (breathing stops), and 3-way scoring of the BerlinQ and StopBang Q predicted OSA. Step 1 of the Philips Sleep Screening Strategy is based on the mentioned predictor variables, resulting in subjects with a low, intermediate and high probability of OSA. In step 2 the intermediate group is split into low and high probability for OSA, based on PM with a RDI cutoff of 15. This 2- step strategy has a sensitivity of 66%, and specificity of 89%. For an estimated prevalence of 9%, the pos. and neg. predictive values will be 38% and 96%, respectively.

Conclusion: Screening for OSA in an employee's population is feasible.

General Conflicts of Interests: *The Presenting Author has no, real or perceived conflicts of interest that relate to this abstract.*

Tobacco-Industry related conflict of interests: *No*

Submitted Late Breaking Abstract ERS 2012 Vienna

EVIDENCE FOR NEURONAL DESYNCHRONY IN THE AGED SUPRACHIASMATIC NUCLEUS CLOCK

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Aging is associated with a deterioration of daily (circadian) rhythms in physiology and behavior. Deficits in the function of the central circadian pacemaker in the suprachiasmatic nucleus (SCN) have been implicated, but the responsible mechanisms have not been clearly delineated. In this report, we characterize the progression of rhythm deterioration in mice to 900 d of age. Longitudinal behavioral and sleep-wake recordings in up to 30-month-old mice showed strong fragmentation of rhythms, starting at the age of 700 d. Patch-clamp recordings in this age group revealed deficits in membrane properties and GABAergic postsynaptic current amplitude. A selective loss of circadian modulation of fast delayed-rectifier and A-type K^+ currents was observed. At the tissue level, phase synchrony of SCN neurons was grossly disturbed, with some subpopulations peaking in anti-phase and a reduction in amplitude of the overall multiunit activity rhythm. We propose that aberrant SCN rhythmicity in old animals-with electrophysiological arrhythmia at the single-cell level and phase desynchronization at the network level-can account for defective circadian function with

This research was supported by the Netherlands Organization for Scientific Research grant 818.02.016. .

J Neurosci 32 (2012) 5891-5899.

SLEEP BENEFIT IN PARKINSON'S DISEASE; THE BENEFIT OF AFTERNOON NAPS

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Introduction Some patients with Parkinson's disease (PD) report a beneficial effect of sleep, with an improved motor functioning upon awaking in the morning, contrary to what would be expected after a night without medication. This so-called sleep benefit (SB) is an intriguing phenomenon, but research is still limited. We further examined SB, with additional attention to possible SB after daytime naps.

Methods We assessed clinical screening questionnaires completed by consecutive PD patients visiting the Parkinson Centre Nijmegen, a tertiary referral centre for extrapyramidal disorders. Questionnaires were analyzed on the subjective presence of SB, general patient characteristics, sleep quality and sleeping habits.

Results We included 240 patients, 113 of whom (47,1%) indicated to experience SB. There was a difference in presence of SB between patients who did take daytime naps (n=98; 40.8%) versus those who did not ($\chi^2 = 22.641$ $p < 0.000$). Of the patients who regularly took an afternoon nap, 13.3% experienced SB after a nap and 20.4% after both night and daytime sleep. Whereas 20.4% only had SB after night sleep and 45.9% was not familiar with SB. Of the non-nappers 42.3% experienced SB.

Conclusion These data confirm that sleep benefit is a significant phenomenon in PD. We found a substantial part of the patients profiting from SB, also after daytime sleep. As such, an afternoon nap could be a valuable addition to regular medical therapy. Patients and medical practitioners should be made aware of these beneficial effects of sleep in PD. Furthermore, research should be conducted to study the underlying mechanisms and enhance the clinical applicability of SB.

Table 1. Naps and Sleep Benefit (SB)

	No SB	*SB only after night sleep*	*SB only after nap*	*SB after both night sleep and nap*	*Total*
Non-regular nappers	82 (57.7%)	45 (31.7%)	2 (1.4%)	13 (9.2%)	**142**
Regular nappers	45 (45.9%)	20 (20.4%)	13 (13.3%)	20 (20.4%)	**98**
Total	**127 (52.9%)**	**65 (27.1%)**	**15 (6.8%)**	**33 (13.8%)**	**240**

Results are shown as N (%).

Presented at SLEEP 2012, APSS 26th annual meeting, Boston.

POOR SLEEP AS A POTENTIAL CAUSAL FACTOR IN AGGRESSION AND VIOLENCE

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Clinical observations suggest that sleep problems may be a causal factor in the development of reactive aggression and violence. In this review we give an overview of existing literature on the relation between poor sleep and aggression, irritability and hostility. Correlational studies are supporting such a relationship. Although limited in number, some studies suggest that treatment of sleep disturbances reduces aggressiveness and problematic behaviour. In line with this, is the finding that sleep deprivation actually increases aggressive behaviour in animals, and angriness, short-temperedness and the outward expression of aggressive impulses in humans. In most people poor sleep will not evoke actual physical aggression, but certain individuals, such as forensic psychiatric patients, may be particularly vulnerable to the emotional dysregulating effects of sleep disturbances. The relation between sleep problems and aggression may be mediated by the negative effect of sleep loss on prefrontal cortical functioning. This most likely contributes to loss of control over emotions, including loss of the regulation of aggressive impulses to context-appropriate behaviour. Other potential contributing mechanisms connecting sleep problems to aggression and violence are most likely found within the central serotonergic - and the hypothalamic-pituitary-adrenal-axis. Individual variation within these neurobiological systems may be responsible for amplified aggressive responses induced by sleep loss in certain individuals. It is of great importance to identify the individuals at risk, since recognition and adequate treatment of their sleep problems may reduce aggressive and violent incidents.

