SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 19, 2008

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Dutch Society for Sleep-Wake Research

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PREFACE

On November 9th 2007 the autumn meeting of the NSWO was hosted by dr. Hans Hamburger in the Wake-Sleep Center of the Slotervaart hospital in Amsterdam. The central theme of this excellent meeting, "Measuring Sleep" was discussed by 11 speakers, who presented their research on, for example, spectral analysis of sleep, measurement of ventilation in sleep-disordered breathing, and the measurement of sleep in mentally ill individuals.
During the meeting the 18th volume of Sleep-Wake Research in The Netherlands, including 28 short papers which were edited by Gé Ruigt and other members of the scientific committee, was presented. NV Organon was gratefully acknowledged for financing the publication of this volume. At the end of the meeting, during the general membership assembly, the Piet Visser challenge trophy for the best poster was awarded to Petra van Houdt.

The third National Sleep Day was held on March 29th 2008, and was organized by the PR committee around the theme "Sleep disorders in Children". A press information file was prepared, the power point presentation of the previous year was adapted and distributed among the 34 sleep centers and research institutes of our country, and a web-based questionnaire was launched. The results of this web-based poll are presented in one of the papers of the present volume.

On April 4th 2008 the 10th edition of the annual clinical symposium 'Epilepsy and Sleep Update@Kempenhaeghe.nl' was held, including a session "Current issues in sleep-disordered breathing", organized jointly by BASS and NSWO in honour of the retirement of dr. Hans de Groen. The mix of excellent talks, a perfect organization and a large attendance made this a memorable day.

The NSWO Board invests much effort in the organization of the International Sleep Medicine Course, to be held November 11th – 14th this year. The course will cover the essential basic and applied aspects of sleep disorders and is intended for university graduates who want to pursue a clinical career in sleep medicine. A maximum of 60 participants can be admitted to this four-day residential course. A final exam offers the opportunity to qualify for the theoretical part of the ESRS certificate as sleep specialist. The course is subdivided into eight daily periods, each consisting of four to five lectures and one workshop, and dedicated to one of the following topics: sleep physiology, sleep monitoring, sleep disordered breathing, insomnia, circadian rhythm sleep disorders, sleep related movement disorders, hypersomnia, and parasomnias. The course will be concluded with a selected set of 'clinical pearls'.

Gerard Kerkhof, president

EDITORIAL NOTE

This year's proceedings of the Dutch Sleep Wake Society are special, since we added two new sections further advancing the objectives of our proceedings. A review section was added and I am extremely pleased to have prof. Ton Coenen as the first contributor providing a personal historic account of sleep research in the Netherlands over the last decades including the genesis of the NSWO. Ton has been the founding father of these proceedings and recently retired as professor at the University of Nijmegen, but still continues to be active in sleep research. A second section has been created to provide space for young Dutch sleep researchers, who have successfully defended their theses, to give a summary overview of their thesis work, which is being accompanied by a commentary from an established NSWO member. In view of the steady flow of dissertations in the field of sleep research in the Netherlands I expect this to become a regular and well appreciated section of these proceedings.

The main body of the proceedings consists as usual of a nice selection of minipapers providing a good overview of the ongoing research in the Netherlands in the field of Sleep and Wake. The overview of academic sites and clinics involved in sleep-wake research in the Netherlands has been completely updated and has been moved to the back of the booklet preceding the updated membership list at the end. Both sections have proved to be a useful reference. The proceedings are also available on the internet site of the NSWO (www.nswo.nl) in pdf format.

I would like to thank all the members of the NSWO for their excellent contributions, which make the annual proceedings not only a national but also an internationally reknown booklet. Special thanks are due to Ton Coenen and Rolf Fronczek for their contributions to the new sections and to my co-editors for their accurate review of all the manuscripts during the past months.

The Dutch Society for Sleep Wake Research greatfully acknowledges sanofi-aventis Netherlands BV for their financial support enabling publication of this 19th annual volume of the Society.

Oss, September 2008
Gé S.F. Ruigt
Chair Scientific Committee
Chief Editor NSWO Proceedings

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SPECIAL REVIEW

A LIFE FULL OF SLEEP

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Prologue

During about 40 years, from 1967 till 2007, I have performed sleep research at the University of Nijmegen. The core direction of my studies dealt with research into the neurophysiology of sleep, wherein the electrical brain activity was measured. A second highlight of my studies was an investigation into the psychophysiology of sleep, wherein the functional and cognitive aspects of sleep stood central. Such investigations almost always included the study of REM sleep, and these studies are prominent in this review. I have frequently worked with laboratory animals such as rats and cats, but have also studied human sleep. I look back to my studies and have them placed in an international and, in particular, a national perspective of the developments in basic sleep research and in concepts of sleep.

The Beginning At Medical Physics

I participated in sleep research before fully comprehending that it was actually sleep research that I was doing. Directly after completing my studies in neurobiology in March, 1967, at the then Catholic University of Nijmegen, I joined the section, 'Medical Physics', part of the Faculty of Medicine. There I became involved with neurophysiological research into the visual system. Under the guidance of professor Ton Vendrik and Henk Gerrits, an attempt was made to study human visual processes by using laboratory animals. I began studying the structure of receptive fields of visual neurons using cats under anesthesia. This was at the time that Hubel and Wiesel performed pioneering studies related to cortical receptive fields of visual neurons for which they later, in 1981, received the Nobel prize. With self produced glass micro-electrodes I made single unit recordings of neurons of the corpus geniculatum laterale, the relay nucleus in the thalamus between retina and visual cortex. On and off cells were found and the receptive field structure with excitatory centre and inhibitory surrounds corroborated what Hubel and Wiesel already had discovered. What was very noticeable was that cell responses to light stimulus fluctuated greatly. The action potentials, heard through loudspeakers, sometimes crackled loudly in response to a light stimulus, while at other times hardly a response could be noticed to the same stimulus. It did not take long before we considered that such differences could result from the depth of anesthesia of the laboratory animal. We made a drastic decision to continue the testing with non-anesthetized animals. In those days single unit measurements with a freely moving cat were technically hardly possible, but as a solution we used a muscle relaxant, flaxedil, that did not work on the central nervous system. Today, such a solution would not be possible under current ethics. Anaesthetized cats were operated upon and at conclusion, still under anesthesia, a recording program was started and flaxedil was administered; immediately thereafter anesthesia was

ended. All pain areas were locally anesthetized, and with an electroencephalogram (EEG), the degree of alertness and consciousness of the cat was measured. The animal lay still, due to the muscle relaxant, and had also to be artificially ventilated, but was further in good condition. The EEG recordings indicated that after finishing anesthesia, the animal was initially predominantly conscious, but later fell asleep quite easily. We could register cell responses in the geniculate body to light stimuli during wakefulness, and as well during sleep. It was even, now and then, possible to produce intracellular recordings whereby input, from the retina, and as well output, to the visual cortex could be determined. The input appeared to be completely independent on the level of consciousness of the animal, while the output was strongly dependent on the level of cat's consciousness. So the 'transfer ratio' fluctuated considerably. This finding was a real 'Eureka' and formed the basis of the later 'sensory gating' theory, that was accepted by diverse modern handbooks about biological psychology, such as Kalat (1) and Toates (2).

I reported the previous findings related to the 'transfer ratio' and 'sensory gating' in the thalamus at my first international congress, the XXV International Congress of Physiological Sciences in Munich in 1971. Wolf Singer, then working at the Max Planck Institute for Psychiatry in Munich, followed me with a presentation. He had performed similar research, but stimulated the reticular formation using electrical stimuli, and could in that manner, modulate the thalamic transfer ratio. Singer had worked with the then well known neurologist Richard Jung from Freiburg (Germany). Jung was also editor-in-chief of the journal, Experimental Brain Research, and was involved in the review process of my article on the transfer ratio (3). After resolving various critical comments, mostly regarding the state of vigilance of the animal, the article was published and reprints were frequently requested. The article formed an important part of my dissertation, where upon I received my doctorate in 1971 (4). Since that time, the process of the 'thalamic' or 'sensory gating' has never lost my attention, and my interest in sleep was born.

The International Scene

During this early period, hardly any Dutch investigations into sleep took place. The psychiatrist Rudi van den Hoofdakker at Groningen was busy with his dissertation dealing with the relationship between EEG and cat behavior, whereas the physician Zelvelder, working at TNO in Delft was publishing articles about sleep medications. At Amsterdam, a group led by Piet Visser was preparing to perform research into sleep. On the other hand, internationally, much was going on. The Italian physiologist Giuseppe Moruzzi (University of Pisa) and the American physiologist Horace Magoun (Northwestern University, Illinois), together produced ground-breaking research into the regulation of sleep and wakefulness. They investigated the 'reticular system' in the brain stem and confirmed the 'active' sleep theory with their report on the 'ascending reticular activating system'. This theory states that certain core areas in the brain are actively involved with sleep, while other areas are involved with wakefulness. Slowly but surely, the 'active' sleep theory replaced the 'passive' sleep theory. The latter theory, implying that sleep exists when the brain no longer receives any stimulation (thus sleep is a passive, de-afferentiation, process), was till that time the leading theory (5, 6).

At the end of the 1950's, the well known sleep expert Herbert Jasper, recognized for his EEG work and the 10-20 placement system of electrodes on the human skull, posed a question to the earlier named Canadian neurophysiologist David Hubel, 'Does brain activity really cease

during sleep?' Hubel, at McGill University (Montreal), reacted and developed a method enabling single-unit measurements with cats (7). Using a self-made micro-drive he was able to make neuronal recordings of freely moving animals. He was, however, unable to comprehend results; at one time neurons displayed a reduction in activity during sleep, while at other times an increase was seen. Hubel stopped his research into sleep, and began to work with the Swede Torsten Wiesel, who was then studying the more popular visual system of cats. The earlier work of Hubel was taken over by the Rumanian born neurophysiologist Mircea Steriade who worked in Quebec (Canada). He was able to better understand Hubel's results by selecting special cells and he described a reduction of neuronal activity during sleep in 'relay' neurons, but a stronger activity among interneurons. Steriade thus remained in the path of Moruzzi and Magoun and concentrated on the regulation of sleep and waking. With his group he performed major studies into neuronal cellular activity with recordings in the brain during sleep and waking (8). He also described 'gating' but he honestly noted the Nijmegen study, in which study he was involved as a reviewer (9).

Towards Psychology

After ending my contract with ZWO (now NWO), I joined the section 'Comparative and Physiological Psychology', a department of the Faculty of Psychology at the Catholic University of Nijmegen. This was led by psychology professor Jo Vossen. He wanted to strengthen his team with an 'electro-physiologist', believing that EEG studies might help to understand human behavior. Single unit measurements, however, could not be undertaken at the Psychological Lab, not only due to the high costs, but also due to the distance between neuronal activity and actual behavior. Behavior was a major research theme in the department, especially natural behavioral patterns of rats and their learning processes. My primary field of study was the EEG of the hippocampus, which is an EEG that shows a strict relationship to behavior, and this was a popular topic at that time. The group of Case Vanderwolf at the University of Western Ontario in Canada was a leading group and produced a classic article dealing with this subject (10). I began taking numerous hippocampal EEG recordings and became impressed with the close relationship between the waves in the EEG and the behavioral patterns of the rat. By observing only the EEG one can almost predict what the rat is doing. In general, the hippocampal EEG shows three patterns: the 'theta' rhythm, a neat regular wave pattern that is displayed during exploratory behaviors, such as walking, standing-up and smelling; a more irregular rhythm, the 'large amplitude irregular activity', that appears mostly during inactive behaviors and sleep; and finally a mixture of these two wave patterns that is observable during so called 'automatic' behaviors such as grooming and eating (11).
Fernando Lopes da Silva at TNO in Utrecht and later at the University of Amsterdam was also interested in theta rhythm and hippocampal EEG, especially in their characteristics and how they are produced (12). In the mean time I was studying the behavioral correlates of this intriguing theta rhythm. Many scientists were doing the same and theories were numerous. The formulation of theories was, however, complicated since theta rhythm appears during exploratory behavior as well during a special type of sleep known as 'REM sleep'; both appearing to have nothing to do with each other. This has always confused researchers. REM sleep, identified in 1953 (13), is a mysterious type of sleep with unusual characteristics. The publication of Eugene Aserinsky and his supervisor, the famous sleep researcher Nathaniel Kleitman from Chicago, have had an enormous impact. Not only because of their description of the active brain, paralysis of muscles and 'rapid eye movements', but primarily because they supposed a relation between REM sleep and dreaming. This led to a flood gulf of

experiments, not only by the famous Bill Dement, but also by other researchers, such as the Frenchman Michel Jouvet (Lyon), who was investigating REM sleep of animals (14). The latter named this type of sleep 'paradoxical sleep', regarding its contrasting features, and to differentiate it from the normal, slow wave, sleep characteristics. The American psychiatrist Allan Hobson, together with his companion the neurophysiologist Bob McCarley at Harvard Medical School at Boston, performed many neurophysiological experiments into REM sleep that combined the Steriade's approach with paradigms from the Chicago group (15).

Sleep and Memory

It is a classical conception that sleep, in some way or another, plays a role in the storage of events or information in memory or in the recollection of such. Aristotle first described this conception in his book '*De somno et vigilia' ['Sleep and vigilance']*,written in about 350 BC. He believed that certain daily activities or events leave an impression on the person that may later be explicitly recalled during dreams. Much later the renowned neurologist Sir John Hughlings Jackson (1881) and the famous German psychologist Hermann Ebbinghaus (1885) blew new life into this theory: 'Sleep may have a function in storing necessary information and in deleting which is unnecessary'. The classical experiment performed by the Americans John Jenkins and Karl Dallenbach in 1924 tried to test that hypothesis. They tested the recollection of groups of non-sense syllables by experimental subjects after sleep and during wakefulness. Subjects learned a group of syllables until these could be recalled perfectly. Learning took place either at the evening just before sleep, or during early daylight hours. Eight hours after learning, the subjects were tested on what they remembered, and more explicitly, a comparison was made between the group who went to sleep immediately after learning, and another group that was tested without a sleep interval in between. It appeared that the group who slept after learning scored about twice as high as those who did not. This was identified as, ´the positive effect of sleep on memory´. One should note, however, that these results could not be duplicated using all kinds of learning tasks (16).
At the start of the Eighties, myself and others decided to further study the possible positive effects of sleep: it was hypothesized that active REM sleep has a consolidation function (*'information processing hypothesis of REM sleep'*). This relates to the idea concerning theta rhythm that manifests itself when a rat is in a ´exploratory´ mode, and also when the rat is in REM sleep. Could it be that the wakefulness theta rhythm is involved by the direct ´on line´ processing of information that leads to storage in an unstable memory path, while the REM theta rhythm during sleep is involved with the indirect ´off line´ processing that selects and stores relevant information into memory?
If the occurrence of REM sleep can be hindered, then that would thoroughly interfere with the storage of information into memory. Exactly around that time, articles appeared wherein some research groups mentioned that deprivation of REM sleep could disturb the storage of information, but the methods they used (putting rats on small platforms surrounding by water which prevents them from showing REM sleep, by avoiding them from falling into the water), were not really convincing. I began with a study whereby I could show that the placement of a rat on such platform interferes with consolidation, and that it is not necessarily due to deprivation of REM sleep. That study brought me to my first congress on sleep research, the Second International Sleep Research Congress in Edinburgh, Scotland in 1975, where I reported my results. It appeared, however, that attendees had more interest in my earlier transfer ratio ('gating') article.

That congress illustrated how small the Dutch world of sleep researchers still was. Except for myself, only a few other Dutchmen were present, such as Michael Corner from the Brain Institute at Amsterdam with a poster presentation on sleep ontogeny, and some members of Rudi van de Hoofdakker's group at Groningen, with a poster display about sleeplessness. Nevertheless, the year 1975 was a memorable year in Dutch sleep research history. In the sport centre Papendal, the first symposium entirely dedicated to sleep was held. Presenters included myself, with a study of neurophysiology of sleep, another by Rudi van den Hoofdakker dealing with sleep problems, and one by Piet Visser holding a general lecture about sleep. Moreover, Henk van Riezen of Organon was busy developing an automatic analysis system for sleep, and Heinz Prechtl from Groningen along with Jan Nijhuis, attracted much attention for their work related to the development and regulation of sleep-wake states among unborn and newly born infants (17). In addition there were some major foreign presentations e.g. by Olga Petre-Quadens from Antwerp about anthropological sleep research and Ian Oswald from Edinburgh with his influential work about sleep medication. My Papendal report about the neurophysiology of sleep was picked up by the magazine Intermediair that devoted attention to this in a large article, which also further led to a publisher, van Gorcum, expressing interest in publishing a book about sleep. Finally, in 1979, my book appeared: *'De slaap: een psychobiologische inleiding' ['Sleep: a psychobiological introduction']*, the first Dutch monograph about sleep (5). Around that time, a colleague of Piet Visser, Anand Kumar, worked hard to draw Dutch sleep researchers together into a work group, *'Sleep and Dream'*. The group, consisting of about twenty persons, met several times but later dissolved. Despite the lack of a formal group structure, contacts and sharing of information between Dutch sleep researchers were achieved.