Kamphuis J, Meerlo P, Koolhaas JM, Lancel M. Poor sleep as a potential causal factor in aggression and violence. Sleep Medicine 13: 327-334, 2012.

WEARABLE WIRELESS PHYSIOLOGICAL MONITORING FOR CHRONOBIOLOGY AND SLEEP

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Personal Health Institute International, Amsterdam, The Netherlands

Introduction

The study of circadian rhythms, continuous monitoring of vital signs or home sleep testing demand continuous non-invasive monitoring of physiological signals. The device has to be ubiquitous to make interference by the device in daily life as minimal as possible. We developed a wearable monitor and studied the reliability for measuring the 24-hour physiological rhythms in everyday life (FP6 EUCLOCK project).

Methods

We chose a three-tier architecture. The first tier is formed by a wearable and wireless sensor-unit, using minimal power. We used ultra-low power micro-electronics, based on patented Sensium technology, designed for medical wireless transmission. The first tier also has a bluetooth Oximeter. Storage and analysis of the signals were implemented in a smart phone (2nd tier). The third tier is a wireless connection to a server with Galaxy software for database management, analysis and reporting. The following signals can be measured: ECG, 2 channel RIP respiration, 3-axis body position and actigraphy, nasal pressure, temperature, light, sound, oximetry and pulse wave.

Wireless transmission is prone to errors of data loss and synchronization. Proprietary algorithms were developed to synchronize data and detect transmission loss. Reliability and validity of the system was assessed in a field experiment with 9 subjects who performed simulated shiftwork. In addition the signals were analyzed to explore the possibility of detecting circadian phase and to verify the synchronization.

Results

Data from a total of 49 recordings were analyzed (up to 128 hours duration). The number of transmission errors ranged from 2% to 10%. Longer transmission errors were due to movements. However, during movements the physiological and sensor artefacts were more dominant than the transmission errors.

Core body temperature, heart rate and respiratory rate simultaneously show a decrease during the night and an increase in the early morning. Interestingly, heart rate and respiratory rate also show an ultradian pattern, which may coincide with the REM/NREM cycle. During the day, however, respiratory effort was more sensitive for external influences.

Conclusion

Neptune is an ultra-low power, wireless, wearable device capable of continuous recording of physiological signals longer than 72 hours. Core body temperature and heart rate seem to be good candidates for the determination of circadian phase. The variety of sensors in Neptune allows it's usage for many sleep applications.

21th Congress of the European Sleep Research Society, 2012, Paris, France

INTERNET-DELIVERED OR MAILED SELF-HELP TREATMENT FOR INSOMNIA? A RANDOMIZED WAITING-LIST CONTROLLED TRIAL

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Cognitive Behavioral Therapy (CBT) is effective in reducing insomnia complaints, but the effects of self-help CBT have been inconsistent. The aim of this study was to determine the effectiveness of self-help for insomnia delivered in either electronic or paper-and-pencil format compared to a waiting-list. Participants kept a diary and filled out questionnaires before they were randomized into electronic (n = 216), paper-and-pencil (n = 205), or waiting-list (n = 202) groups. The intervention consisted of 6 weeks of unsupported self-help CBT, and post-tests were 4, 18, and 48 weeks after intervention. At 4-week follow-up, electronic and paper-and-pencil conditions were superior ($p < .01$) compared to the waiting-list condition on most daily sleep measures (Δd = 0.29–0.64), global insomnia symptoms (Δd = 0.90–1.00), depression (Δd = 0.36–0.41), and anxiety symptoms (Δd = 0.33–0.40). The electronic and paper-and-pencil groups demonstrated equal effectiveness 4 weeks after treatment (Δd = 0.00–0.22; $p > .05$). Effects were sustained at 48-week follow-up. This large-scale unsupported self-help study shows moderate to large effects on sleep measures that were still present after 48 weeks. Unsupported self-help CBT for insomnia therefore appears to be a promising first option in a stepped care approach.

Published as: Lancee, J., van den Bout, J., van Straten, A., & Spoormaker, V. I. (2012). Internet-delivered or mailed self-help treatment for insomnia? A randomized waiting-list controlled trial. Behaviour Research and Therapy 50(1), 22-29.

END EXPIRATORY LUNG VOLUME AS A PREDICTOR OF OBSTRUCTIVE SLEEP APNEA SEVERITY

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Introduction
One of the contributing factors to upper airway collapse in obstructive sleep apnea (OSA) is reduced end expiratory lung volume (EELV). There is evidence for correlation of apnea hypopnea index (AHI) with EELV in supine position during sleep. In respiratory function testing however, EELV is routinely measured in sitting position and during wake ($EELV_{sit}$). Aim of the study was to establish the relationship between $EELV_{sit}$ and OSA. We hypothesized that $EELV_{sit}$ may affect the severity of OSA.

Methods
In an observational study the relationship between $EELV_{sit}$ and OSA in 59 adult patients of Orbis Medical Centre, Sittard (The Netherlands) was assessed using a regression analysis. $EELV_{sit}$ was evaluated by helium dilution technique, and severity of OSA by apnea hypopnea index (AHI) based on polysomnography measurements. In addition $EELV_{sit}$ was compared to other predictors of OSA; Epworth sleepiness scale (ESS), Mallampati-score, body mass index (BMI), and neck- and abdominal circumference, by means of a multiple regression analysis.