REM Sleep Deprivation in Rats

Even though REM sleep deprivation seemed not to have direct negative effects on memory consolidation, I was still convinced that the theta rhythm of REM sleep was, in some way, involved with the processing and recall of earlier obtained information. I received a grant from the university and NWO to continue my research. My then PhD students, Zach van Hulzen and Gilles van Luijtelaar, together using advanced EEG techniques and properly controlled experiments, were able to perform adequate experimentation. The methodology to prevent rats from entering REM sleep by placing them on a small platform surrounded by water seemed unreliable. Three alternative methods, rather than the stressful platform technique, were designed: a) the arousal technique, b) the pendulum technique, and c) the multiple platform technique. Combining these three techniques with accurate EEG recordings during adequate learning tasks seemed the best way to go. But results were not forthcoming. Our rats, even after deprivation, fulfilled their learning tasks as did their non-deprived controls. Sometimes it indeed appeared that proper recall of their learning tasks was less, but with well-controlled experiments it appeared that the use of the small platform for deprivation induced so much stress that consolidation and accurate recall of earlier learned tasks was negatively influenced (18). In other words, REM sleep, or the lack of it, had no measurable effect on memory recall, even when we used our less stressful sleep deprivation methods. We performed this type of research between 1975 till 1985. After ten years, and after the acquisition of two PhD's (19, 20), we had to disappointedly conclude that there was no clear proof that REM sleep had any recognizable effect on the storage of information in permanent memory, or the retrieval of this information. Such research was discontinued by us and many others, and the topic was forgotten.

Surprisingly, it seemed that ten years later, the 'world' again took up the question of whether sleep, and especially REM sleep, was involved in memory processes. Now it had the added technologies of EEG techniques combined with modern imaging technologies, such as MEG and fMRI. The scientific world has a short memory! No clear, convincing results were structurally obtained and REM sleep was exchanged for REM sleep in combination with 'deep' sleep, and again later with only 'deep' sleep. We are now at this stage. At the last congress of the World Federation of Sleep Research Societies held in September 2007 in Cairns, Australia, lectures were presented by proponents of the active role of sleep on memory, such as those from the Belgian Pierre Maquet (University of Liège), the German Jan Born (University of Lübeck), and the group of Bob Stickgold and Allan Hobson (Harvard Medical School, Boston). They presented nice research with rather positive results. Their cheerful results remain, but the question also remains of why the theory had to be modified so often and why replications of similar results by others are so difficult to obtain. I am very curious about the expected results of colleagues at the University of Amsterdam (Winnie Hofman) and at the Netherlands Institute for Brain Research (Eus van Someren and Ysbrand van der Werf), who are currently further investigating the effect of sleep on memory recall.

Let me present my own vision about this matter. Sleep is indeed involved in memory storage, but rather in a passive than in an active manner. I return to an old declaration: the interference hypothesis, in the past explaining the positive effect of sleep on learning. The cause of less good storage of information must be conceded to the fact that the learning process may be negatively affected by the processing of newer incoming information. The processing of the latter interferes with the storage of older information. Interference, however, is minimal during a sleeping period, where no or very little new information is received. Hence, less is forgotten from the learning task taking place just before the sleeping period. Stated otherwise, during wakefulness an ongoing consolidation process takes place but this process can be disturbed or distorted by newer incoming influences. The process is similar to food digestion that always takes place, even during sleep, but does so less efficiently during vigorous activity. Future research should determine whether the positive effect of sleep on memory storage is due to an 'active' mechanism (consolidation hypothesis) or to a 'passive' mechanism (interference hypothesis) (21).

The REM Sleep Deprivation Paradigm

We at Nijmegen were not the only ones using the deprivation of REM sleep paradigm. Michael Corner and Majid Mirmiran working at the Netherlands Institute for Brain Research (Amsterdam) have been studying REM sleep deprivation since the Seventies and Eighties and applied it to young rats, to determine the effects of chronic deprivation on brain development. They followed a different hypothesis than us, namely: the *'ontogenetic hypothesis of REM sleep'*. This holds that REM sleep plays a role in the development of young brains. Using the anti-depressant drug chlorimipramine, REM sleep was chronically abolished and recordings of cortical and reticular neurons were taken to determine if any deprivation effects exist. They accumulated a treasure trove of results about neurophysiological ripening of the brain and development of sleep, but could find no evidence of an exclusive role for REM sleep in these processes. At Rotterdam, Michael Djolzic and his PhD student Ukponmwan were studying the behavioral effects of REM sleep deprivation. They found that deprived rats show a reduction in the behavioral effects induced by opiates and displayed an interaction between REM sleep and the endogenous opiate

system and degree of vigilance. However, firm conclusions about the function of REM sleep were difficult to make (22).

The same holds for international research into the effects of REM sleep deprivation. As earlier indicated, the major and most popular technique used for sleep deprivation is the small platform on which the rat is placed; the popularity of this technique is due to its simplicity. Thousands upon thousands of rats have, for shorter or longer periods, spent time on such platforms, highly stressed and with their heat regulating tails immersed in mostly cold water! The only truth that researchers could agree upon is that they accumulate REM sleep pressure during their long deprivation periods, that later results in a REM sleep rebound process as soon as they are placed in a normal situation. All other behavioral effects are variable and not valid. The 'deprivation paradigm' used by researchers studying REM sleep has always been contentious, not only due to the poorly controllable side-effects, but also due to a more theoretical concern. Specifically, by using instrumental techniques, REM sleep is replaced by wakefulness. Consider now that REM sleep, a period that is characteristically similar to wakefulness, may have the same functional effect on behavior. This is what the *'neural excitability-hypothesis of REM sleep'* implies. REM sleep ensures that during the long night the 'wakefulness' functions, such e.g. as the memory function, just continue. Could it be that REM sleep deprivation changes nothing functional? Along with others at the World Conference '2001 Sleep Odyssey' in Punta del Este (Uruguay), I pleaded for banning the small platform technique in this type of research (23).

Deprivation of Sleep

Alongside REM sleep deprivation, total sleep deprivation has also been applied in various experiments. Van den Hoofdakker's group at Groningen began with this, when in the Sixties, the German psychiatrist Schulte accidentally discovered that sleep deprivation had an anti-depressive effect. This was quite amazing since it was already well known that there was a relationship between sleep disorders and depression. The Groningen objectives were not only to investigate clinical therapy options, but also to determine a theoretical base for the anti-depressive effect of sleep deprivation. The clinical importance is actually small since any therapeutic effects of keeping awake at night disappear quite quickly, since a very long deprivation period is not possible. The group was searching what in fact caused the stimulating effect of sleep deprivation. Simon Elsenga thought that he found this by noting an increase in body warmth, caused by stimulating energy consumption, as an effect of the long deprivation. That activation might be essential to gain an anti-depressive effect (24).
The research was expanded when Serge Daan, who studied circadian rhythms with Jürgen Aschoff at Andechs (Germany) and Colin Pittendrigh (*'father of the biological clock'*) at Stanford, together with the physicist Domien Beersma joined the research. In cooperation with the Swiss group of Alexander Borbély, the *'two process theory of the regulation of sleep'* was developed (25). This 'two process' theory states that sleep is regulated via a homeostatic process (process S) and a circadian process (process C). The homeostatic process implies that the longer one does not sleep, the need for sleep increases, while the circadian process implies that there are specific times when sleep should take place. Many characteristics of sleep can be explained using this elegant and convincing model, and it is perhaps one of the most important findings of Dutch sleep research.

Two suppositions are now followed in relation to depressions: the first is that during the day, among depressive persons, process S is insufficiently strong, and is at night not strong

enough to induce a comfortable sleep. By preventing sleep for one night, process S is rather increased, resulting in proper sleep and is followed the next day by diminished depressive feelings. The second idea is that depressions are created when circadian rhythms are disturbed, e.g. become out of phase, for example the sleep-wake rhythm no longer runs synchronous with the temperature rhythm. Anti-depressive light therapy is based on the latter idea, and advises the sufferer to be seated before intense light that can restore the rhythmic phases. Marijke Gordijn in her dissertation (1999) about chronobiology and depression, however, could not reliably confirm either of the preceding hypotheses. She returned the focus onto the activation-changing aspects of sleep deprivation, to which depressive patients feelingly react (26). Along with a leading exponent, Anna Wirz-Justice from Basel and together with Gilles van Luijtelaar, I compiled an overview article in 1988 about the effects of light therapy on depression, stressing its possible effect mechanisms; however, a reliable explanation could still not be given (27).

Circadian Rhythms and the Biological Clock

Studies on circadian rhythms have been popular in the Netherlands for decennia. At Leiden University, Wop Rietveld and Gerard Kerkhof have been thoroughly investigating the biological clock of the human brain. They paid special attention to temperature rhythms and their relation to 'morning' and 'evening' types of persons, to the (scarce) pros and (many) cons of night workers, and to variations in daily vigilance (28). Hans van Dongen is currently in the United States investigating this topic along with vigilance specialist David Dinges. They are studying which factors affect degrees of vigilance related to people working long hours, and their predictive values on operational performance (29). The, young deceased, Ger Groos used neurophysiologic recordings and studied the biological clock in the nucleus suprachiasmaticus together with Joke Meijer (30), while Gert-Jan Lammers and Sebastiaan Overeem at the LUMC in Leiden performed large scale vigilance investigations in narcoleptic patients. Annika Smit, one of my PhD students, was doing the same. She noted that, *'excessive daytime sleepiness'*, among narcoleptic patients is so high in the late afternoon that they could hardly perform various tests and these had to be stopped because they could not remain awake (31). Lammers and Overeem also studied the reduction of the hypothalamic hypocretin-orexin neuropeptide among narcoleptics; the outcomes of these studies provide a possible new perspective on therapy for these patients (32).

Currently, Eus van Someren and associates at the Netherlands Brain Institute in Amsterdam, are investigating the hypothesis that among older people and Alzheimer patients, the biological clock has so depreciated that this is no longer sufficiently strong to control and regulate changes in sleep and wakefulness. To better delineate between light and darkness (day and night), they are using strong light to better activate the internal clock (33). They noted promising therapeutic results. Body temperature also seems to play an important role in sleep regulation. There are two triggers for falling into sleep: entering darkness and a decrease in body temperature. If the night is warm there is a greater likelihood that we will sleep poorly; dissipating body warmth becomes more difficult what hinders the fall in body temperature. Upon the body's entrance into darkness, the pineal gland hormone melatonin is produced that facilitates falling asleep. Together with many of my psychology students, Marcel Smits in Ede, has been further investigating the effect of this hormone. He administered exogenous melatonin to children suffering the *'delayed sleep phase syndrome'*, in the hope that it would restore natural sleep patterns (34). Positive results are obtained, however the question remains of whether this hormone is a falling into sleep medication or

rather a hormone that determines sleep rhythms. In any case, melatonin is currently frequently used to limit jet-lag consequences.

We have now landed in the Nineties when the Dutch Society for Sleep-Wake Research (NSWO) was established. Plans to establish such a society were made at the Ninth European Congress of Sleep Research in Jerusalem in 1988. On June 7, 1990 the NSWO started, with newcomer Hilbert Kamphuisen (Leiden) as chairman and old hands Guus Declerck (Kempenhaeghe) and Rudi van den Hoofdakker (Groningen) as board members. I had the honor of being chosen as chair of the scientific committee. The NSWO, showing the growth of the Dutch 'sleep world' with more than 100 members, became a think-tank wherein everything related to sleep and wakefulness was analyzed and discussed and a yearbook was produced: '*Sleep-wake research in the Netherlands*'. That annual booklet, which I have initiated in 1990, became a popular publication. Another publication was produced in 2001 under the auspices of the NSWO, the *'Handboek slaap en slaapstoornissen' ['Handbook sleep and sleep disorders']* (35), edited by Lex van Bemmel, Domien Beersma, Hans de Groen and Winnie Hofman.

Falling Asleep and Sleeplessness

During sleep the brain is flooded with the inhibitory neurotransmitter (GABA) that desensitizes nerve cells by hyperpolarizing them. This has some memorable effects: neurons receiving electrical signals cannot transmit them easily (explaining the 'gating' process), while they themselves come in a much different firing pattern. Their spontaneous activity is lessened and the scarce activity is grouped together and a *'burst-pause firing mode'* pattern is the result. Additionally, brain cells begin to fire in a synchronized manner. This results that they become quiet and inactive, while somewhat later they begin to fire simultaneously in a burst manner. This explains why large and slow EEG wave patterns can be seen during sleep. In contrast, upon wakefulness brain cells become much more active (due to activating neurotransmitters such as glutamate and acetylcholine), but also more desynchronized. They behave in a more independent manner and cells fire in a *'tonic firing mode'* discharge pattern. Here we witness much smaller EEG waves that have a much higher frequency. In this tonic mode they also transmit all incoming information, and no 'gating' is shown (36, 37).

What are now the determinants of the switch from the 'tonic firing mode' to the 'burst-pause firing mode' of thalamocortical cells, or stated otherwise, from wakefulness to sleep?
At specific times the biological clock sends messages to the sleep controlling reticular core of the brain that signal one to fall asleep. This group of neurons inhibits the 'reticular activating system', controlling wakefulness. Following this, neurons in the thalamus and cortex become de-activated by the lowering of their membrane potentials by the inhibitory actions of GABA. If the hyperpolarization is sufficient, the neurons enter the burst-pause firing mode. One of the most important elements in falling asleep is the 'dampening' of the reticular activating system. And that does not always occur. Often, the brain is not sufficiently 'empty' before one attempts to sleep. Stress and personal problems lead to a restless and discomforting state and activation of the 'emotional' brain and, in turn, also in stimulating the wakefulness system. Finally, the sleep system is inhibited and one cannot enter sleep, and if one does, sleep is often shallow and quickly interrupted.
Sleep medications such as benzodiazepines can provide help in such instances. These medications support the inhibiting neurotransmitter GABA. They attach to the GABA

receptor complex, through which the neuronal membrane is so modified, that GABA can better connect to its receptor (38). Since more chloride ions stream into cells than normal, the 'breaking' effect is increased. Benzodiazepines, through this process of *'allosteric modulation'*, have a vigilance reducing, sleep inducing characteristic. In this way, surely in a short term, they help one to better sleep. But the underlying sleep problem is not resolved, and long term use of such medications is often unavoidable. Continuous use of sleep medications almost always leads to habituation and reduced effectiveness of such 'cures'; the body builds up tolerance. The end of the story is that people suffering from insomnia often become habitual chronic users of medications, while sleep is not really improved.

The non-medicinal treatment of sleeplessness is based on the principle of *'relaxation'*, to achieve rest in the brain, and thus limit the activating influences of emotion. The basis for this treatment is training one to control or stop ones thoughts. Ed Klip, at the University of Groningen has carried out long term research into this alternative for the sleeping pill. He wondered whether he could train people to sufficiently relax, to stop or to reduce annoying thoughts, and thus enter sleep more easily (39). Based on behavioral therapeutic psychological techniques, he produced a course, *'Slapen kun je leren' ['You can learn to sleep']*, that was shown on television (TELEAC) and heard on radio at the close of the Eighties. The course results were positively evaluated by Aart Oosterhuis, connected with the epilepsy clinic of Dr. Hans Berger at Breda (40). A repetition of the same type of course, now named *'Beter slapen? Doe het zelf!' ['Better sleep? Do it yourself!']*, followed in 2005 and was given by Ingrid Verbeek affiliated with the epilepsy and sleep clinic Kempenhaeghe (41). It also yielded positive results, but long term positive effects of the behavioral sleep therapy need to be evaluated, for the reason that many insomniacs still prefer a pill, even with all its side effects, instead of a therapeutic talk.

Side Effects of Sleep Medication

Almost all modern sleep medications belong to the family of the benzodiazepines. All have a sedating, vigilance decreasing effect, reduce stress, and have anti-epileptic and muscle relaxing properties. They also, however, have a strong tendency to induce forgetfulness or memory loss (amnesia). These large numbers of side effects have benefits but also large disadvantages. The sedating effect is a great disadvantage, just as is the memory reducing effect, although this is less important if benzodiazepines are primarily used as a sleep medication, but of greater importance when they are used to reduce anxiety (42). One becomes more relaxed, but concurrently more drowsy and forgetful. The pharmaceutical industry is thus busily searching for drugs that have more specific characteristics; drugs that have the ability to just reduce anxiety or only have hypnotic effects. The pharmaceutical company Schering (Berlin) asked whether we would test several beta-carbolines that were thought to have partial agonistic effects of benzodiazepines (having one or at least some of the classical benzodiazepine effects). It appeared that abecarnil did indeed have an anxiety reducing effect, with only a minor hypnotic (sedating) influence (43). This advantage was insufficient however to get a firm place on the market as an anxiolytic, although it is currently under development for the treatment of *'generalized anxiety disorder'*. The 'hypnotic' pharmaceutical market is relatively conservative, and other newer, non-benzodiazepines-like sleep medications, such as zolpidem (Stilnoct) and zopiclone (Imovane) also appear to have insufficient advantages to successfully replace the classic benzodiazepines. The result is that the sleep medication market is still filled with

benzodiazepines such as the popular hypnotics temazepam (Normison) and lorazepam (Temesta).