Results
$EELV_{sit}$ was a predictor of AHI, R=-0.392 (p=0.003). Multiple regression analysis demonstrated that abdominal circumference explained 15.5% of variance of AHI, and together with $EELV_{sit}$ 23.4% of the variance of AHI was explained. Other predictors were not significant.

Conclusion
$EELV_{sit}$ contributes to the severity of OSA and might therefore be useful to differentiate between high and low risk patients for OSA in screening and diagnostics settings. Abdominal circumference also appeared to predict severity of OSA and had even more impact on AHI compared to $EELV_{sit}$.

Acknowledgements for support of this study are made to M. van Straalen, L. Lebon-Muerders, J. Muerders and R. Hoogerwerf.

This study will be presented by poster at the ERS-congress of 2012 in Vienna.

NOCTURNAL HYPOKINESIA AND SLEEP QUALITY IN PARKINSON'S DISEASE

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Introduction
More than half of patients with Parkinson's disease (PD) have difficulties turning around in bed. This nocturnal hypokinesia is considered one of the factors responsible for the high prevalence of sleep disorders in PD. To date, little is known about the possible association between sleep disruption and problems turning around in bed. We therefore studied a large cohort of patients with PD, looking specifically at the relation between sleep quality on the one hand, and the presence and frequency of nocturnal hypokinesia on the other.
Methods
We included 240 consecutive PD patients visiting the Parkinson Centre Nijmegen, a tertiary university referral centre. Clinical and demographic data were obtained. Nocturnal hypokinesia was assessed using question 35 of the Parkinson's Disease Quality of Life Questionnaire. The presence was rated on a 5-point Likert scale, ranging from 1='all of the time' to 5='never'. Patients scoring 1-3 on the item were considered to have clinically relevant nocturnal hypokinesia. The Pittsburgh Sleep Quality Index (PSQI) was used to quantify sleep quality, higher scores indicating poorer sleep quality.
Results
Out of 240 patients, 135 had difficulties turning around in bed. PSQI scores were significantly higher in patients with nocturnal hypokinesia (PSQI 7.7±4.1) compared to those without (PSQI 6.1±3.4, p=0.001). A regression model correcting for age, disease duration and Hoehn & Yahr stage showed a significant influence of nocturnal hypokinesia on sleep quality (R-squared = 0.42, standardized-beta = 0.163, p=0.026). Finally, there was a linear relationship between frequency of nocturnal hypokinesia and sleep quality.
Conclusion
This is the first study that documents that nocturnal hypokinesia negatively affects sleep quality in PD. Nocturnal hypokinesia therefore merits therapeutic attention, including optimal night-time dopaminergic treatment and education about turning strategies in bed.

JAGS in press.

OBJECTIVELY ASSESSED ACTIVITY RHYTHMS AND SELF-RATED SLEEP IN A LARGE POPULATION-BASED COHORT OF THE ELDERLY

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Introduction
The diurnal rhythm of activity changes profoundly with age in all animals studied so far, including humans. Aging also affects sleep. It is insufficiently known to what extent these two age-related changes are associated. We assessed the cross-sectional association between objectively measured activity rhythms and self-rated sleep in a large population-based study.

Methods
1734 actigraphy recordings of at least 72 hours (138 ± 14 hours, mean ± SD) were collected in participants (age 62 ± 9.4 years) of the Rotterdam Study. Activity rhythms were assessed by calculating the interdaily stability and intradaily variability. A higher interdaily stability reflects a more stable rhythm over days; a higher intradaily variability gives an indication of higher fragmentation of the rhythm. Sleep was assessed with a diary which was kept during actigraphy.

Results
A higher interdaily stability was associated with less use of sleep medication ($\beta=-0.10$, $p<0.001$), a longer total sleep time ($\beta=0.08$, $p<0.001$), less napping during the day ($\beta=-0.26$, $p<0.001$), a better perceived sleep quality ($\beta=0.11$, $p<0.001$), and less perceived impairment due to sleep loss ($\beta=-0.14$, $p<0.001$), even after adjustment for multiple demographic and lifestyle parameters. Intradaily variability showed similar but inverse associations with sleep parameters and an additional positive association with number of awakenings after sleep onset ($\beta=0.07$, $p=0.004$. Results are in line with the moderate negative correlation ($r=-0.49$, $p<0.01$) observed between interdaily stability and intradaily variability.

Conclusion
Self-rated sleep is significantly associated with the stability and fragmentation of the activity rhythm. Of all sleep characteristics, napping was most strongly associated with a less stable and more fragmented activity rhythm in the elderly. Given the modest effect sizes, it is most probable that both shared and specific mechanisms underlie the variation in sleep characteristics and activity rhythms.

A.I. Luik and L.A. Zuurbier were supported by a Netherlands Organization for Scientific Research grant (NWO-VIDI: 017.106.370) awarded to H. Tiemeier.

Presented at APSS-SLEEP 2012, Boston, MA, USA.