One of the most serious side-effects of benzodiazepines is the effect they can have on driving a car. The American researcher, Jim O'Hanlon working at the University of Groningen, pointed out this serious negative property. His warning resulted in the placement of the yellow sticker on such medications containing the statement: 'this medication can influence driving ability'. In 1980, O'Hanlon designed a recording equipment to be installed in cars that could detect the influence of psycho-active drugs on driving ability along public roads. His sensational article, appearing in Science (1982), showed that drivers had much more difficulty following a straight line when under the influence of sleep medications or tranquillizers (44). They swerve back and forth along the roadway, even if the drug is taken the night before. This type of research, begun by O'Hanlon along with Johan de Gier at Groningen, was brought to Maastricht. Since their departure, the study is now continued there by Annemiek Vermeeren. This important societal relevant type of research is also now being performed by Karel Brookhuis at Groningen and Edmund Volkerts at Utrecht (45). It is not yet clear how the effect of benzodiazepines on performance comes about, but it is a good guess that it is related to the effect of reduced vigilance.
Nevertheless, one must be careful about making such a conclusion. What might also be true is that the amnesic effects of benzodiazepines, resulting from a reduction in alertness and vigilance, give rise to less adequate information processing. But consider the following experiment on the memory inhibiting effects of diazepam (Valium) that I performed along with my PhD student Mariëlle Gorissen. We wanted to determine whether amnesic effects were coupled with decreased vigilance so we induced a just as great vigilance-lowering effect through sleep deprivation. Preventing sleep for one night causes a reduction in alertness that is just as great as taking 15 mg of diazepam, both seen subjectively and objectively. Actually, however, sleep deprivation hardly induced disturbances among memory processes, while diazepam displayed vigorous disturbances of memory. One must therefore conclude that a decrease in vigilance alone cannot explain the impairment of memory processes (46, 47). Other factors, such as more specific benzodiazepine actions, may play a role. Much more work has to be done to understand the benzodiazepine's effects on driving and memory.

Automatic Sleep Classification

Since the publication in 1968 of the Rechtschaffen and Kales manual for visual sleep scoring (48), numerous attempts towards a computer assisted identification of sleep stages have appeared. In 1975 a new sleep analysis system, largely based on criteria established by Rechtschaffen and Kales, was developed by Anand Kumar at Piet Visser's group. At around the same time, Henk van Riezen at Organon, worked at producing such a system using EEG recordings of experimental animals, such as cats or rats. Finally, Gé Ruigt and Jan van Proosdij at the same company developed a good working automatic sleep classification system in rats, applying the EEG, EMG, and a movement indicator. This system can recognize six stages of sleeping and waking: active and quiet waking, quiet and deep sleep, pre-REM sleep and REM sleep (49). Gilles van Luijtelaar and myself, at about the same time, built a system on the basis of hippocampal EEG and EMG, that can discriminate, among rats, between light and deep sleep, REM sleep, and wakefulness (50). At Nijmegen we used the system for our deprivation experiments, while at Organon they used their system to detect characteristics of pharmaceuticals.

A main question was whether psychotropic drugs can be classified due to their effects on the EEG. This was not an easy topic, because all kinds of problems arose, such as the interaction of the effect of the chemical substance on the EEG with the actual behavior of the animal. To control this, Frans Krijzer at Duphar in Weesp, developed a method wherein the animal was placed on a 'slowly rotating drum' (51). This held behavior, thus vigilance, constant, and in this way he performed 'vigilance-controlled' pharmaceutical EEG studies on drug profiles. A second problem was the *'pharmacological dissociation'* of psychotropic drugs. All drugs leave their own 'fingerprint' on the EEG, but this fingerprint need not to run in parallel with the effects of the drugs on behavior. This may hinder the automatic identification of sleep stages. Let me give an example from our own research. Benzodiazepines increase higher frequencies in the EEG that are normally paired with increased alertness, but they also induce less vigilant behaviors that are commonly associated with lower frequencies in the EEG. This conflicting action on EEG and behavior is named 'pharmacological dissociation' (52). Nevertheless, Ruigt and his colleagues have succeeded in producing EEG profiles of various classes of psychotropic drugs by studying their influence on both EEG and sleep-wake behavior under a number of controlled conditions. Using a computer-based discriminant analysis of the EEG, they are able to differentiate between substances having anti-depressive, anti-psychotic, and anti-convulsive characteristics. The former system works well with these substances, but works less well on substances associated with anxiolysis and hypnosis, given their various working actions (53). All new developments are based on gaining more information from the EEG and we are also busy with such. We are currently evaluating a system designed by Philip van den Broek that establishes the correlation dimension of the EEG, a new parameter for the complexity of the EEG, which may be involved in accurately measuring the vigilance level in human and animal subjects (54).
Bob Kemp from Leiden has followed the pathway of the earlier successful work by Kumar. He is part of a task group on signal analysis within the EC concerted action, *'Methodology for the analysis of the sleep-wakefulness continuum'*, which has developed a computer-based sleep- wake analyzer that does not suffer from the limitations of standard manual scoring. The analyses include all sleep- wake related characteristics, as well as all REM sleep processes.
Now he is also involved with the *'somnolyzer classification'* system that still uses the original
Rechtschaffen and Kales criteria, but is fully automated and validated, yielding a refined analysis of human sleep (55). Slowly, however, doubts are growing whether the classical Rechtschaffen and Kales criteria discriminating four stages of sleep based on spindles and delta waves, are the best criteria for staging the complicated, gradual process of sleep.

Absence Epilepsy and Sleep

While studying the effects of REM sleep and deprivation of this type of sleep, Gilles van Luijtelaar and I encountered a remarkable EEG phenomenon found in a certain rat strain. This WAG/Rij strain displayed a unique set of EEG characteristics that could not be detected by our automatic sleep-wake detection system; too many abnormal EEG characteristics appeared. We quickly discovered that these peaked EEG patterns could be associated with epilepsy. They were called *'spike- wave discharges'* and appeared in two forms. We wrote an article in 1986 about this anomaly, *'Two types of electrocortical paroxysms in a strain of rats'* (56). The article attracted much attention, and was a 'gift from heaven' since we were somewhat disillusioned with REM sleep research, and the WAG/Rij rat, displaying epileptic phenomena, proved a welcome present. This rat strain suffers from a form of epilepsy, which

in children, is known as *absence epilepsy*. It is a mild form of epilepsy with short attacks accompanied by very small muscular contractions and a decrease in consciousness. I will not say too much about this research here since it already has attracted worldwide attention and this rat has become a pop star (57). This was highlighted in 2002 with our PhD student Hanneke Meeren. All previous theories considered that epilepsy was from *'centrencephalic'* origin, thus located in a deeply laying part of the brain. But Meeren showed, against all asserted conceptions, that absence epilepsy originates in a certain part of the brain cortex (the peri-oral cortex), and spreads rapidly about the cortex and concurrently into the deeper part of the brain (*'cortical focus theory of absence epilepsy'*) (58, 59). We are now busy trying to discover what the actual cause of this type of epilepsy is. What is really going wrong in this small super-sensitive part of the brain cortex?

Extra fascinating to me is that this form of epilepsy appears so similar to sleep. This is verified by the interest shown by epilepsy researchers who also perform sleep research (60).
Just as in sleep, epilepsy and therefore also 'absences', are characterized by reduced consciousness, more or less similar to sleep, and in both cases the body becomes almost totally insensitive to external events. In absence epilepsy the key word is 'absence', since the wakeful consciousness system is truly reduced: the person is really absent. As is well known this absence is also a sleep characteristic. But even if we are unconscious, we still receive experiences through our unconscious system; this is continuous and we are continuously evaluating such incoming stimuli.
We are thus, for example, still quicker and easier awoken by a stimulus that may be important, such as the crying of a newborn baby, an unexpected light indicating fire, or some noisiness in the living room or breaking of glass. These may be events that warn us of danger. This 'reversible' characteristic of sleep is much different from other non-physiological low vigilance states, such as when in a coma or under narcosis. A person may be awakened by intense stimuli, but also quite easily by less intense weak stimuli that have some personal meaning, either positive or negative (61). This unconscious 'sensitivity' has an important survival value. Consider a hare sleeping in its grassland bed, which, by the least unfamiliar sound or movement, quickly awakes to escape impending danger. Such incoming information can also be detected during an absence epilepsy attack. That state may be ended through a relevant stimulus. It is possible to cut an absence attack by presenting a meaningful stimulus to the epileptic brain. This has been proved experimentally by our PhD student, Pim Drinkenburg, who showed that an absence could be aborted by a meaningful stimulus that was learned through prior conditioning (62). In practical therapy this may not be so important, but it has meaningful theoretical implications, for understanding mechanisms of consciousness.

Winnie Hofman, at the University of Amsterdam and working as consultant to the Health Council of the Netherlands, has been carrying out experiments to the effects that stimuli, such as traffic and air plane noise, may have on sleep. The attempt is to determine the effects, both subjectively and objectively, of such bothersome noises on the quality of human sleep. The outcome of a meta-study to air traffic noise, concluded that interference with sleep began at noise intensities of between 55 to 60 dB, but changes in the sleep pattern even began much earlier (63). Children are less sensitive for sounds, while older people show just a greater sensitivity. It was earlier thought that one could become accustomed, insensitive, to high sound levels, but that is often not the case. The advice from the Dutch Health Council indicated that annoying sound levels can cause health problems and thus should be avoided. This type of noise can interfere with sleep, e.g. cause sleep stage changes and, more seriously, awakenings. In 1989, myself, together with some department colleagues, became

involved with a study about the effects of noise caused by nightly air flights, on people living near the airport Maastricht-Aachen in the south of Limburg. (64). We found that airplane sound levels beginning at about 60 dB did cause awakenings, but this was true for neutral stimuli. The noise sensitivity threshold did not, however, apply to more meaningful, non-neutral stimuli, as described earlier (e.g. cry of a baby). The latter shows a more 'chaotic' relationship to sleep disturbances, not dependent on sound intensity, but more to its meaningfulness to the subject. Via a *'general health questionnaire'*, it was found that some groups of people are indeed extremely sensitive to high sound levels, and are greatly annoyed by such. This group of people may become awake by air traffic sounds starting at about 40 dB or even lower; they find it highly disturbing. This great variation in sensitivity to sounds makes it extremely difficult to establish 'politically' appropriate and acceptable airport sound level policies, affecting people living near airports. Great positive economic effects (important to the airport and companies involved), must be weighed against the more negative effects on personal health, which is an almost impossible assignment.

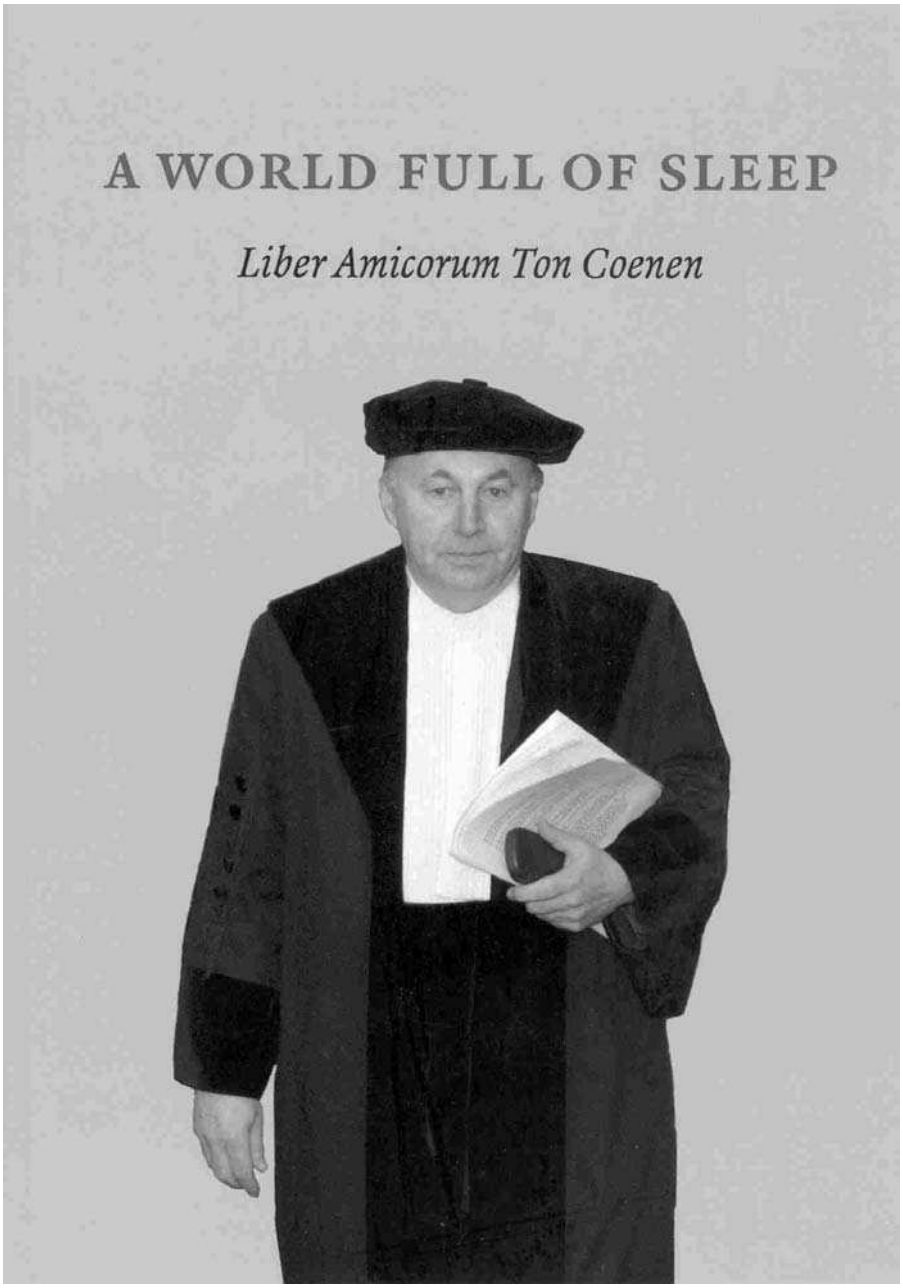
The Mystery of Dreaming

Humankind has always been interested in dreams. How can we interpret a dream and can something be learned from such? These are pressing questions. Since the discovery of REM sleep in 1953 by Aserinsky en Kleitman (13), and its reputed relationship to dreaming, have investigations into dreaming expanded. Great numbers of people were taken into sleep laboratories, electrodes attached to their heads, and as they finally entered into REM sleep, were awoken. They were asked two questions: Were you dreaming and if yes, what about?
From personal experience you have probably discovered that dreams are quickly forgotten, and a short time later, details cannot be recalled. Even though dreams have a fleeting character, about 90% of people suddenly awakened from REM sleep, can give a clear report on what they have dreamed. One sure conclusion is that REM sleep is accompanied by dreaming!
An inconvenient and highly unexpected outcome, however, was found in control experiment wherein subjects were awakened from normal (non-REM) sleep. A small, but rather consistent number (about 5%) were able to recall dreaming. No matter how the experiment was contrived, the results were the same, and science cannot ignore this finding (6, 65). In other words, REM sleep is always accompanied by dreaming, but is not exclusive to that state. I have often proposed that dreaming is associated with higher brain activity during sleep; this is always present during REM sleep, but now and then may also appear during normal sleep (65). This might also explain dreamlike experiences (*'hypnotic hallucinations'*), one might experience while falling into sleep, since brain activity may then fluctuate quite heavily. That dreaming is not only found during REM sleep has relevant consequences. One must be aware that data surrounding REM sleep cannot always be extrapolated into making conclusions about dreaming. A second problem related to dream research is the fact that it is never the 'real' dream that is analyzed, but merely the recall that later occurs during wakefulness. No one really knows the relationship between the dream itself and the memory thereof. In his famous text book '*Psychology: an international perspective'* (66), Michael Eysenck quotes a statement made by myself (67), 'A dream is what someone describes upon awakening and researchers infer a one-to-one relationship between the dream and the way it is reported. It is therefore impossible to exclude such confounding factors as poor memory, overestimation, suppression or the effects of psycho-emotional factors on recall'.

Frank Heynick, an American expat psycholinguist working in Groningen and Eindhoven, had considerable difficulties with the latter statement. Heynick (68) studied the language used by people in their dreams. He proposed that, *'dream language'*, is a sort of archaic primitive remnant of speech. The essence of Heynick's thinking (formulated in a Freudian framework) was: 'It is impossible that a dream, being a primary, non-logical, old process, is integrated in a secondary new, logical, process as speech and language'. Nevertheless, he found instead, that the language used in dreams is the same as used in daily life, with the same logical sentences and often complicated grammar. The problem with the rather unclear relationship between what we dream and what we recall later, might possibly be smaller in a *'lucid dream'*. This phenomenon was introduced by the Dutch psychiatrist Frederik van Eeden in 1913 (69). He claimed that, occasionally, people have dreams in which they know that they are dreaming and that they can sometimes control their own dream content. These dreams are called lucid dreams. It is mostly noticed that these types of dreams seldom occur, and mostly by certain types of people. I have, however, the feeling that it is a more common experience. Consider the dream that may arise, while sleeping out late on a Sunday morning and still in a slumbering state somewhere between wakefulness and sleep. During that moment one seems capable of picking up again and again the theme of the dream, and even giving it some direction. This 'lucid dream' topic is undergoing further research by Victor Spoormaker at Utrecht, who was trained by Stephen LaBerge at Stanford University, a pioneer in this area. The lucid dream phenomenon can perhaps be used as a new paradigm for further dream research since current paradigms to study dreams seem to have reached in an impasse. I hope that a new edition of Spoormaker's (70) recently published booklet (2004), *'Alles over dromen', ['Everything about dreaming']*, will contain new information on this great mystery of life. But it is my belief that this intriguing dream phenomenon will still remain a mystery for a long time. Moreover, current investigators, living in a publish-or-perish world, still seem to shy away from this risky topic.

Epilogue

After many, many years, an end has come to my activities related to sleep (but with a few exceptions such as some industrial sleep projects (71), PhD students, and teaching a popular sleep course). The Department of Biological Psychology will reduce sleep investigations to a great deal in the year that I formally will leave the university (2008). I did not succeed to build up a group that was able and willing to further delve into such studies, although many ideas presented here infected people and spread over the world. In diminishing sleep research several factors play a role: interest in other, more popular, scientific areas, personal interests, but, most importantly, the scientific climate of the research institute itself, in striving to a closer coherence among research groups. Sleep, as subject, is not seen as a great attraction for researchers, and suffers from this attitude. That is disappointing and inappropriate since the study of sleep can yield great insights into the functioning of the human brain and indirectly on the enigma of consciousness (37, 72, 73). It is as it is; I can cope with it after enjoying so many years of intriguing research. The study of this very normal aspect of human life still has numerous mysterious and unexplainable elements. So was (and is) my life, the night filled by experiencing sleep, the day filled by studying sleep. A life full of sleep!



The author, Prof. Ton Coenen, in ‘A world full of sleep’ (74)

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PH. D. THESES

HYPOCRETIN DEFICIENCY: NEURONAL LOSS AND FUNCTIONAL CONSEQUENCES

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INTRODUCTION

The dual discovery of hypocretin

The hypocretins were discovered in 1998 nearly simultaneously by two different groups. One group named these newly found peptides hypocretins because of their hypothalamic origin and a weak sequence homology to the incretin hormone family. Only six weeks later, another group named the same peptides orexins, because intracerebroventricular injection of these neurotransmitters stimulated food intake in rats (ορεξη = appetite).

Hypocretin is produced by neurons in a subregion of the hypothalamus, the dorsolateral hypothalamus, centered around the fornix and adjacent areas. In rats, estimates of the number of hypocretin containing neurons range from 1,000 to 4,000, depending on the antiserum and/or estimation method. In the human brain, this number was estimated at 15,000-20,000 using in situ hybridization and 50,000-80,000 using immunocytochemistry. The cell bodies of hypocretin producing neurons all lie together in a rather small area, but this does not hold at all for their projections, which are found throughout the brain. In accordance with this finding, hypocretin receptors are also found throughout the brain.

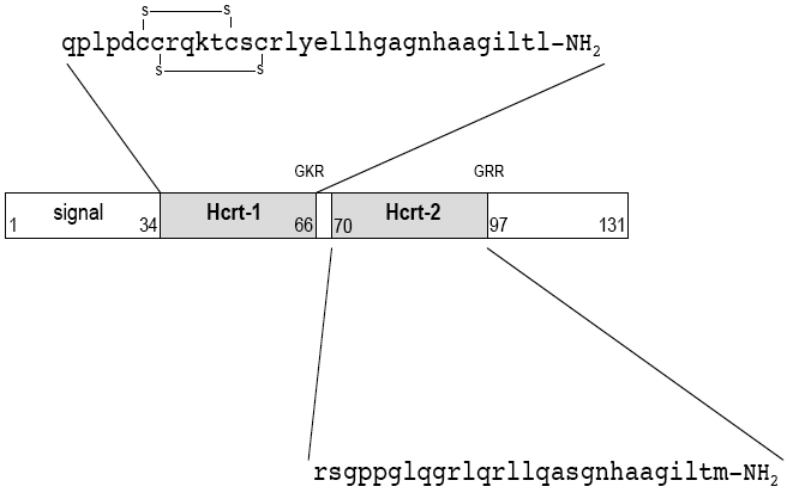

Figure 1. GKR and GRR depict dibasic residues, that are potential cleavage sites for prohormone convertases. The derived aminoacid sequence for hypocretin-1 and hypocretin-2 are shown as well. The C-terminal end of both peptides are amidated. Note the two intrachain disulfide bridges in hypocretin-1.

Hypocretin and Narcolepsy

When hypocretins were first discovered they were thought to be mainly involved in the regulation of food intake. Local injection of hypocretin-1 in several hypothalamic areas, such as the dorsomedial nucleus, induced feeding behaviour, while administration of hypocretin-1 antibodies suppressed feeding in rats. This prevailing view underwent a change following the discovery that dogs (Dobermans and Labradors) suffering from an autosomal recessive inheritable form of the sleep disorder narcolepsy have a mutation in the type 2 receptor for hypocretin. This prompted the view that hypocretins are crucial for the regulation of sleep. As said, hypocretin neurons project widely throughout the brain, but closer scrutiny revealed a notable concentration in wake stimulating areas. Soon further evidence for the role of hypocretin in regulating sleep and activity/arousal was found in man. In healthy persons hypocretin could be detected in the cerebrospinal fluid, but in narcoleptic patients the amount was so low that its presence could not be detected. Further research showed that the lack of hypocretin was caused by a specific loss of hypocretin containing neurons. At present it is not clear how the amount of cell loss translates to disease severity. How these cells are lost is also at yet unknown. The most popular hypothesis concerns an autoimmune process that selectively targets hypocretin neurons, but no direct proof for such a process has yet been found. The strongest argument for this hypothesis is the fact that almost all narcolepsy with cataplexy patients share the same major histocompatibility complex (MHC) subtype of immune system (HLA, Human Leukocyte Antigen, DQB1*0602).

The hypocretin system in other disorders

Abnormalities of sleep resembling those seen in narcolepsy, inspired an interest in hypocretin function in neurodegenerative disorders, such as Alzheimer's Disease, Parkinson's Disease and Huntington's Disease. Furthermore, intriguing reports about sleep disturbances and even a state resembling cataplexy in the Prader-Willi Syndrome have led to an interest in hypocretin functioning in this genetic disorder that affects the hypothalamus. Therefore, we decided to study post-mortem brain material from these disorders.

Involvement of hypocretin in narcoleptic symptoms other than sleep

Although the link between hypocretin deficiency and the sleep-related symptoms of narcolepsy has been well established, there are other consequences of a lack of hypocretin that have to be studied in more detail. Most importantly, it is still unknown how a lack of hypocretin results in the emotion-triggered cataplectic attacks that characterize narcolepsy (see box 3). In fact, the relationship between hypocretin deficiency and cataplexy is stronger than that with excessive daytime sleepiness.

SCOPE OF THE THESIS

Part I - The Hypothalamus and its Hypocretin Neurons

In the first part of this thesis the question was examined whether or not hypocretin neurons are lost in neurological disorders in which sleep disturbances similar to those in narcolepsy occur. Furthermore, a screening for auto-antibodies was described, aimed at finding evidence for a putative autoimmune aetiology of human narcolepsy, followed by a report on a placebo-controlled double-blind N=1 trial with intravenous immunoglobulins (IVIg) in one narcoleptic patient.

Part II - When Hypocretin Neurons are Absent: Narcolepsy

In the second part of this thesis the consequences of a loss of hypocretin neurons were examined, with a focus on non-sleep-related symptoms of narcolepsy, i.e. obesity (metabolism and autonomic control), vigilance impairment and skin temperature regulation.

PART I: THE HYPOTHALAMUS AND ITS HYPOCRETIN NEURONS

Prader-Willi Syndrome[9]

Prader-Willi Syndrome is characterized by mental retardation, hypogonadism, growth deficiency and most notably by an insatiable hunger. Prader-Willi Syndrome is the most common genetic cause of obesity. Furthermore, patients suffer from excessive daytime sleepiness, and some case reports suggest that a minority of patients experience cataplexy-like attacks. CSF hypocretin values are normal in Prader-Willi Syndrome, although slightly lower than normal values have been reported. To determine whether the hypocretin system is involved, we studied post-mortem hypothalami of eight adult and three infant Prader-Willi Syndrome patients and 11 controls. No difference in the total number of hypocretin-containing neurons was found between Prader-Willi Syndrome patients and controls. When the control subjects from the Prader-Willi Syndrome study were analyzed together, the total number of hypocretin neurons tended to decline with age.

Parkinson's Disease[1,4]

Although Parkinson's Disease (PD) is primarily characterized by motor symptoms such as tremor and rigidity, sleep disturbances occur often, and include excessive daytime sleepiness, fragmented nocturnal sleep and rapid eye movement (REM)-sleep behavior disorder. The combination of these symptoms suggests an overlapping etiology with narcolepsy. Hypocretin levels in CSF were reported to be normal in Parkinson's Disease when samples were obtained using a spinal tap, but another study reported low or even absent levels in ventricular CSF.To assess hypocretin function in Parkinson's Disease we determined the total number of hypocretin containing neurons in nine PD patients and nine controls. Hypocretin levels were also determined in post-mortem ventricular CSF of these subjects. Furthermore, cortical brain tissue hypocretin levels were determined in nine PD patients and 16 controls. We found that the hypocretin system was affected in PD. The hypocretin concentration in the cortex was almost 40% lower in PD patients than in controls. Ventricular CSF levels were lower by almost 25%. The total number of hypocretin neurons was about one half of that of controls. In rodents, a reduction in the number of hypocretin neurons of 60-70% results in REM sleep disturbances, which suggests that the cell loss in PD can explain at least part of the sleep disturbances commonly seen in this disorder.

Huntington's Disease[11]

Huntington's Disease is a neurodegenerative genetic trinucleotide repeat disorder with a dominant mode of inheritance characterized by abnormal dance-like body movements (chorea) and personality changes. Furthermore, patients suffer from severe weight loss, sleep disturbances and autonomic dysfunction, which could partly be due to alterations in hypocretin signalling. Although spinal CSF hypocretin levels were normal in human patients, the density of hypocretin neurons was reported to be decreased in two mouse models of the disease. In order to validate and extend these data in Huntington's Disease patients, we counted the total number of hypocretin neurons in 8 HD patients and 8 controls. Hypocretin levels were also measured in post-mortem ventricular CSF of these subjects. Furthermore, cortical brain tissue hypocretin levels were determined in 19 HD patients and 16 controls.

Both the total number of hypocretin neurons and the hypocretin concentration in the cortex were 30% lower in HD patients. However, ventricular CSF hypocretin levels were similar to controls. This reduction in hypocretin signalling is in contrast with the strong reduction seen in the R6/2 mouse model of the disease and the contribution to the clinical symptoms of HD patients remains to be investigated.

Narcolepsy: Screening for Autoantibodies[7]

In narcolepsy there is a severe decrease (>95%) of hypocretin containing neurons in the lateral hypothalamus, leading to a general absence of hypocretin in the cortex and in CSF. It is not known how these neurons disappear. The most popular hypothesis concerns an autoimmune process that selectively targets hypocretin neurons. However, no direct evidence for this putative autoimmune process has so far been found. We screened the CSF of 54 patients and the serum of 76 patients and 63 controls for the presence of autoantibodies directed against neurons in the lateral hypothalamus. Detectable autoantibodies were present in only two patients, but also in two controls. Therefore, as shown by immunostaining, humoral immune mechanisms appear not to play a major role in the pathogenesis of narcolepsy, at least not in the clinically overt stage of the disease.

Narcolepsy: Trial with Intravenous Immunoglobulins[2]

In line with the prevailing autoimmune theory to explain the pathogenesis of narcolepsy, treatment with high-dose prednisone after acute manifestation of hypocretin deficiency has been tried in an 8-year old boy. This was not effective. However, two open-label studies suggested that treatment with intravenous immunoglobulins (IVIg) shortly after disease onset may dramatically reduce the frequency and severity of cataplexy. We performed a double-blind N=1 study in a 55 year old female narcolepsy patient who was suffering from typical narcolepsy with severe cataplexy for 7 years. Open label treatment with IVIg resulted in what appeared to be a dramatic success. However, this striking effect disappeared during the subsequent double-blind placebo-controlled n=1 trial, in which there was no difference between placebo and IVIg treatment. Nevertheless, the placebo effect was impressive. The patient reported fewer cataplectic attacks after the first drug administration of the study, which concerned the placebo. Our findings stress the need for strict adherence to common methodological standards involving blinding and the use of a placebo for future trials.

PART II: WHEN HYPOCRETIN NEURONS ARE ABSENT: NARCOLEPSY

Vigilance[8]

Excessive daytime sleepiness (EDS) is considered to be the main complaint in narcolepsy. However, this focus on inadvertently falling asleep may have led to undervaluation of the perhaps most serious complaint: impaired performance in the waking state. This realisation suggested that tests aiming to measure vigilance might be useful in narcolepsy. The Sustained Attention to Response Task (SART) appeared to be a good candidate. This test takes only a short time to perform and is easy to administer, which make it useful in a clinical setting. To explore the role of the SART in quantifying vigilance as an essential aspect of the severity of narcolepsy, we compared the SART with 2 instruments commonly used to measure sleepiness: the MSLT and the Epworth Sleepiness Scale (ESS). We found that the SART, measuring attention, was abnormal as often as the MSLT, measuring sleepiness. Still, the two tests measure different aspects of the disease, as SART and MSLT results showed no correlation with each other or with the Epworth Sleepiness Scale. The range of the MSLT

latency was considerably larger in controls than in patients, while the reverse applied to an even stronger degree for the range of the SART error scores.

Obesity[12]

Obesity is a consistent feature of narcolepsy. The identification of hypocretin deficiency as the cause of human narcolepsy with cataplexy and the potential role of hypocretin peptides in metabolic control has sparked interest in the pathophysiology of obesity in narcolepsy. Obviously, eating too much or moving too little are straightforward explanations. In contrast to such expectations narcoleptic subjects in fact consumed less food than healthy controls, while there were no signs pointing to a reduced amount of physical activity. Therefore, the link between hypocretin deficiency and obesity must be less straightforward than assumed. We studied basal metabolic rate and variation in blood pressure and heart rate in hypocretin-deficient narcoleptic subjects and healthy controls, hypothesizing that sympathetic tone might be diminished and/or that basal metabolic rate would be reduced in narcoleptic subjects. We did not find a reduced basal metabolic rate in narcoleptic subjects. However, we did find a higher variability in heart rate and blood pressure, which could point to a changed sympathetic tone. The role of this latter finding in the pathophysiology of obesity in narcolepsy remains to be elucidated.

Thermoregulation[5,6,10]

In healthy subjects there is a relation between skin temperature and sleep. When the temperature of the distal skin (hands and feet) increases relative to the temperature of the proximal skin, the process of falling asleep is facilitated. This increase in the temperature of the hands and feet results from increased blood flow in the skin of the extremities and is, among other factors, controlled by the hypothalamic circadian clock, as is sleep. Because narcolepsy is characterized by hypothalamic alterations, we studied skin temperature in narcoleptic patients. We found that the distal skin temperature was higher in narcoleptic subjects compared to healthy controls throughout the day in the waking state, while the proximal skin temperature was lower. The increase in the gradient between the distal and the proximal skin temperature (the distal-to-proximal gradient, DPG) was related to a shorter subsequent sleep latency. Once asleep, narcoleptics maintained their elevated distal skin temperature and DPG, whereas proximal skin temperature increased to reach normal levels. This dramatic alteration of daytime skin temperature control in narcolepsy suggests that hypocretin deficiency in narcolepsy affects skin temperature regulation, which in turn may affect sleep and vigilance.

Our next goal was to investigate a contribution of skin temperature regulation disturbances to impairments in the ability to maintain vigilance and wakefulness, two major complaints of patients with narcolepsy. The Psychomotor Vigilance Task and the Maintenance of Wakefulness Test were repeatedly assessed, while skin and core body temperature were manipulated using a thermosuit and hot or cold food and drinks. Compared to core cooling, core warming improved the time-on-task decline in Psychomotor Vigilance Task response speed by 25%. Slightly increasing core body temperature, -which was relatively low in the narcolepsy patients-, towards a more normal level, thus improves vigilance. As compared to distal skin warming, distal skin cooling increased the time that the patients were able to maintain wakefulness by 24%. Cooling the hands and feet and warming the proximal skin thus decreases daytime sleepiness in narcolepsy. Core body and skin temperatures causally affect vigilance and sleepiness in narcolepsy. This may have future therapeutic consequences.

Apart from sleepiness and decreased vigilance, disturbed night time sleep is another core symptom of narcolepsy that can severely affect quality of life. Nocturnal polysomnography shows a fragmentation of the normal sleep pattern and frequent arousals. To investigate a causal contribution of temperature alterations to the disturbed sleep in narcolepsy, we manipulated proximal and distal skin temperature during nocturnal polysomnography. Throughout the night, skin temperature was manipulated to slowly cycle within a range normally observed during sleep. The sleep-inducing combination of proximal skin warming and distal skin cooling led to a 160% increase in the duration of slow wave sleep, a 50% increase in REM-sleep and a 68% decrease in wakefulness, compared to the wakefulness-inducing combination of proximal skin cooling and distal skin warming (note, that due to the protocol used, temperature manipulations can only be compared to one another, but not to a 'thermoneutral' situation). These effects are similar in magnitude to the effects of the currently used hypnotic sodium oxybate (gamma hydroxybutyrate). Skin temperature manipulations under controlled conditions thus ameliorated the typical nocturnal sleep problems of narcoleptic patients - i.e. they led to increased slow wave sleep and decreased wakefulness–, making their sleep more comparable to that of healthy persons. These results indicate that skin temperature control could have clinical relevance in the management of disturbed nocturnal sleep in narcolepsy.

Table 1. Overview

	Hypocretin System			
	In Vivo	***Post Mortem***		
Disorder	*Spinal CSF*	*Ventricular CSF*	*Tissue Level*	*Hcrt-1 IR Cell Number*
Narcolepsy	↓↓↓↓	↓↓↓↓	↓↓↓↓	↓↓↓↓ (-95%)
Prader-Willi Syndrome	=	=	=	=
Huntington's Disease	=	=	↓ (-30%)	↓ (-30%)
Parkinson's Disease	=	↓ (-25%)	↓ (-40%)	↓↓ (-50%)
Alzheimer's Disease	?	?	?	?
Normal Aging	=	?	?	=/↓?