CHRONIC SLEEP REDUCTION IN ADOLESCENTS WITH DELAYED SLEEP PHASE SYNDROME AND EFFECTS OF MELATONIN TREATMENT

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Introduction. Chronic sleep reduction, resulting from insufficient and/or poor sleep over a long time period, is a common phenomenon in adolescents. This increasing social problem has severe negative psychological and behavioral daytime consequences. As it is often caused by an interaction of biological and social factors, it is most likely also related to the biological clock and a delayed melatonin rhythm. Well timed and well dosed exogenous melatonin treatment might therefore be able to diminish chronic sleep reduction. This study aims to: (1) investigate whether adolescents with Delayed Sleep Phase Syndrome (DSPS) have more chronic sleep reduction than adolescents from the general population; (2) examine whether melatonin treatment affects chronic sleep reduction in adolescents with DSPS.
Methods. 116 adolescents diagnosed with DSPS (55.2 % boys, mean age 15,4 years, mean DLMO = 22:23 h) completed the Chronic Sleep Reduction questionnaire (CSRQ; Meijer, 2008) at baseline (before treatment). To date, 38 adolescents also completed the CSRQ after two months of 1-5 mg melatonin treatment, administered 3-5 hours before DLMO.
Results. Adolescents with DSPS had a mean score of 44.21 on the CSRQ at baseline. This was significantly higher ($t = 12.088$, $p < .001$) than the mean score that was found in a group adolescents from the general population (mean score = 33.69; Dewald et al., 2012). In comparison to baseline, chronic sleep reduction was significantly diminished after melatonin treatment ($t = -11.145$, $p < .001$) in adolescents with DSPS. Furthermore, this reduction was present on all CSRQ subscales (shortness of sleep ($t = -11.211$, $p < .001$), irritation ($t = -2.168$, $p = .037$), loss of energy ($t = -7.602$, $p < .001$) and sleepiness ($t = -6.578$, $p < .001$)). After melatonin treatment, adolescents with DSPS scored 31.40 on the CSRQ. This was lower than adolescents in the general population, although just not statistically significant ($t=-1,530$, $p = .133$).
Conclusions. Adolescents with DSPS have more chronic sleep reduction than adolescents from the general population. Melatonin treatment in adolescents with DSPS significantly decreases chronic sleep reduction to a level that is comparable to that of adolescents in the general population. Apparently, chronic sleep reduction is an important characteristic of DSPS.

Abstract submitted for presentation at the 21st congress of the European Sleep Research Society.

SLEEP IN CHILDREN WITH ASTHMA: RESULTS OF THE PIAMA STUDY

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Introduction. Children with asthma are thought to have impaired sleep quality and quantity. In this study we investigated which of many sleep aspects are associated with asthma.
Methods. The sample consisted of 2529 children (11 years) who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. Parents reported about asthma symptoms (wheezing, dyspnea, prescription of inhaled corticosteroids, asthma diagnosis) and children reported about different aspects of sleep (bedtime, rise time, sleep quality, daytime sleepiness/tiredness). Results were analyzed with (logistic) regression analysis.
Results. Children with frequent asthma symptoms significantly more often reported that they felt sleepy or tired during the day (34.4% experienced daytime sleepiness/tiredness at least once a week) than children without asthma symptoms (22.2%), and children with infrequent asthma symptoms (21.9%). This association was not confounded by gender, age of the child, parental educational level, or smoking inside the house; nor was the effect modified by gender. There were no associations between asthma and bedtime, time spent in bed or sleep quality.
Conclusions. Children with frequent asthma symptoms more often experienced daytime sleepiness/tiredness than children with infrequent or no asthma symptoms. Children with asthma did otherwise not differ much from children without asthma with regard to sleep.

Maanen A van, Wijga AH, Gehring U, Postma DS, Smit HA, Oort FJ, Rodenburg HR, Meijer AM. Sleep in children with asthma: results of the PIAMA study. Submitted for publication.

SLEEP IN THREE GENETIC SYNDROMES ASSOCIATED WITH INTELLECTUAL DISABILITY: CRI DU CHAT SYNDROME, DOWN'S SYNDROME AND JACOBSEN SYNDROME

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Introduction The prevalence of sleep problems in individuals with intellectual disability (ID) seems to vary between genetic syndromes associated with ID. Different types of sleep disturbance may reflect underlying causes of sleep problems and these types of sleep disturbance may vary between genetic syndromes.
Methods We examined and compared five types of sleep disturbance as well as severity of sleep problems in individuals with Cri du Chat syndrome (CDC), Down's syndrome (DS), Jacobsen syndrome (JS) and individuals with non-specific ID (NS). We used Simonds and Parraga's Sleep Questionnaire (1982) to assess prevalence of types of sleep disturbance and to explore differences in types of sleep disturbance and severity of sleep problems between the four diagnostic groups.
Results In each group, mean scores for Snoring were significantly higher than those for Sleep apnea and Snoring was the most prevalent type of sleep disturbance in CDC, DS and JS. The mean score on Complaints related to sleep was remarkably high in the JS group. There were no differences in severity of sleep problems between groups.
Conclusions These findings suggest that snoring is an important underlying cause of sleep problems in individuals with CDS, DS and JS.

Table: Composite Sleep Index (CSI) by diagnostic group

Group	*N*	*Mean (SD)*	*CSI ≥ 4* [a] *n (%)*
Cri du Chat syndrome	25	1.08 (1.75)	3 (12)
Down's syndrome	25	0.48 (1.12)	1 (4)
Jacobsen syndrome	25	1.68 (2.16)	5 (20)
Non-specific ID	25	1.60 (2.31)	3 (12)

[a] CSI > 4 indicates a severe sleep problem

Maas APHM, Didden R, Korzilius H, Curfs LMG. Exploration of differences in types of sleep disturbance and severity of sleep problems between individuals with Cri du Chat syndrome, Down's syndrome, and Jacobsen syndrome: A case control study. Research in Developmental Disabilities 2012; 33: 1773-1779.