CSF, Cerebrospinal Fluid; IR, immuno-reactie; hcrt-1, hypocretin 1.

GENERAL CONCLUSIONS

Neuronal Loss and Narcoleptic Symptoms[1]

As stated in the first part of this thesis, a loss of hypocretin containing neurons is not limited to narcolepsy, but also occurs in other disorders. The speed of the process that targets hypocretin containing neurons in narcolepsy is unknown, but the process is highly selective and complete, in contrast to the situation in Parkinson's and Huntington's Disease, where the hypocretin cell loss is not complete and where various neuronal populations are at risk. We know that other cell types are reduced to a lesser extent (for example the melanin-concentrating hormone neurons in Huntington's Disease), but maybe other cell types to an even greater extent (for example dopamine neurons in Parkinson's Disease) than the hypocretin containing neurons.

A complicating issue is the fact that it is difficult to distinguish a loss of neurons from a loss of a cell marker, such as hypocretin-1. Strictly speaking, a decreased number of neurons that express hypocretin-1 does not mean that there is actually a loss of these neurons. Neurons that used to express hypocretin-1 could still be present and functionally active. In fact, some

researchers hypothesize that hypocretin neurons are not actually lost in narcolepsy, but just stop making hypocretin. The fact that the expression of dynorphin and neuronal activity-regulated pentraxin (NARP), which are normally co-expressed by the majority of hypocretin neurons, is also lost in narcoleptic hypothalami, does still not prove that the neurons are really gone. These cells may produce fewer peptides on a global level. However, despite this unanswered question, the functional consequences of a 'real' loss of neurons on the one hand or a loss of 'only' the marker on the other hand, are similar. But if the neurons that formerly produced hypocretin are still alive and can be turned intro active hypocretin neurons again, this could potentially be a way to cure narcolepsy.

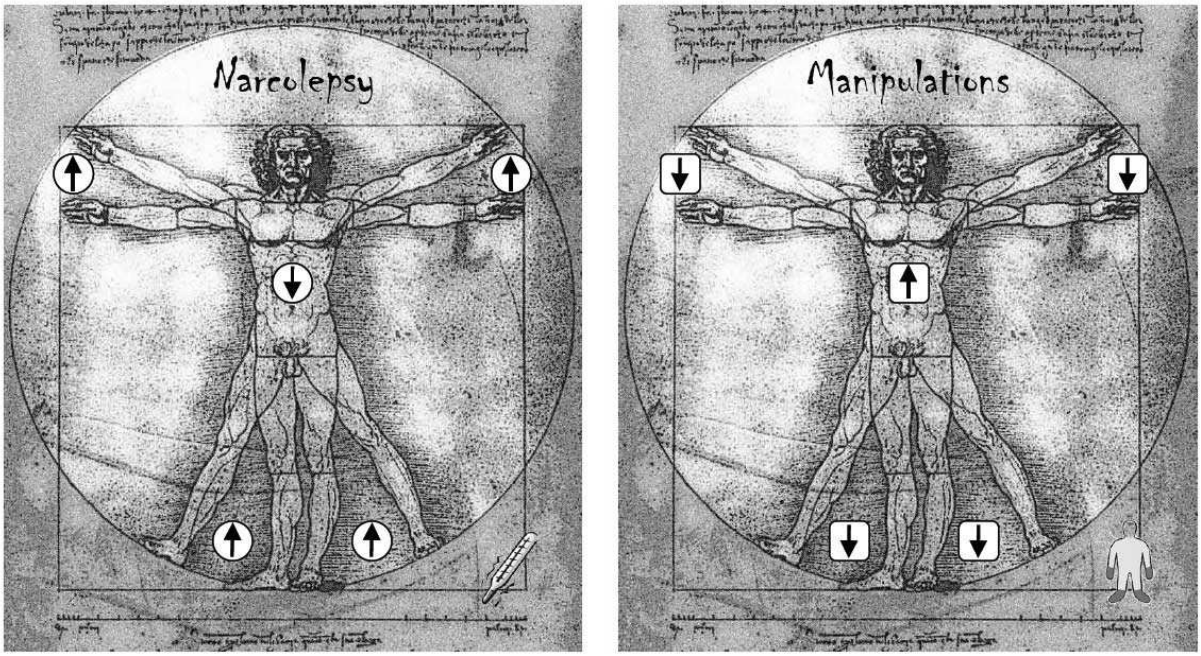

Figure 2. Scheme indicating the alterations in skin temperature control we found in narcolepsy (left, circles) and the manipulations of skin and core body temperature that had beneficial effects on vigilance, sleepiness and night time sleep (right, squares). Note that the beneficial manipulations (right) are all in the opposite direction compared to the alterations found (left).

Whether the moderate loss of hypocretin containing neurons in Parkinson's Disease and Huntington's Disease will lead to clinical symptoms remains an intriguing question. In rodents a loss of 60-70% of hypocretin neurons results in REM-sleep disturbances. This would imply that the more than 50% loss we found in Parkinson's Disease (reflected in lower ventricular CSF levels) could at least partially explain the sleep disturbances (excessive daytime sleepiness, REM-sleep Behavior Disorder) commonly seen in this disorder. The loss of hypocretin containing neurons in Huntington's Disease is less severe (with normal ventricular CSF levels) and is thus less likely to result in clinical symptoms.

The exact contribution of a loss of hypocretin neurons to sleep disturbances still needs to be studied. This should involve studying post-mortem hypothalami of patients, whose sleep disturbances were well documented during the last few years of their lives. Furthermore, we found an indication for a decrease in hypocretin cell number with age in the controls of our study looking into hypocretin functioning in Prader-Willi Syndrome. This raises the interesting question whether this would mean that the hypocretin system would be affected to an even greater extent in a brain showing advanced ageing, i.e. Alzheimer's Disease.

Body Temperature and Narcolepsy

In narcolepsy a relatively high skin temperature of the hands and feet compared to the temperature of the proximal skin is related to a shorter sleep latency. By manipulating skin and core body temperature we were able to influence sleepiness, vigilance and night time sleep. Note that the beneficial manipulations were all in a direction that counteracted the narcoleptic alterations in temperature that we found earlier. This indicates that the hypothalamic circuitry involved in the coupling between temperature and sleep are basically intact in narcolepsy and that manipulation of core body and skin temperature can causally affect sleep and vigilance in narcolepsy.

Of course, these findings were obtained in a laboratory setting under strictly controlled circumstances. The narcoleptic alterations in skin temperature control and the beneficial effects of manipulation thus need to be replicated and confirmed in a different setting: outside the hospital and at home. One could then even think of practical applications such as chairs or bedding that measure and differentially manipulate proximal and distal skin temperature. At this point, the findings can be summarized as follows: To stay alert, drink your hot coffee, but don't hold it, and hold your ice cream, but don't eat it.

Narcolepsy: Search for the Cause and Therapy[3]

The last few years have seen an enormous increase in knowledge concerning the role of hypocretin in the regulation of sleep. However, more studies are needed to assess the effects of hypocretin deficiency on other important aspects: metabolism, vigilance, autonomic control and temperature regulation in humans.Regarding narcolepsy, the two most exciting future fields of research are the search for the cause and the search for a new therapy.

PUBLICATIONS

Thesis

Fronczek R. Hypocretin Deficiency: Neuronal Less and Functional Consequences. Leiden 2008. ISBN 978-90-9022577-7.

Papers

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FROM BENCH TO BEDSIDE AND BACK. THE DOCTORATE THESIS OF ROLF FRONCZEK: HYPOPOCRETIN DEFICIENCY: NEURONAL LOSS AND FUNCTIONAL CONSEQUENCES

A.W. de Weerd
Sleepcenter SEIN Zwolle

Rolf Fronczek (1981) defended his doctorate thesis entitled "Hypocretin deficiency: neuronal loss and functional consequences" in Leiden on January 30, 2008. His promotores were Professors Gert van Dijk and Dick Swaab. Gert Jan Lammers was co-promotor.
The cover of the thesis immediately attracts attention. Two mythological figures, probably Thanatos (Death) and Hypnos (Sleep), watch over a sleeping human lying in a crib smoothly surrounded by a substance that looks like water or a cloud at the front cover, but which proves to be the cerebral cortex at the back cover. Indeed, an intriguing start!
The thesis represents the next part of the impressive work from the narcolepsy oriented sleep group in Leiden with theses from Lammers, Overeem, Fronczek and more to come, all based on high quality international publications. Hypocretin loss is the leading theme. In the first chapters work done in close cooperation with the Netherlands Institute for Brain Research (Dick Swaab and co-workers), is presented. These contributions vary from purely technical: visualization of hypocretin receptors, to more clinically oriented hypocretin measurements in Prader Willi Syndrome, Huntington Disease and Parkinson's Disease. The latter is in particular an example how institutes can work together in a fruitful way. The fourth chapter in this part of the thesis regards the main question about hypocretin in narcolepsy: what is behind the loss of this protein in that disorder? The auto-immune hypothesis is theoretically plausible, but has not been proven previously and also can not be substantiated in a study done by Overeem with Fronczek as one of the co-authors. Finally, a N=1 study of treatment by immunoglobulines is described. Although not very convincing, this study gives at least no endorsement for an auto-immune disturbance underlying narcolepsy.
The second part of the thesis is clinically oriented. Probably the first chapter will have major impact on how Dutch clinicians do the diagnostic work-up of patients suspected of narcolepsy and how they start state of the art therapy. The paper is published in the Nederlands Tijdschrift voor Geneeskunde (2007;151:856-861) and widely available. More limited to the practice of Sleep Medicine, but published in the world's leading sleep journal, is the chapter promoting measurement of vigilance in addition to sleepiness as part of the assessment of narcolepsy. A short and elegant test, the SART, was chosen, validated and its results compared to those of the MSLT. For all persons interested in Sleep Medicine the message is clear: implement the SART in the diagnostic phase of the work-up and use it in the follow-up. Hopefully an electronic version of the test comes available for all workers in sleep and wake disorders in the near future. The third chapter gives convincing data on a normal metabolic rate in rest, precluding this factor as contributor to the well known overweight in many narcolepsy patients.
In the final part of the thesis we go at least partly back to the laboratory. Together with the research group lead by Eus van Someren, intriguing and well conducted studies were done with as main question the relation between hand- and more proximally measured temperature and its impact on sleep and sleep propensity in narcolepsy patients. These studies were a continuation of work by Eus van Someren, Roy Rayman and co-workers,

dedicated to the influence of peripheral temperature on sleep. The results of the cooperation of the Leiden and the Amsterdam group were summarized in one sentence during the defense of the thesis: the narcolepsy patient may have better sleep when he takes a hot drink before bedtime (higher core temperature) and keep a cold object in the hand. Although this sounds as an easy advice, doubts remain whether this is really the practical solution for bad sleep which is one of the five core symptoms of narcolepsy. The three chapters discussing the findings in normal and narcolepsy patients and the results of manipulating peripheral and central temperature and its gradients make fine reading and are food for thought.
In summary: when you are one of the lucky people who have the book, read it from front to back and implement the major messages in your approach to narcolepsy patients. If you do not have the book: try to get one!

R. Fronczek. Hypocretin Deficiency. Neuronal loss and functional consequences Thesis Leiden, January 2008. ISBN: 978-90-9022577-7

RESEARCH PAPERS

THE SLEEP PRESSURE SCORE IS NOT USEFUL IN THE ASSESSMENT OF PERIODIC LEG MOVEMENTS

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INTRODUCTION

In a pilot study in patients with moderate periodic limb movement disorder (PLMD)[1] (mean PLMI 16.3) we investigated the use of a numeric algorithm for polysomnographic assessment of sleep disruption and resultant sleep pressure due to leg movements (SPS_L). For further insight we did a second study in a group of patients with severe PLMD (mean PLMI 51,3).

The SPS_L is comparable to a previously described sleep pressure score (SPS)[2] in apneu syndromes. This SPS reflects the relationship between the total arousal index (ARtotI), respiratory arousal index (RAI), and spontaneous arousal index (SAI). This algorithm appeared to be an useful measure for the study of the relationship between nocturnal sleep and wake during daytime in adults and young children with an apneu syndrome[3]. In analogy we defined the SPS_L as: SPS_L = (LMAI / ARtotI) x (1-SAI / ARtotI), in which LMAI is the number of leg movements with arousal, the ARtotI the number of all arousals and the SAI the number of spontaneous arousals, all indexed per hour of sleep. In the previous study in mild PLMD we found a clinically relevant relation to one important sleep parameter, time in deep sleep (SWS, $r = 0.51$, $p < 0.05$) but not to other objective measures of sleep or subjective parameters of sleep quality or feelings of tiredness during daytime. As these findings gave no final verdict whether the sleep pressure score is useful in PLMD, we decided to continue the study in patients with severe PLMD in order to get more certainty.

METHODS

Twelve patients (8 men), with periodic leg movements and arousals participated in this study. The age range was 26-77 years, mean age 54 yrs. All patients underwent two consecutive 24hours polysomnographic recordings at home (PSG) with a Medcare Somnologica4 system. The registrations for the study were done in 2006 – 2007 before the new AASM rules were completed. The recording standards were EEG (C3/A2, C4/A1, O2/A1, O1/A2), electro oculography (ROC/A1, LOC/A2) and chin electromyography (EMG), according to criteria outlined by Rechtschaffen and Kales[4]. Furthermore electrodes were placed on both m. tibialis anterior, to monitor the EMG of the legs. Plethysmography bands were used to monitor chest and abdominal movements and a nasal pressure transducer to monitor airflow together with pulse oximetry to evaluate oxygen saturation. Electrodes for ECG, a snore sensor and a body position monitoring device were added. Sleep was staged as defined by Rechtschaffen and Kales. Limb movements and PLMs were scored as defined in the ASDA Atlas Task Force Report[5]. To detect and assess arousals we used the criteria proposed by the ASDA[6] together with the additional criteria by Zucconi et al[7]. As leg movements followed by an arousal (LMA) are considered to be most relevant, it is recommended to classify this parameter in particular. From the data obtained we selected the following parameters: the sleep stages in

percentage of total sleep time (TST), sleep efficiency (SE) calculated as total sleep time / total time in bed, the total number of all arousals (ARtot), subdued in: spontaneous arousals (SA) and leg movement arousals (LMA). All patients filled out questionnaires regarding subjective sleep quality, the Groninger sleep quality scale (GSS)[8], mental and physical tiredness scores as mentioned by the multidimensional fatigue inventory (MVI)[9] and excessive daytime sleepiness, using the Epworth Sleepiness Scale (ESS)[10] . From the MVI we chose general tiredness (AV) as parameter for our study. These questionnaires were completed directly after the first PSG night and the patients were asked to consider the past 6-8 weeks in answering the questions.

RESULTS AND DISCUSSION

The calculated leg movement sleep pressure score ($SPS_{L)}$ for each patient is plotted against sleep efficiency (SE), superficial NREM 1 + 2, deep sleep (SWS) and the leg movement arousal index (LMAI). There seems to be no clinically relevant correlation with SE (r = -0.05, p < 0,05). nor with the percentage of SWS (r = 0.12, p < 0.05) The same holds for the correlation between NREM 1 + 2 sleep and the SPS_L (r = -0.19, p < 0.05). The correlation between SPS_L and LMAI is not surprisingly positive (r = 0.47, p < 0.05). Thus there is no correlation between the SPS_L and any of the chosen parameters for sleep quality.

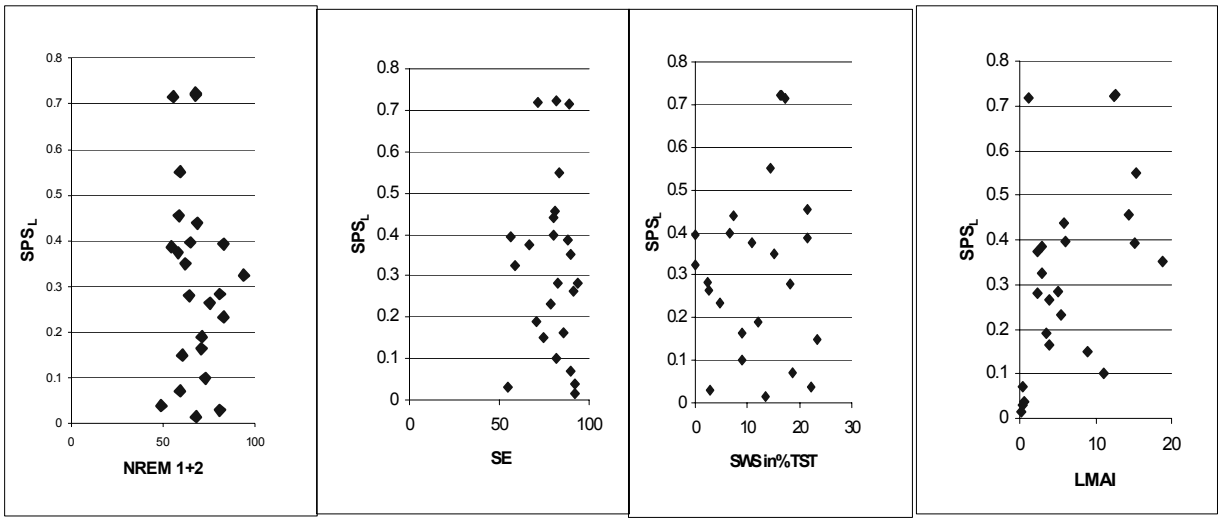

Figure 1 The SPS_L in relation to objective measures of sleep and wake.

The scores for general tiredness(AV), subjective sleep quality (GSS) for the night under study and the sleepiness during daytime (ESS) were compared to the SPS_L. These correlations are shown in table1. It is known that there is a large variability in PLMS from night to night Again low and clinically irrelevant correlation coefficients were found for all comparisons with no important differences between both nights.

Table 1.

Comparison first night	*Correlation coefficient (all p < 0.05)*	*Comparison second night*	*Correlation coefficient (all p < 0.05)*
AV versus SPS_L	- 0,07	AV versus SPS_L	- 0,23
GSS versus SPS_L	+ 0,17	GSS versus SPS_L	+ 0,29
ESS versus SPS_L	- 0,14	ESS versus SPS_L	- 0,20

CONCLUSIONS

The prevalence of periodic leg movements in sleep and the influence on sleep quality or impact on daily well-being has been subject of study by many other investigators[11,12]. In the discussion whether PLMS are associated with disturbed sleep pro and contra arguments can be found. We were hopeful that the SPS_L might shed new light on these controverses. But in contrast to mild PLMD patients, we even did not find any clinically relevant correlation with sleep parameters from the PSG, subjective sleep quality or daytime tiredness.

In conclusion the SPS_L seems to be not useful in the work-up of patients with PLMS.The present results and those of the previous study even may suggest that PLMS are of no importance at all in terms of their relation to quality of sleep and its consequences for quality of life during daytime

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EEG CORRELATION DIMENSION AS A QUANTITATIVE PARAMETER FOR THE LEVEL OF VIGILANCE IN ANIMALS AND HUMANS

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INTRODUCTION

Correlation dimension analysis of the electroencephalogram (EEG) is a relatively new technique that has been used to establish the complexity of EEG patterns (1, 2). The application of this non-linear time series analysis provides a measure for complexity, reflecting the number of sub-processes contributing to the generation of the EEG signal. It is a measure of the dimensionality of the space occupied by the attractor of the signal. This method has already shown its ability to excel over traditional spectral techniques oin a number of application areas. In this paper the application of EEG correlation dimension is discussed as a sensitive quantitative parameter for the assessment of the level of vigilance of a subject. Studies are reviewed in which application of the EEG correlation dimension is used.

Anaesthesia in rats (1, 3)

A rat study was performed to test the usefulness of EEG correlation dimension as an indicator of the depth of anaesthesia. The EEG of rats was recorded, when they were anaesthetized with increasing concentrations of the volatile anaesthetic sevoflurane. Information concerning the depth of anaesthesia was obtained by measuring the force of the withdrawal reflex of the hind paw as a response to a noxious electrical stimulus. Results regarding the EEG correlation dimension were related to the force of the withdrawal response and to the concentration of the anaesthetic. The study demonstrated that correlation dimension relates to the force of the withdrawal reflex and thus indirectly to anaesthetic depth. Correlation dimension starts from a quite high value in the wakeful vigilant rat, and drops gradually with increasing concentrations of sevoflurane to a low value. At this high anaesthetic concentration the rat is in deep anaesthesia, as indicated by absence of the withdrawal reflex,. In the left part of Figure 1 the relation between the correlation dimension and the depth of anaesthesia is shown. This relation shows that correlation dimension of the EEG is a suitable indicator of the depth of anaesthesia.

Anaesthesia in humans (1)

In this study the EEG of patients was recorded. This was done during steady state levels of propofol anaesthesia, as indicated by the OASA (Observer's Assessment of Sedation and Anaesthesia) scale, which is traditionally used to define depth of anaesthesia. Correlation dimension was tested as an indicator of the depth of anaesthesia, by relating it to the OASA score. When the anaesthetic depth deepened, the correlation dimension decreased. A sharp decrease in correlation dimension was found between OASA values 4 and 3 (the surgical depth of anaesthesia). Figure 1 (right graph) shows the relation between the orrelation dimension and the concentration of propofol, as well as the OASA scale values. During propofol anaesthesia the correlation dimension is particularly sensitive to changes in the depth of anaesthesia, as measured by the OASA, at the transition from light to deep

anaesthesia. The correlation dimension value can be calculated on line and might thus be useful for monitoring and steering the level of anaesthesia of patients. It may also be a more objective measure for anaesthetic depth compared to the more subjective OASA scale.

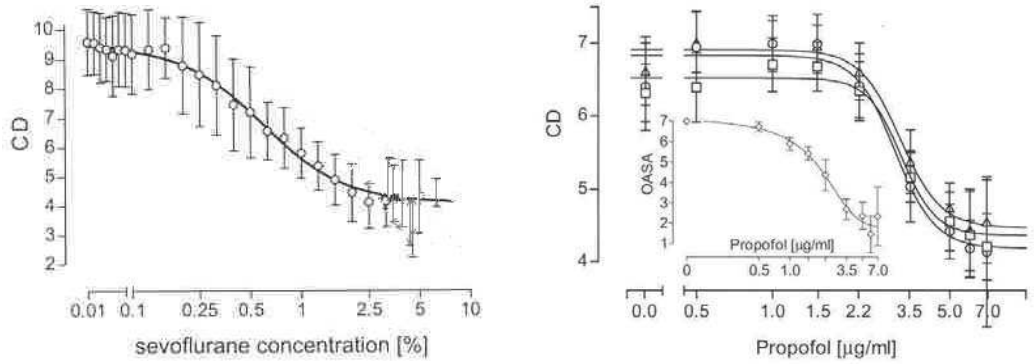

Figure 1. The relation between the anaesthetic concentration and correlation dimension is shown in rats (left) and in humans (right). In rats sevoflurane is used as anaesthetic, while propofol was used in humans. In the inset of the right graph the dose response relationship between the OASA-score and the anaesthetic is shown.

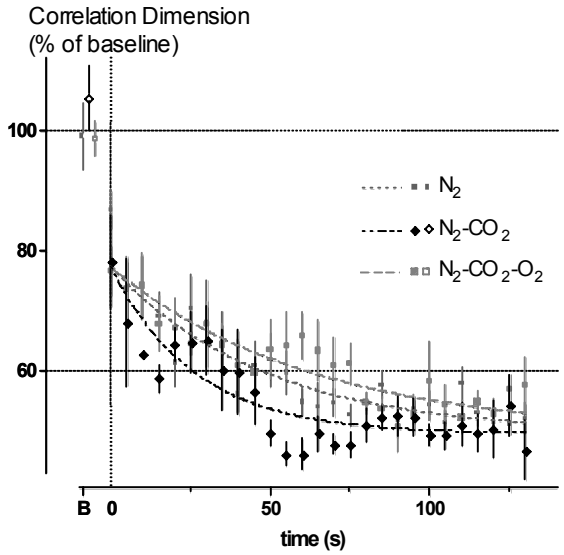

Figure 2. Correlation dimension of the EEG (mean and SD) of the three euthanasia treatments in the baseline and in the 120 s period after placing the animals in the system.

Euthanasia in chickens (4)

In this experiment the correlation dimension was estimated using EEG recordings made during the stunning of chickens. The correlation dimension was found to be a useful measure for following the euthanasia process and the loss of consciousness of chickens. Three gas mixtures for euthanasia were tested (N_2, N_2CO_2 and a two-phase technique, in which animals are first anaesthetized in a mix of $N_2CO_2O_2$, and after anaesthesia are killed by replacing O_2 by CO_2). Correlation dimension was computed using EEG epochs of the entire trace from placing the animals in the euthanasia system untill the death of animals Since absolute values of correlation dimension vary between individual chickens, the changes in correlation dimension were expressed as percentage change relative to baseline. Figure 2 shows the course of the correlation dimension during the entire process. The baseline value is

considered as 100% and all subsequent values were expressed relative to this value. Studies have revealed that animals are deeply unconscious when they show a reduction in the correlation dimension to 60% of the baseline value.

Sleep and wake states in chickens (5)

This study investigated whether the EEG correlation dimension could be used to identify the complexity of 'wake' 'drowsy' and 'sleep' patterns in unrestrained chickens. Broiler chickens were instrumented with EEG electrodes and EEG signals were recorded together with a behavioural code. Based on visual inspection of the EEG and behavioural observations, the state of vigilance was classified into three behavioural categories: wakefulness, drowsiness and sleep. Correlation dimension analysis was carried out on the EEG recorded during these three categories. The values of the correlation dimension for wakefulness was 7.04 ± 1.16 (mean and SD); for drowsiness 6.63 ± 0.98; and for slow wave sleep 5.99 ± 0.74. The differences between the three groups are significant, despite the fact that they are relatively small,. Consistent with data obtained from man and rat is that waking has the highest value and slow wave sleep the lowest, with drowsiness in between.

Sleep-wake states in humans (6)

Students were prepared for polysomnographic recordings with EMG, EOG and EEG electrodes. The EEG was recorded between 0.1 and 35 Hz and a correlation dimension analysis was performed off-line on the EEG. The following sleep-wake stages were identified: pre-sleep (waking just before going to sleep), the classical stages of sleep, i.e. stage 1, stage 2, stage 3, stage 4 and REM sleep, and two waking states, post-sleep 1 (immediately after waking, perhaps showing sleep inertia), and post-sleep 2 (20 minutes after waking).

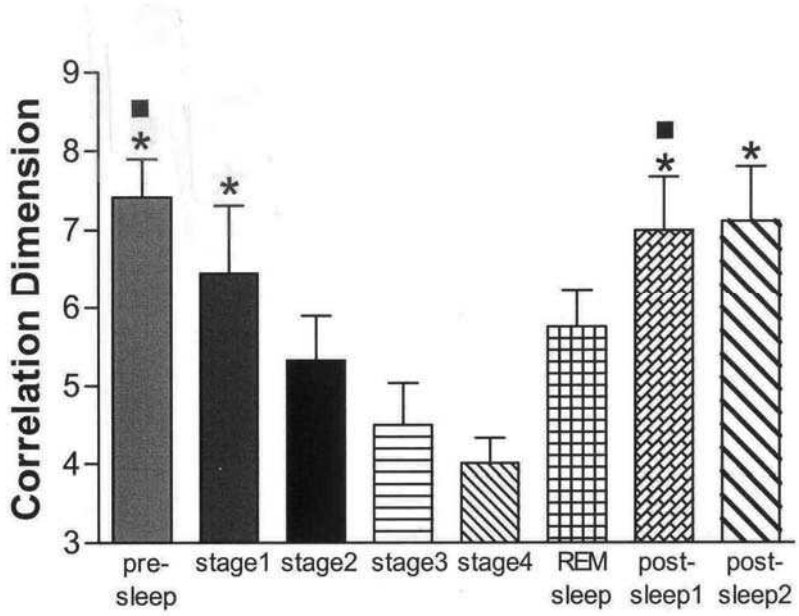

Figure 3. Correlation dimensions (means and SDs) of the pre-sleep, sleep stages 1, stage 2, stage 3 and stage 4, REM sleep and the post-sleep 1 and post-sleep 2 stages. Squares and stars indicate significant differences between the groups (post-sleep 1 > stage 1 *; post-sleep 2 > stage 1 *; pre-sleep > stage 1 *; pre-sleep > post-sleep 1 ■).

In Figure 3 the correlation dimensions of the EEG belonging to the several sleep-wake stages are shown, with the statistical differences between groups. The conclusion is that all sleep-wake stages are characterized by their own value of correlation dimension. Deep sleep stages 3 and 4 have the lowest values, light sleep stage 2 a higher value and the transitional stage 1 the highest of all sleep stages, even a bit higher than REM sleep. As expected the waking state (pre-sleep and post-sleep 2 have the highest values, while post-sleep 1, showing some sleep inertia, has a value in between stage 1 and pre-sleep. These data indicate the sensitivity of correlation dimension in expressing adequate levels of vigilance.
In an analogue experiment in rats (7), the correlation dimension values for the EEG were: 9.2 ± 0.6 for active wakefulness, 8.0 ± 0.9 for passive wakefulness, 6.3 ± 0.4 for slow wave sleep and 8.8 ± 0.9 for REM sleep. All differences appeared to be statistically different.

Cognitive load in humans (7)
This study aimed to assess the effects of mental load in humans on the EEG correlation dimension. EEG was recorded under three conditions, a baseline condition and two cognitive task conditions. Cognitive tasks were a time estimation task, in which the subjects has to estimate an interval of 20 seconds, and a calculation task, consisting of continuously adding up two numbers. The latter task was supposed to induce a higher mental load than the former, which was confirmed by by a subjective rating scale (baseline period 1.6 ± 1.8; time estimation task 4.4 ± 1.6; calculation task 7.3 ± 1.9; all values were significantly different). The correlation dimension appeared to be higher in both mental tasks compared to baseline (baseline 5.78 ± 1.52; time estimation task 7.17 ± 1.96; calculation task 8.03 ± 2.23). Also the two tasks differed significantly with the highest value for the calculation task. It is concluded that cognitive and mental activity is associated with a higher correlation dimension in the EEG, implying that this is a sensitive parameter in the analysis of electrical brain activity.

DISCUSSION

All studies show a sensitive relation between the value of the correlation dimension and the level of vigilance. The two anaesthesia experiments, performed in rat and man, show a gradual decrease from a high value of about 7 to 10 to a low value of 4. From the relation of the correlation dimension with the OASA scale values it appears that 5 is about the surgical level of anaesthesia. This is also the value associatedwith unconsciousness in chickens in the euthanasia experiment (60% of baseline). The validity of the correlation dimension as a parameter for the level of vigilance was most evident from studying the correlation dimension for different sleep-wake stages. The study also indicated the sensitivity of the parameter.
The absolute values in the various studies are unfortunately not directly comparable, as the values depend slightly on adjustment of the assumptions for calculation of the correlation dimension, and these adjustements were not exactly the same in the different studies. Nevertheless, the main take home message is that high vigilance, associated with attentive waking, has high values of correlation dimension of 7 to 10, REM sleep follows with 6 to 9, slow wave sleep 5 to 7, anaesthesia 4 to 5, and coma 2 to 3. All in all, this implies that the correlation dimension may be used as an adequate, quantitative measure for the level of vigilance.

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UNIFORM EEG ACTIVATION OVER THE CORTEX DURING WAKEFULNESS AND REM SLEEP IN RATS

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INTRODUCTION

Maquet et al.[1,2] recently showed a differential activity profile over the human cortex during REM sleep using metabolic neuroimaging with FDG-PET. The frontal cortex was not activated in contrast to other cortical region, such as the parietal cortex. Based on this finding Hobson[3,4] launched the speculative but interesting hypothesis that the frontal cortex had the ability to control the logic of waking thoughts. The deactivation of the frontal cortex during REM sleep and by inference during dreaming might explain the hallucinatory and bizarre character of some dreams. A kind of 'censor' seems to be present in the frontal cortex, which is deactivated in REM sleep and the ability of logic reasoning is diminished. The finding of deactivation in the frontal cortex contradicts the traditional view of a diffuse activation of the entire cortex, expressed during general EEG desynchronization. In the latter view, the cortical activation during REM sleep is comparable to the degree of cortical activation during wakefulness.
In this paper we tried to examine whether the abovementioned differential cortical activity profile could be confirmed by spontaneous as well as flash-evoked potentials in rats recorded over the frontal and parietal cortices during different vigilance states (active and passive wakefulness, non-REM sleep and REM sleep). The hypothesis was tested whether the cortex is activated during REM sleep over the parietal cortex, while being deactivated over the frontal cortex. The correlation dimension of the spontaneous background EEG, expressing the complexity of the EEG signal, was also calculated for both leads and the different vigilance states.

METHODS

Ten 16-17 months old Wistar rats were permanently implanted with active epidural electrodes over the right anterior frontal as well as the right parietal cortex. EEG was recorded between 0.1 and 100 Hz. During recording the rat was placed in an observation box, which was equipped with a glass window in the front wall, allowing to observe the rats during the experiment while stimulating them with intense flashes (approximately 1.5 Mcandle with a duration of 10 μsec) of light delivered by a flash lamp. Visual evoked potentials were recorded at a sample frequency of 1024 Hz. Each animal was recorded for one hour to obtain visual evoked potentials and background EEG during all stages of vigilance. Four behavioural conditions (active wakefulness, passive wakefulness, non-REM sleep and REM sleep), could be distinguished based on EEG and behavioural patterns. All data were encoded in a WINDAQ program and analysed by means of a Brain Vision Analyser.

RESULTS AND DISCUSSION

In Figure 1 visual evoked potentials recorded over the frontal cortex during all four states of vigilance are shown. The shape of these potentials is relatively similar to those of the parietal cortex (not shown). Both the P85 (positive wave at 85 msec post-stim) and N120 (negative wave after 120 msec) amplitudes differed significantly during the different states of vigilance (two way ANOVA, $p<0.05$). The P85 and N120 waves are larger during sleep compared to wakefulness with intermediate values for REM sleep and passive wakefulness. A post-hoc analysis showed a marginal difference between wakefulness and REM sleep. The difference in amplitude between evoked potential components is a general finding in these experiments[5].