DETERMANTS OF INITIATED AND CONTINUED BENZODIAZEPINE USE IN THE NETHERLANDS STUDY OF DEPRESSION AND ANXIETY

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Background Longitudinal research on determinants of initiated and continued benzodiazepine (BZD) use is inconsistent and has identified many possible determinants. It is unclear which of those are most important in the prediction of BZD use. We aimed to identify the most important predictors of initiated and continued BZD use. Therefore, we analyzed the most consistently identified determinants from previous research plus some new determinants.

Methods We identified baseline and 2-year longitudinal predictors of initiated BZD use (vs nonuse) among 2205 baseline BZD nonusers and of continued use (vs discontinued use) among 369 baseline BZD users in the Netherlands Study of Depression and Anxiety using logistic regression analyses

Results During follow-up, BZD use was initiated by 4.9% of BZD nonusers at baseline. Initiated use was predicted by insomnia (odds ratio [OR], 1.60), enduring anxiety symptoms (OR, 2.02), entering secondary care during follow-up (OR, 2.85), and past BZD use (OR, 3.57). Positive life events during follow-up reduced the likelihood of BZD initiation (OR, 0.76). Of BZD users at baseline, 54.2% continued use during the entire follow-up period. Continuation of BZD use was predicted by higher age (OR, 1.03), severe anxiety (OR, 1.85), and a long duration of BZD use (OR, 1.54). Leaving secondary care was associated with less continued BZD use (OR, 0.29).

Conclusion Insomnia and anxiety were the main risk factors of initiated use, whereas advanced age and anxiety severity were the main risk factors of continued use. Sex, education, pain, and physical health seemed to be less important.

Funded by Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002)

Manthey L, Giltay EJ, van Veen T, Neven AK, Zitman FG, Penninx BW. Determinants of initiated and continued benzodiazepine use in the Netherlands study of depression and anxiety. Clin Psychopharmacol. 2011 Dec;31(6):774-9.

CORRELATES OF (INAPPROPRIATE) BENZODIAZEPINE USE: THE NETHERLANDS STUDY OF DEPRESSION AND ANXIETY (NESDA)

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Aim Results on determinants of benzodiazepine (BZD) use in general and inappropriate use were inconsistent and mostly univariate. The relative importance of sociodemographic, psychological and physical determinants has never been investigated in a comprehensive, multivariate model.

Methods We included 429 BZD users and 2423 non-users from the Netherlands Study of Depression and Anxiety (NESDA) in order to investigate sociodemographic, psychological and physical determinants of BZD use and inappropriate use by logistic and linear regression analyses.

Results BZDs were used by a considerable proportion of the 2852 NESDA participants (15.0%). BZD use was independently associated with older age, singleness, unemployment, treatment in secondary care, higher medical consumption (more severe) anxiety, depression (OR [95% CI]=1.95 [1.29, 2.93]), comorbidity, insomnia, SSRI (OR [95% CI]=2.05 [1.55, 2.70]), TCA and other antidepressant (OR [95% CI]=2.44 [1.64, 3.62]) use. Overall, BZD use was rarely in accordance with all guidelines, mainly because most users (82.5%) exceeded the recommended duration of safe use. Inappropriate use was independently associated with older age (β=0.130) and chronic illnesses (β=0.120). Higher scores on agreeableness were associated with less inappropriate use.

Conclusions Mentally or physically vulnerable subjects were most likely to use BZDs. The most vulnerable (i.e. the old and physically ill) BZD users were at highest risk of inappropriate BZD use. Without further evidence of the effectiveness of BZDs in long-term use, caution in initiating BZD prescriptions is recommended, particularly when patients are chronically ill and old, as those are most likely to display inappropriate use.

Funded by Netherlands Organisation for Health Research and Development (ZonMw, grant number 10-000-1002)

Manthey L, van Veen T, Giltay EJ, Stoop JE, Neven AK, Penninx BW, Zitman FG. Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). Br J Clin Pharmacol. 2011 Feb;71(2):263-72.

THE DIAGNOSTIC VALUE OF SLEEP HISTORY DUE TO NON-ORGANIC INSOMNIA

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Introduction:
Video-polysomnography (VPSG) is the golden standard for diagnosing sleep disorders. Since VPSG is an expensive and time-consuming investigation, it is often omitted when non-organic insomnia is suspected. We aimed to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of sleep history alone in identifying non-organic insomnia.

Methods:
Data were retrospectively collected from the medical records of the Amsterdam Center for Sleep and Wake disorders (ASWC). All patients of 18 years and older who visited the ACSW for the first time in 2010 were included. At their first visit, all patients had undergone an extensive sleep history by a sleep specialist. Subsequently, all patients underwent VPSG. Sleep disorders were divided into two groups: 1) organic insomnia (OI), including sleep related breathing disorder, RLS, PLMD, bruxism and parasomnia and 2) non-organic insomnia (NOI), including psychofysiological insomnia and delayed sleep phase disorder. The provisional primary diagnosis after sleep history was compared with the primary diagnosis after VPSG.

Results:
A total of 746 patients was included in this study. Of these patients, 303 patients (35.3% male) had a provisional diagnosis of NOI and 443 patients (55.5% male) of OI.
Based on VPSG, 22.1% of the patients with a provisional diagnosis of NOI had OI. The majority of these patients with OI on VPSG had a sleep related breathing disorder and 9.9% of all patients whose history suggested NOI showed an apnea-hypopnea index >15 on VPSG. Of all patients with a provisional diagnosis of OI, 27,5% was diagnosed with NOI after VSPG.
We calculated that the sensitivity of sleep history in detecting NOI is 65.9% with a specificity of 82.7%. The PPV was 77,9% and the NPV was 72,5%.

Conclusions:
Detailed sleep history alone is insufficient in excluding OI. About 10% of patients whose history suggests NOI had moderate to severe sleepapnea. These patients run serious health risks, especially when their insomnia is treated with benzodiazepines. Therefore we think that additional sleep investigations should be recommended in NOI patients.

ESRS 2012 J Sleep Res (2012, Suppl 1) 21: 157.

CHRONIC SLEEP RESTRICTION CAUSES A DECREASE IN HIPPOCAMPAL VOLUME IN ADOLESCENT RATS THAT IS NOT EXPLAINED BY CHANGES IN GLUCOCORTICOID LEVELS OR NEUROGENESIS

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Sleep loss strongly affects brain function and may even predispose susceptible individuals to psychiatric disorders. Since a recurrent lack of sleep frequently occurs during adolescence, it has been implicated in the rise in depression incidence during this particular period of life. One mechanism through which sleep loss may contribute to depressive symptomatology is by affecting hippocampal function.

In this study we examined the effects of sleep loss on hippocampal integrity at young age by subjecting adolescent male rats to chronic sleep restriction (SR) for 1 month from postnatal day 30 to 61. They were placed in slowly rotating drums for 20h per day and were allowed 4h of rest per day at the beginning of the light phase. Anxiety was measured using an open field and elevated plus maze test, while saccharine preference was used as an indication of anhedonia. All tests were performed after 1 and 4 weeks of SR. We further studied effects of SR on hypothalamic-pituitary-adrenal axis activity and at the end of the experiment brains were collected to measure hippocampal volume and neurogenesis.

Behavior of the SR animals was not affected, except for a transient suppression of saccharine preference after 1 week of SR. Hippocampal volume was significantly reduced in SR rats compared to home cage and forced activity controls. This volume reduction was not paralleled by reduced levels of hippocampal neurogenesis and could neither be explained by elevated levels of glucocorticoids.

Our results indicate that insufficient sleep may be a causal factor in the reductions of hippocampal volume that have been reported in human sleep disorders and mood disorders. Since changes in HPA activity or neurogenesis are not causally implicated, sleep disturbance may affect hippocampal volume by other, possibly more direct mechanisms.

Novati A, Hulshof HJ, Koolhaas JM, Lucassen PJ, Meerlo P. Chronic sleep restriction causes a decrease in hippocampal volume in adolescent rats that is not explained by changes in glucocorticoid levels or neurogenesis. Neuroscience 190:145-155, 2011.

WHITE MATTER DIFFUSION CORRELATES WITH SPINDLES AND SLOW WAVES

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The characteristic oscillations of the sleeping brain, spindles and slow waves, show trait-like within-subject stability and a remarkable interindividual variability, which correlates with functionally relevant measures such as memory performance and intelligence. Yet, the mechanisms underlying these interindividual differences are largely unknown. Spindles and slow waves are affected by the recent history of learning and neuronal activation, indicating sensitivity to changes in synaptic strength and thus to the connectivity of the neuronal network. Because the structural backbone of this network is formed by white-matter tracts, we hypothesized that individual differences in spindles and slow waves depend on the white-matter microstructure across a distributed network. We recorded both diffusion-weighted magnetic resonance images and whole-night high-density electroencephalography (EEG) and investigated whether individual differences in sleep spindle and slow wave parameters were associated with diffusion tensor imaging (DTI) metrics: white-matter fractional anisotropy and axial diffusivity, quantified using tract-based spatial statistics. Individuals with higher spindle power had higher axial diffusivity in the forceps minor, the anterior corpus callosum, fascicles in the temporal lobe, and the tracts within and surrounding the thalamus. Individuals with a steeper rising slope of the slow wave had higher axial diffusivity in the temporal fascicle and frontally located white-matter tracts (forceps minor, anterior corpus callosum). These results indicate that the profiles of sleep oscillations reflect not only the dynamics of the neuronal network at the synaptic level, but also the localized microstructural properties of its structural backbone, the white-matter tracts.

Funded by the Netherlands Organization of Scientic Research (NWO) VICI Grant 453.07.001 to EvS; NWO VIDI Grant 016.095.359 to YvdW.

Presented at APSS-SLEEP 2012, Boston, MA

SUSTAINED ATTENTION TO RESPONSE TASK (SART) SHOWS IMPAIRED VIGILANCE IN A SPECTRUM OF DISORDERS OF EXCESSIVE DAYTIME SLEEPINESS