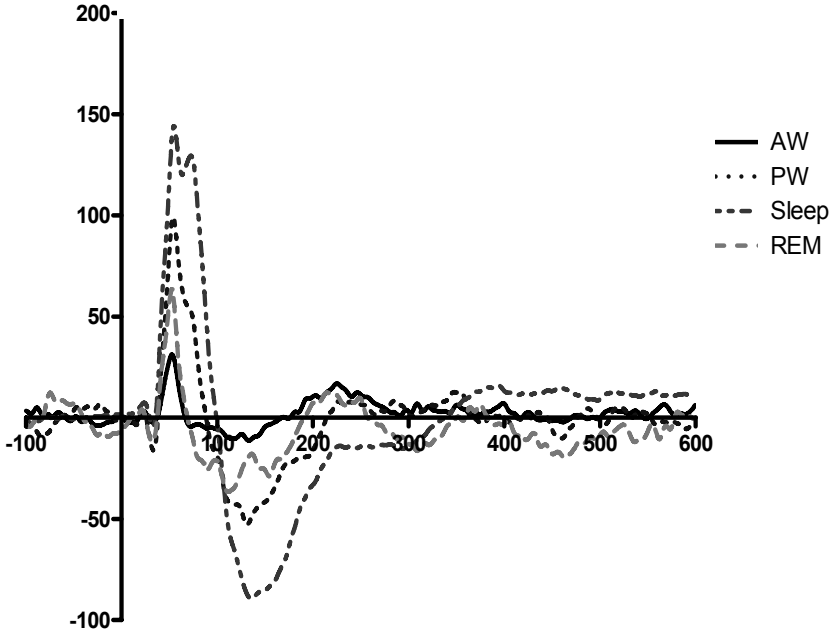


Figure 1. Visual evoked potentials recorded over the frontal cortex during the four states of vigilance (AW: active wakefulness; PW: passive wakefulness; Sleep: slow wave sleep; REM: REM sleep)

In Figure 2 visual evoked potentials are shown for active wakefulness and REM sleep recorded over the frontal and the parietal cortex. Evoked potential waveforms for REM sleep and active wakefulness are significantly larger for parietal areas than for frontal areas ($p<0.0001$). However, more relevant for the objectives of this study is the comparison between the evoked potentials of wakefulness and REM sleep over the frontal cortex in relation to the same comparison for the parietal cortex. As Figure 2 shows, cortical evoked potentials appear to closely resemble each other during active wakefulness and REM sleep for both the frontal and parietal cortices without significant differences, although a post-hoc test showed a marginal difference between potentials for frontal REM sleep and active wakefulness with frontal REM sleep evoked potential amplitude being slightly larger than evoked potentials duing active waking.

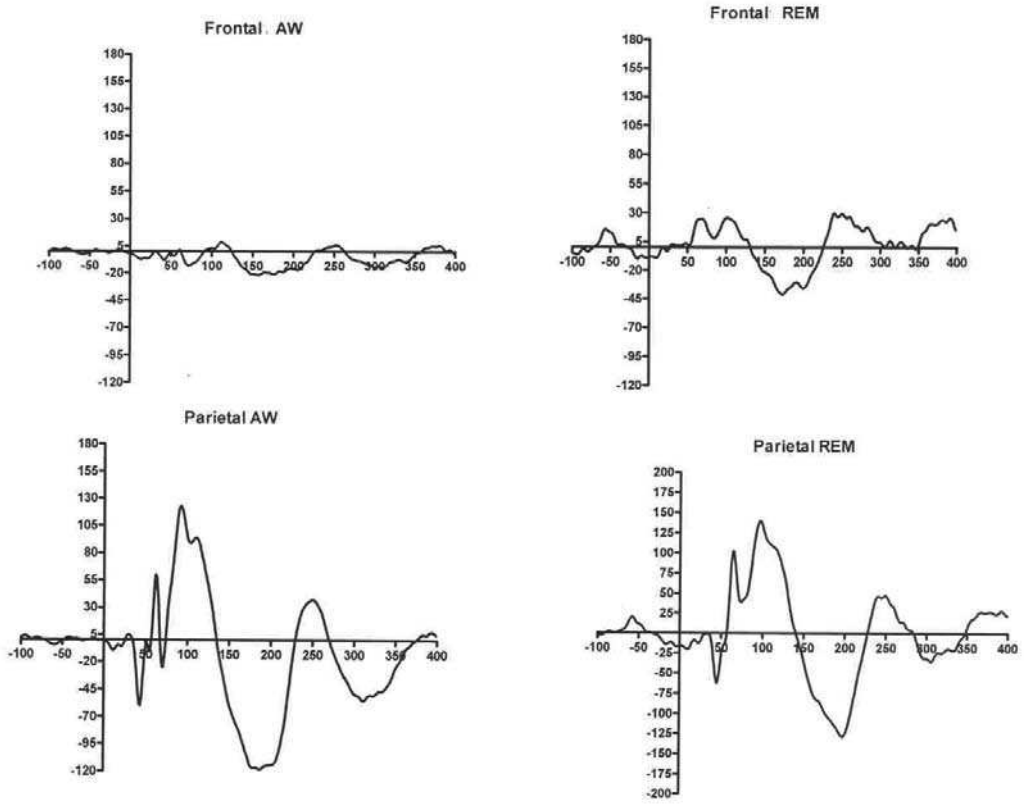
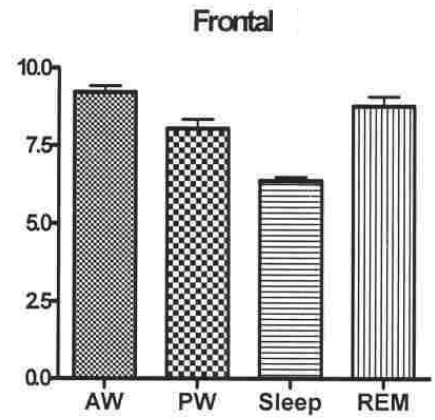
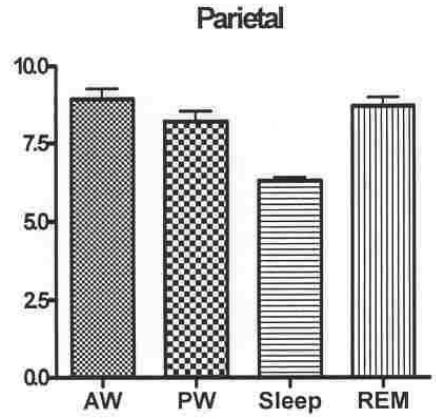


Figure 2. Visual evoked potentials recorded in the frontal cortex (upper part) and parietal cortex (lower part) during active wakefulness (left) and REM sleep (right). X axis represents time and Y axis voltage in mV. (AW is active wakefulness and REM is REM sleep)



	AW	PW	Sleep	REM
Mean	9.222	8.035	6.358	8.762
Std. Deviation	0.6448	0.9297	0.3639	0.8924
Std. Error	0.2039	0.3099	0.1213	0.3155



	AW	PW	Sleep	REM
Mean	8.922	8.190	6.275	8.687
Std. Deviation	1.070	1.019	0.3520	0.7839
Std. Error	0.3384	0.3396	0.1173	0.2771

Table 1. Correlation dimensions for frontal (left) and parietal (right) background EEG (AW: active wakefulness, PW: passive wakefulness, Sleep: slow wave sleep, REM: REM sleep).

In Table 1 the results of the correlation dimension analysis are shown. Analysis was performed by the correlation dimension macro designed by van den Broek[6]. All differences in correlation dimension values between states of vigilance, except for REM sleep, are statistically significant (one-way ANOVA, $p<0.0001$). This is true for both recording locations. The correlation dimension is highest for active wakefulness and slowly decreases when animals reach the state of slow wave sleep. During REM sleep the correlation dimension is lies exactly between the values of active wakefulness and passive wakefulness (see Table 1).
When integrating the evoked potential data the conclusion is inevitable that the activation pattern over the parietal cortex is well comparable for active wakefulness and REM sleep. This is also true for the frontal area, be it that the amount of frontal activation during REM sleep is slightly lower than the activation during active wakefulness. The amplitude of the evoked potential components is slightly larger during REM sleepprobably due to a marginally lower activation level[5]. The correlation dimension of the frontal EEG is also just lying in between active and passive wakefulness. The latter differences, however, are small.

CONCLUSIONS

Visual evoked potentials recorded over the frontal and parietal cortices represent the typical features of evoked potentials for the different states of vigilance, such as active and passive wakefulness, slow wave sleep and REM sleep. Evoked potentials during REM sleep best matched those recorded during active and passive wakefulness for both recording areas. All in all, this suggests that in rodents, in contrast to human neuroimaging data, frontal cortical activation during REM sleep is comparable to frontal cortical activation during wakefulness. Whether this is due to a discrepancy between humans and rats, or between recording techniques, is an issue which can only be resolved by future research.

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EFFECTS OF ORAL-APPLIANCE THERAPY ON THE UPPER AIRWAY MORPHOLOGY: A CEPHALOMETRIC ANALYSIS

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INTRODUCTION

The obstructive sleep apnea-hypopnea syndrome (OSAHS) is a sleep related breathing disorder, characterised by repetitive partial (hypopnea) or complete (apnea) airway obstructions and disruptive snoring during sleep[1]. These repetitive upper airway obstructions can cause recurrent arousals from sleep, ultimately resulting in excessive daytime sleepiness, neurocognitive impairment, and a higher risk of motor-vehicle accidents and cardiovascular disease events[2-5].
Severity of the disease is usually expressed by the apnea-hypopnea index (AHI) defined as the mean number of apneas and hypopneas per hour sleep. Based on the AHI, OSAHS may be classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30)[6].
Continuous positive airway pressure (CPAP) is generally considered the treatment of first choice[7]. However, oral-appliance therapy is an effective alternative in treating OSAHS patients[2]. Most oral-appliances used in a clinical setting are mandibular advancement devices which keep the mandible and its attached musculature in a protruded position. This has been shown to enlarge the upper airway and to decrease upper airway collapsibility[8].
Cephalometry (is a widely available, inexpensive, and easy to perform radiographic imaging technique to examine upper airway craniofacial and soft tissue structures[9]. It has also been used to visualize changes in upper airway morphology with oral-appliance therapy[10,11]. However, it is unclear to what extent there is a relationship between changes in the upper airway morphology with oral-appliance therapy and the treatment response to this therapy.
Therefore, the aims of this study were to assess changes in the upper airway morphology associated with oral-appliance therapy in OSAHS patients, using cephalometry, and to relate these possible changes to treatment response.

METHODS

Patients:
To compare the effectiveness of an oral appliance with CPAP for the treatment of OSAHS in a separate randomized controlled trial, patients were recruited. Patients were eligible if OSAHS was diagnosed (apnea-hypopnea index > 5)[6]. Based on dental, medical and psychological exclusion criteria (e.g. previous treatment of OSAHS, endocrine dysfunction, severe cardiac or pulmonary disease, mental retardation, psychiatric disorder, extensive periodontal disease or tooth decay, active temporomandibular joint disease, restrictions in

mouth opening, partial or complete edentulism) patients were selected for this trial and consequently randomized for either CPAP- or oral-appliance therapy.
For this present study, the patients randomized to the oral appliance group (n=46) as well as patients who switched from CPAP to oral-appliance therapy before follow-up (n=6) were included.

Study design:

At baseline, patients had been subjected to a polysomnographic evaluation. At this stage, a lateral cephalogram of all patients was made to determine relevant cephalometric variables. When initiating oral-appliance therapy the mandible was set at approximately 50% of the patient's maximum protrusion. After having adapted to this protrusive position during a two week period, patients were allowed to further adjust the oral appliance during a 6 weeks period. When OSAHS symptoms (e.g. snoring, excessive daytime sleepiness, apneas and/or hypopneas) persisted, patients advanced the mandible each night with 1 to 2 increments (i.e. 0.2-0.4 mm). This "titration" of the oral appliance was continued until OSAHS symptoms had adequately improved or until further protrusion of the mandible resulted in discomfort. After a titration period of about 2 to 3 months the treatment effect was assessed with a second polysomnogram. Furthermore, a second lateral cephalogram was made with the oral appliance intra-orally. The degree of protrusion of the oral appliance was identical during the follow-up polysomnographic evaluation and the follow-up lateral cephalogram.
The outcome measures were the relative improvement of the apnea-hypopnea index and an apnea hypopnea index <5 following oral-appliance therapy.

Intervention:

All patients were instructed to adopt conservative measures and to use their oral appliance whenever they slept. The oral appliance used (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a forward and downward position. The mandibular protrusion could be adjusted with 0.2 mm increments with a propulsion screw, which was incorporated anteriorly in the oral appliance.

Polysomnography:

Polysomnography (Embla® A10 digital recorder, Medcare, Reykjavik, Iceland) for baseline and follow-up evaluations was conducted ambulatory in the patient's home. All polysomnograms were evaluated according to standardized criteria and scored by the same neurophysiologist (JvdH), who was unaware of the patient's treatment assignment.

Cephalometric analysis:

All lateral cephalograms were taken using a ProMax Cephalostat (Planmeca, Helsinki, Finland). A trace-protocol was designed and all tracings were performed using Viewbox 3.1.1.6 software® (Viewbox, Athens, Greece). To minimize identification error all tracings were subsequently performed by one observer (MD) and repeated after a one week period. Mean outcomes of both tracings were used for further statistical analysis. All linear cephalometric measurements were converted to life size values.

Statistical analysis:

To compare outcomes between demographic and cephalometric variables at baseline and follow-up, paired Student's *t*-tests were performed. A *p*-value <0.05 was predefined in all cases to indicate statistical significance. Subsequently, the differences (Δ) in upper airway morphology between baseline and follow-up variables were selected for regression analysis. For matters of broad inclusion of possible determinants, the level of α was set at 0.2 for the univariate analyses only. The dependent variable for the univariate linear regression analysis was the relative improvement of the apnea-hypopnea index following treatment. All significant variables yielded from univariate linear regression analyses concerning pharyngeal dimensions were subsequently submitted for multivariate linear regression

analysis. A backward model was constructed with a relative improvement of the apnea-hypopnea index being the dependent variable.

RESULTS AND DISCUSSION

Treatment response:
The mean (± SD) apnea-hypopnea index decreased from 35.8 ± 27.5 at baseline to 7.3 ± 13.6 at follow-up, signifying an improvement of 76 ± 37 %. Two patients showed an increase of the apnea-hypopnea index, from 9 to 19 and from 15 to 17, respectively. The lowest oxyhemoglobin saturation during sleep significantly improved from 79 ± 8 % at baseline to 88 ± 7 % at follow-up and the mean (± SD) score on the Epworth sleepiness scale significantly improved from 12.8 ± 5.7 at baseline to 6.8 ± 5.4 following oral-appliance therapy.
Cephalometric analysis:
Concerning pharyngeal dimensions increases were found for the posterior airway space at the level of the base of the tongue (Pas-BT) (1.2 ± 3.6 mm), at the level of the second vertebra (Pas-C2) (1.6 ± 3.7 mm) and at the level of the uvular tip (Pas-Ut) (1.8 ± 2.6 mm) with the oral appliance intra-orally. Moreover, both the distance from the hyoid to the mandibular plane (Hy-MP) and the distance between hyoid and the sella-nasion line (Hy-SN) decreased (-9.2 ± 3.8 mm and -3.4 ± 4.1 mm, respectively), indicating a more cranial position of the hyoid bone.
Regression Analysis:
Univariate linear regression analysis demonstrated that an increased posterior airway space at the level of the second vertebra (Pas-C2) and an increased posterior airway space at the level of the uvular tip (Pas-Ut) showed a significant association with a relative improvement of the apnea-hypopnea index (Table 1). Logistic regression analysis for predicting an apnea-hypopnea index<5 with oral-appliance therapy yielded no significant predictive cephalometric variables.

Table 1. Univariate analysis of cephalometric variables predicting a relative improvement of the apnea-hypopnea index with oral-appliance therapy.

Variable	*↓ AHI % § (Beta)*	*Standard error*	*95% CI*
Δ C2a-P2a (mm)	-0.23	1.67	[-3.57;3.12]
Δ Pas-C2 (mm)	-3.37	1.36	[-6.11;-0.63]*
Δ Pas-BT (mm)	-2.70	1.41	[-5.53;0.13]
Δ Pas-Ut (mm)	-5.36	1.89	[-9.17;-1.56]*

* $p < 0.05$
§ Relative decrease of the apnea-hypopnea index as a result of oral-appliance therapy
Abbreviations: AHI = apnea-hypopnea index, CI = confidence interval

Multivariate linear regression analysis for predicting the extent of the relative improvement of the apnea-hypopnea index, yielded a model with the increase in posterior airway space at the level of the uvular tip (ΔPas-Ut) as strongest predictor (beta = -5.40, 95% CI [-9.17;-1.56], $p<0.05$).

CONCLUSIONS

In this study we found that the posterior airway space increased significantly at the level of the second vertebra (Pas-C2), base of the tongue (Pas-BT), and at the level of the uvular tip (Pas-Ut) as a result of oral-appliance therapy. Furthermore, this study shows that oral-appliance therapy provided an overall improvement of OSAHS-related parameters. Additionally, the hyoid bone was located more cranially with oral-appliance therapy. An increase of posterior airway space at the level of the second vertebra and uvular tip were the best predictors for a relative improvement of the apnea-hypopnea index. In order to assess the possible changes in upper airway morphology, the clinician could make a cephalogram with the mandible in maximal occlusion and another cephalogram with an intra-orally placed wax bite-registration, keeping the mandible in a protrusive position. These findings could be of value, together with other clinical and physiologic predictors for treatment response, in order to preselect suitable candidates for oral-appliance therapy.