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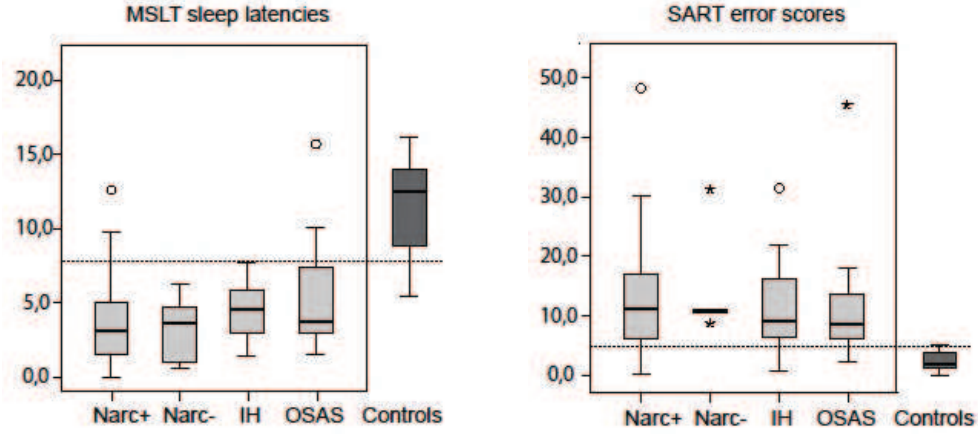
Introduction. The Sustained Attention to Response Task (SART) comprises withholding key presses to 1 in 9 of 225 target stimuli; it proved to be a sensitive measure of vigilance in a small group of narcoleptics.
Methods. We studied SART results in 96 patients from a tertiary narcolepsy referral centre. Diagnoses according to ICSD-2 criteria were narcolepsy with (n = 42) and without cataplexy (n = 5), idiopathic hypersomnia without long sleep time (n = 37), and obstructive sleep apnea syndrome (n = 12). The SART was administered prior to each of 5 MSLT sessions. Analysis concerned error rates, mean reaction time (RT), RT variability and post-error slowing, as well as the correlation of SART results with mean latency of the Multiple Sleep Latency Test (MSLT) and possible time of day influences.
Results. Median SART error scores ranged from 8.4 to 11.1, and mean RTs from 332 to 366 ms. SART error score and mean RT did not differ significantly between patient groups. SART error score did not correlate with MSLT sleep latency. RT was more variable as the error score was higher. SART error score was highest for the first session.
Conclusions. We conclude that a high SART error rate reflects vigilance impairment in excessive daytime sleepiness irrespective of its cause. The SART and the MSLT reflect different aspects of sleep/wakefulness and are complementary.

Figure 1. MSLT sleep latencies and SART error scores of patient groups and controls



The horizontal dotted lines represent cut-off values for MSLT (8 minutes) and SART (5 errors).

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WHY SHOULD SALIVARY MELATONIN BE MEASURED IN PATIENTS TO BE TREATED WITH MELATONIN?

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INTRODUCTION

Several pharmacopoeas recommend that melatonin should be administered 1or 2 hour before desired bed time although a meta-analysis showed that melatonin is not effective if administered in this way. However, when melatonin is administered at a time related to Dim Light Melatonin Onset (DLMO) it is remarkably successful in improving sleep. To establish the clinical relevance of measuring DLMO we reviewed the literature.

METHODS

The databases PubMed and Embase were searched as to publications between January 1990 and May 2011 using the key words 'human', 'melatonin', 'dim light melatonin onset', 'treatment' and their combinations.

RESULTS

1. Diagnosis: DLMO is the best characterisation of the 24-h melatonin rhythm, which is strongly associated with the circadian sleep-wake rhythm. Knowledge of DLMO increases the accuracy of the diagnosis of Delayed Sleep Phase Disorder with 32.5%. 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.

2. Optimal treatment success: Two 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. Exogenous melatonin, administered 5 hours before DLMO phase advances melatonin rhythm and the sleep-wake rhythm which is associated with it maximally. These effects are dose-depended. Knowing DLMO in children with chronic sleep onset insomnia and late DLMO is associated with a 92% treatment success rate.

Presented at the ESRS congress in Paris, September 2012

MANUAL VS. AUTOMATED ANALYSIS OF POLYSOMNOGRAPHIC RECORDINGS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction: The sleep quality, as assessed by polysomnography (PSG), of patients with Chronic Obstructive Pulmonary Disease (COPD) can severely be disturbed. The manual analysis of PSGs is time-consuming and computer systems have been developed to automatically analyse PSGs. Studies on the reliability of automated analyses in healthy subjects show varying results, and the purpose of this study was to assess whether automated analysis of PSG by one certain automatic system in patients with COPD provide accurate outcomes when compared to manual analysis.

Methods: In a retrospective study the full-night polysomnographic recordings of patients with and without COPD were analyzed automatically by Matrix Sleep Analysis software and manually. The outcomes of manual and automated analyses in both groups were compared using Bland-Altman plots and Students' paired t-tests.

Results: 50 PSGs from patients with COPD and 57 PSGs from patients without COPD were included. In both study groups agreement between manual and automated analysis was poor in nearly all sleep and respiratory parameters, like total sleep time, sleep efficiency, sleep latency, amount of REM sleep and other sleep stages, no. of arousals, apnoea-hypopnoea-index and desaturation-index.

Conclusion: Automated analysis of PSGs by the studied automated system in patients with COPD have poor agreement with manual analysis when looking at sleep and respiratory parameters and should therefore not replace the manual analysis of PSG recordings in patients with COPD.

Acknowledgements: this study was supported with an unrestricted grant from GlaxoSmithKline. The funding agency did not have any involvement in the study design, data collection, data analysis, interpretation of data, manuscript preparation and/or in the decision to submit the paper for publication.

Published as: G Stege, PJE Vos, PNR Dekhuijzen, PHE Hilkens, MJT van de Ven, YF Heijdra, FJJ van den Elshout. Manual vs. automated analysis of polysomnographic recordings in patients with chronic obstructive pulmonary disease. Sleep Breath 2012, DOI 10.1007/s11325-012-0714-2.

A WARM BEDROOM DOES NOT HAMPER SLEEP ONSET

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Introduction

Nocturnal sleep coincides with higher skin temperatures and is affected by the environmental temperature. It is advised for nocturnal sleep to keep the bedroom temperature between 19 °C and 22 °C[1]. Subjective discomfort increases when the temperature deviates from this range. Both micro and macro sleep structure are likely to be impacted negatively[1], although this is only supported by studies that applied very high or very low bedroom temperatures[1,2], commonly not to be expected in the bedroom. Hence we investigated the effect of a relatively warm bedroom, but not hot, on sleep onset (SOL).

Methods

12 healthy sleepers (6 male) visited the sleep laboratory on 2 different days for a sleep onset attempt. Room temperature was set at 18°C in the neutral condition and at 25°C in the warm bedroom condition. Sleep onset was determined online using PSG and SOLs were scored post hoc. Subjective thermal comfort was measured using VAS (100 mm) scales. Paired samples t-tests ($\alpha = 0.05$, 1-sided) were performed using SPSS 16.0.

Results

The bedroom temperature was significantly ($p < 0.001$) higher in the warm room (24.8°C ± 0.1) than in the neutral room (17.8°C ± 0.1). No differences in SOL were observed between the two conditions (neutral room: 12.8 min ± 2.4 versus warm room: 9.4 min ± 2.1; $p = 0.14$). The warmer bedroom temperature was more appreciated than the neutral bedroom temperature (59.3 ± 4.6 mm versus 39.3 ± 6.0 mm, $p < 0.001$).

Discussion

Our results stretch the range for the sleep onset latency: a bedroom temperature during sleep attempt that is above 22°C, but below 25°C is no problem, as long as the room temperature decreases after sleep onset. In addition, the results suggest that the subjective system is more sensitive for changes in bed room temperature than the sleep onset latency.

Presented as a poster at the 21st Congress of the European Sleep Research Society in Paris.

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CIRCADIAN MODULATION OF SLEEP IN RODENTS

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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 the homeostatic process is reflected by the slow-waves in the non-rapid eye-movement (NREM) sleep electroencephalogram. The circadian process is controlled by a pacemaker located in the suprachiasmatic nucleus of the hypothalamus and provides the sleep homeostat with a circadian framework.

This review summarizes the changes in sleep obtained after different chronobiological interventions, the influence of mutations or lesions in clock genes on sleep, and research on the interaction between sleep homeostasis and the circadian clock.

Research in humans shows that the period of consolidated waking during the day is a logical consequence of the interaction between an increasing homeostatic sleep drive and a circadian signal, which promotes waking during the day and sleep during the night. In the rat it was shown that under constant homeostatic sleep pressure still a small circadian modulation of the amount sleep and waking is observed, which was the result of a circadian modulation of waking and NREM sleep episode duration. Under similar conditions humans show a clear circadian modulation in REM sleep, whereas in the rat a circadian modulation in REM sleep was not present. Therefore in the rat, the sleep homeostatic modulation in phase with the circadian clock seem to amplify the relatively weak circadian changes in sleep induced by the circadian clock.

Knowledge about the interaction between sleep and the circadian clock and the circadian modulation of sleep in other species than humans is important to better understand the underlying regulatory mechanisms.

This research was supported by the Netherlands Organization for Scientific Research (NWO, grant 818.02.016, TD).

Progress in Brain Research (2012) 199: 203-218.

CIRCADIAN MODULATION OF SLEEP LATENCIES IN THE RAT

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Objectives: Sleep latency, sleep duration, and sleep efficiency are among the main characteristics of sleep quality in humans. In different sleep deprivation protocols, NREM and REM sleep latencies demonstrate a robust circadian pattern. It is unknown whether other mammals also show circadian modulation in sleep latency. We have previously found that repeated 2h sleep deprivations alternated with 2h rest, redistribute sleep over 24 h in the rat. Noteworthy, NREM sleep remains circadian modulation under this protocol, whereas REM sleep does not. The latter suggests that, in contrast to humans, the circadian control over REM sleep is weak in the rat. Here, we apply the same protocol to investigate circadian modulation of sleep latencies in the rat.

Methods: EEG and EMG recordings were performed in freely moving rats (n=8) exposed to constant dark conditions. Starting at the onset of subjective day (CT 0), twelve 2h-periods of sleep deprivation (SD) were alternated with twelve 2h-periods of rest (48 h). At the onset of the 2h rest periods of the second day, NREM and REM sleep latency were determined applying definitions similar to those of humans: NREM sleep latency - the time between release from SD and the first consolidated NREM sleep episode lasting >=30 sec; REM sleep latency - the time between the first consolidated NREM sleep episode after release from the SD and a subsequent REM sleep episode lasting >=30 sec.

Results: NREM sleep latency showed minor variation across the six periods of rest. The latency to enter REM sleep showed a gradual but significant shortening in the course of the subjective day (from more than 20 min to ~10 min), followed by an abrupt increase at the start of the subjective night (>20 min). In the middle of the subjective night REM sleep latency decreased again to values comparable to those found at the end of the subjective day. At the end of the subjective night REM sleep latency increased again to ~20 min. As a result, REM sleep latency showed a complex bimodal circadian pattern ($p<0.05$, Duncan after ANOVA).

Conclusion: The biomodal modulation in REM sleep latency can be caused by the changes in monoamines level and brain temperature, and may be related to the nocturnality of the rat. The absence of a circadian modulation in NREM sleep latency, and the presence of a bimodal circadian pattern of REM sleep latency are further indications for key differences in circadian sleep regulation between humans and the rat.

ESRS 2012 J Sleep Res (2012) 21 suppl1: 328-329.

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Annual Proceedings of the NSWO
Volume 23, 2012

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