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LONG TERM FOLLOW UP OF MELATONIN THERAPY IN CHILDREN WITH ADHD AND CHRONIC SLEEP ONSET INSOMNIA

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INTRODUCTION

Chronic sleep onset insomnia (CSOI) is frequently reported in children with Attention Deficit Hyperactivity Disorder (ADHD) with rates up to 28 % in medication free children with ADHD [1]. CSOI in children is associated with daytime fatigue, impaired daytime functioning and impaired health status [2-4]. Recent research shows that children with ADHD and CSOI have the characteristics of a delayed endogenous circadian pacemaker, such as a delayed sleep onset and wake up times with normal sleep maintenance [5-7]. Exogenous melatonin has proven to be effective in the treatment of CSOI in children with ADHD [8,9]. The thought behind melatonin therapy for the treatment of CSOI in children with ADHD is that properly timed exogenous melatonin in the afternoon or evening advances the DLMO and in this way facilitates falling asleep at an earlier time in the evening [10,11].
However, despite the fact that exogenous melatonin is frequently used to treat sleeping problems in children with various disorders [12-14] , little is known about the safety of this therapy in children on the long term. There are concerns that long term use of exogenous melatonin may influence the human reproduction system and pubertal development. Melatonin could initiate or worsen a seizure disorder because of the presumed pro-convulsive properties of the drug. Data about the long term effectiveness of melatonin on sleep onset insomnia, behavior and mood are scarce. In this study we assessed the long term safety and efficiency of long term exogenous melatonin treatment in children with ADHD and CSOI.

METHODS

A self-constructed, structured questionnaire was sent to the parents of 100 children with ADHD and chronic sleep onset insomnia. Before sending questionnaires parents were approached by telephone for obtaining permission to send them a questionnaire. Between November 2001 and June 2005 these children participated in a randomized, double blind, placebo-controlled trial of melatonin treatment [8]. Melatonin treatment was continued after this trial. The questionnaire consisted of a mixture of multiple choice, numeric open ended and scaled questions, 19 in total. These questions assessed the following items: does the child still use melatonin; - what is the current dosage; - what is the time of administration; - has the child experienced any adverse side effects; - has the child experienced any co-morbidities during melatonin treatment; - what were the effects of melatonin on sleep onset problems, behavior and mood according to the parents; - has the child at a certain stage temporarily or permanently discontinued melatonin; - if so, what were the effects of discontinuation of

melatonin on sleep and behavior and what were the reasons for discontinuing melatonin, if applicable;

RESULTS

Patient demographics

94 children were included in this study. The response rate was 93 %. The mean follow up time of this study was 3.66 years (SD 1.21).

Current usage of melatonin and reasons for discontinuing treatment

64.9 % of the children still used melatonin daily and 11.7 % used it occasionally. Reasons for discontinuing the treatment were: sleep onset insomnia had improved (36.4 %); melatonin treatment discontinuation by the treating physician (18.2 %); lack of effect of the treatment (13.6 %); adverse effects (13.6 %) and other reasons (18,2 %).

Period of discontinuing melatonin

71,3 % of the children temporarily discontinued melatonin therapy, mostly during a holiday period. 92.3 % experienced a delay in sleep onset time and 30.8% a delay in wake up time after discontinuation. Most patients (85.5 %) resumed the treatment after the stopping period.

Effectiveness of melatonin therapy

Melatonin therapy had the greatest impact on sleep onset problems. 87.8 % of the parents found that melatonin is an effective treatment for the sleep onset problems of their children Although less distinct, many parents (70.5 and 60.9 %) found that melatonin treatment also improved the behavior and mood of their child.

Adverse effects

20.8 % of the children experienced adverse effects which were attributed to the melatonin treatment. Adverse effects are presented in table 1. In 5 (26.3%) children the adverse effects persisted. during continuation of treatment. Adverse effects that persisted were sleep maintenance insomnia, excessive morning sedation, decreased mood and headache, profuse perspiration and daytime laziness. 3 children discontinued the melatonin therapy because of persistent adverse effects.

Table 1.

Adverse effect	*%*	*Adverse Effect*	*%*
Dizziness	4.3	Visual disturbances	2.1
Bedwetting	3.2	Excessive morning sedation	2.1
Sleep maintenance insomnia	3.2	Constipation	1.1
Headache	2.1	Profuse perspiration	1.1
Nausea	2.1	Decreased mood	1.1
Skin pigment changes	2.1	Daytime laziness	1.1
Nightmares	2.1	Change in behavior	1.1

Co-morbidity during melatonin treatment

7 parents (7.4%) reported unusual co-morbidity in their children. Co-morbidity they reported were: pertussis, pneumonia, adverse reaction on narcosis, coeliac disease and food allergy, Osgood-Schlatter disease, viral eye infection and visual disturbances with no specific cause. None of the children had epilepsy before they started with melatonin. During the follow up period no new cases of epilepsy developed.

DISCUSSION AND CONCLUSION

The results of this study provided evidence that long term use of exogenous melatonin has no safety concerns in children. There were no serious adverse effects and no new cases of epilepsy developed. A small percentage of the children in this study developed co-morbidities during melatonin therapy. We find it highly unlikely, however, that this co-morbidities is directly related to melatonin therapy. Long term use of melatonin was well tolerated by most children.

Long term use of melatonin continued to be an effective therapy with the greatest impact on sleep onset insomnia and to a lesser extent on behavior and mood.

Melatonin is usually required for a longer period of time for the treatment of sleep onset insomnia. After a follow up duration of 3.66 years about 75 % of the children still used melatonin. Discontinuing melatonin therapy usually leads to a delay in sleep onset time and to resumption of melatonin use.

Although, we concluded that long term melatonin use is a safe and effective therapy for the treatment of chronic sleep onset insomnia in children with ADHD, this study has certain limitations. First, the effects of long term melatonin use on pubertal development and fertility couldn't be properly assessed by this study and requires a prospective study with frequent assessment of Tanner stages and fertility. Second, the rate of adverse effects was probably overrated because many children started with methylphenidate therapy during follow up and this was not evaluated in the questionnaire. Adverse effects caused by the use of methylphenidate were possibly attributed to melatonin use.

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CULTURE DIFFERENCES IN THE SLEEP OF DUTCH ADOLESCENTS

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INTRODUCTION

The shift in the timing of sleep and wakefulness towards later hours is one of the most prominent changes during the transition from childhood to adulthood. Hormonal and social changes during puberty induce a phase delay in bedtime, although the biological need for sleep is increased.[1,2] The delay in sleep times has been described in many studies across the world and across many cultures.[1-4] Studies on cross-cultural comparisons between adolescent sleep patterns are, however, almost non-existent.[5] It is evident that, besides the biological changes, social settings play an important role in the changes in adolescent sleep. The early start times of schools, increasing school demands and increasing social activities, as well as an increase in extra-curricular activities and 'side-jobs' also influence the delay in bedtimes. Cultural differences in beliefs and values concerning sleep, differences in ideas about the relation between sleep and health and differences in bedtime routines and sleeping arrangement can have an additional impact on sleep.
In this paper the effect of differences in cultural background on sleep in adolescents is studied within the social setting of similar school start times and school demands of a Dutch multi-cultural high school. It is expected that the adolescents will show an age related phase delay in their bedtimes, irrespective of their cultural background. Cultural differences in sleep culture and in parental influence on sleep are expected to result in differences in bedtimes between the cultural groups, especially during the school week. As no differences are expected in rise times during school days, due to the strict school start times, differences in sleep period duration are to be expected. Shorter sleep period duration in the school week is expected to have a negative influence on sleep quality and mood.

METHODS

A group of 332 adolescents (149 boys, 151 girls) between 12 and 18 years, enrolled in the highest level (HAVO/VWO) of a Dutch multicultural high school, participated in the study. Out of this group 300 subjects were divided in 3 cultural subgroups on the basis of their ethnic background: Dutch (58.3%), Moroccan (22%) and Middle Eastern (19.7%). There were 3 subsequent age group: 12/13 yrs (31%), 14/15 yrs (23.3%) and >16 yrs (45.7%). For 32 adolescents the cultural background was too diverse and they were excluded from the study.
A questionnaire was administered containing questions on the situation at home, parental influence on sleep, sleeping arrangement, sleep pattern, sleep behavior and the use of multimedia in the bed room. Sleep quality, mood and chronotype were measured by means of the Sleep Quality Scale, the shortened version of the Profile of Mood States and the Owl/Lark scale, adjusted for adolescents, respectively. In the literature these scales have been administered in adolescent populations in various cultures.[4-6] The effect of cultural differences on the sleep of adolescents was tested with (multi)variate analysis.

RESULTS AND DISCUSSION

All adolescents showed a significant phase delay of their bedtimes with age, irrespective of cultural background (Figure 1). The phase delay was found for school days ($F(299,2) = 21.37$, $p < 0.000$) as well as for weekend days ($F(299,2) = 19.24$, $p < 0.000$). This is in agreement with the literature.[1,4] In the weekend the bedtimes were 1.5 to 2 hours later than during the school week. As expected age did not have an effect on the rise times on school days.[5] This was caused by the strict school timings that forced the children to get up in time. During the weekend there was a trend for the adolescents to get up later with increasing age, but this failed to reach significance. In general the rise times on the weekend were around 3 hours later than the rise times during the school week.

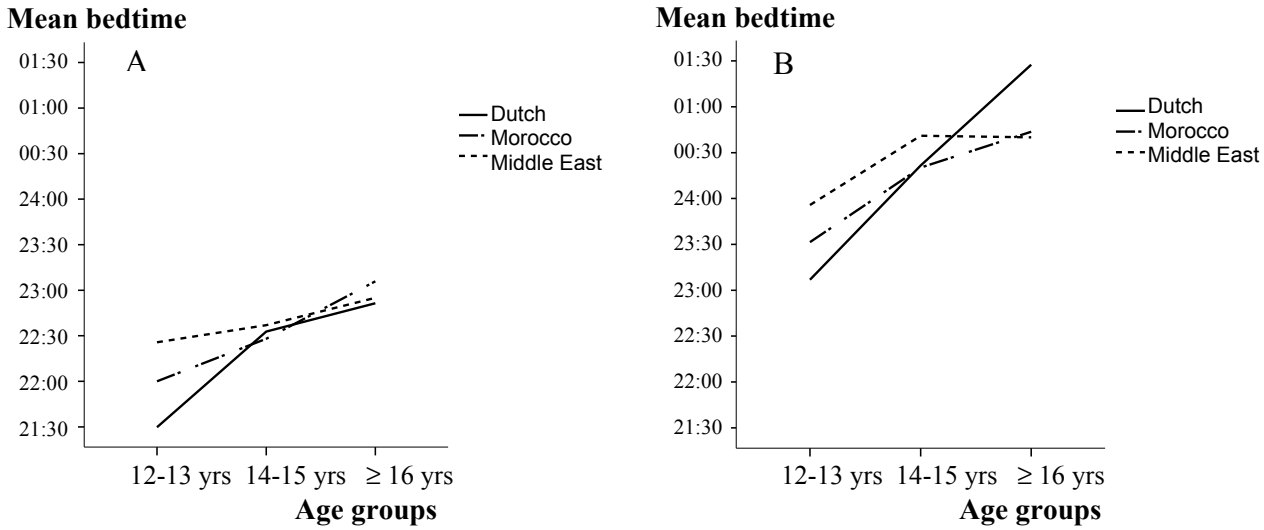

Figure 1. Bedtimes during school days (A) and weekend days (B) of adolescents with Dutch, Moroccan and Middle Eastern background for the 3 age groups.

Cultural background had a significant effect on bedtimes during the school week ($F(299,2) = 3.19$, $p < 0.05$). The main contribution to this effect was caused by the youngest children in the Middle Eastern group, who went to bed 1 hour later than the Dutch children ($p < 0.000$) and 30 minutes later than the Moroccan children (n.s.) in the same age group. As expected, on school days no difference was found between the rise times of the cultural groups. Because of their later bedtimes on school days the average sleep period duration of the youngest children in the Middle Eastern group was 30 - 40 minutes less (see Table 1) than in the other cultural groups ($F(92,2)$, $p < 0.01$). This difference disappeared in the older age groups. In the weekend bedtimes as well as rise times were not influenced by cultural differences.

Carskadon et al.[2] found that the biological sleep need does not decrease during puberty. As the school timings may have forced the children to follow a stricter time schedule for their sleep during the school week, this could have masked their actual sleep need. As a result during the school week the rise times were the same in all age groups. This was not the case when the adolescents were asked to choose their own optimal bedtime and rise time without taking the school timings into account. The desired rise times as well as the desired bedtimes were significantly delayed with age ($F(299,2) = 8.83$ and $F(299,2) = 9.13$, respectively, $p < 0.000$). The desired sleep duration did not change with increasing age. The desired bedtimes were on average 40 minutes later than the real bedtimes on schooldays. For the desired rise times this difference was more pronounced: on average the desired rise times were 2:15 hrs

later than the real rise times on school days. These findings are in agreement with earlier studies[2,3].
Cultural background did have a significant effect on the desired bedtime, but not on the desired rise time during the school week ($F(299,2)=3.59$, $p < 0.05$). The desired bedtime of the Dutch group was 22 minutes earlier ($p < 0.05$) than the Moroccan group and 25 minutes earlier ($p < 0.05$) than the Middle Eastern group.

Table 1. Duration of sleep period (minutes)* per cultural group and per age group.

	Neth.		*Morocco*		*M. East*	
Age	*Sch*	*Wnd*	*Sch*	*Wnd*	*Sch*	*Wnd*
12-13 yrs	9.5	10.4	9.4	10.9	8.8	9.9
14-15 yrs	8.6	9.7	8.5	9.7	8.6	9.7
≥ 16 yrs	8.4	9.0	8.6	9.9	8.3	9.8

*Sch = School week, Wnd = Weekend

Table 2. Sleep quality scores* per cultural group and per age group

Age	*Neth. Mean (sd)*	*Morocco Mean (sd)*	*M. East Mean (sd)*
12-13 yrs	10.3 (2.7)	10.2 (3.1)	10.6 (2.6)
14-15 yrs	9.3 (2.3)	9.7 (3.4)	8.5 (3.7)
≥ 16 yrs	10.4 (2.4)	7.7 (3.4)	8.5 (3.8)

*Low sleep quality = 0, high sleep quality = 14

The delay in bedtimes with age had a significant negative effect on the subjective sleep quality ($F(298,2) = 5.19$, $p < 0.01$). See Table 2. Post-hoc tests showed that the youngest age group had a significantly better sleep quality than the 2 older age groups ($p < 0.05$). Only in the oldest group there was an effect of cultural background ($F(298,4) = 2.52$, $p<0.05$). The Dutch group had a better sleep quality than the Moroccan group ($p < 0.01$) and the Middle Eastern group (n.s.).
There was a significant relation between the sleep period duration and mood on school days ($F(300,60) = 1.94$), $p < 0.000$). Children with shorter sleep periods on school days had a more depressed mood ($p < 0.000$), showed more anger ($p < 0.000$), more fatigue ($p < 0.02$) and more tension ($p < 0.02$) than children with longer sleep periods. In the weekend shorter sleep period were only related with a more depressed mood ($F(300,20) = 2.23$, $p < 0.005$). Cultural background had a significant effect on the relation between sleep period and mood on school days ($F(300,100) = 2$, $p < 0.000$). Dutch children with a shorter sleep period were less depressed ($p < 0.000$), less tense ($p < 0.05$) and felt less anger ($p < 0.005$) and less fatigue ($p < 0.001$) than Moroccan or Middle eastern children.

Table 3. Bedtimes of Dutch, Moroccan and Middle-Eastern adolescents in 3 age groups with "active" parents and with "passive" parents.

Active parents	*Bedtime school days*			*Bedtime weekend days*		
	Du	Mo	M-E	Du	Mo	M-E
12/13 yrs	21:27	21:58	22:22	22:59	23:34	23:50
14/15 yrs	22:39	22:28	22:33	0:41	0:11	0:45
≥ 16 yrs	22:47	23:23	22:54	1:13	0:34	0:32
Passive parents	*Bedtime school days*			*Bedtime weekend days*		
	Du	Mo	M-E	Du	Mo	M-E
12/13 yrs	21:49	22:05	23:15	0:06	23:25	1:15
14/15 yrs	22:11	22:28	22:45	23:11	0:41	0:33
≥ 16 yrs	22:59	22:50	22:56	1:50	0:53	0:49

Parents who had determined and controlled the bedtimes of the children when they were 10 years old and who were still stimulating their children to go to bed at a certain time, were categorized as 'active' parents. Parents who did not stimulate their children were the 'passive' parents (see Table 3). The bedtimes during schooldays as well as during the weekend of the adolescents with active parents were significantly earlier than the bedtimes of the group with passive parents ($F(300,1) = 5.5$, $p < 0.02$ and $F(300,1) = 8.52$, $p < 0.001$ respectively). On schooldays there was a significant difference between the cultural groups with active parents ($F(207,2) = 3.09$, $p < 0.05$). Dutch children went to bed 20 minutes earlier than children from Morocco ($p < 0.05$) and 25 minutes earlier than Middle Eastern children ($p < 0.01$). No significant cultural effect was found for weekend bedtimes. Even when they are actively stimulating their children to go to bed on schooldays, parents with different cultural backgrounds seem to have different ideas about optimal bedtimes for their children.

CONCLUSIONS

This study supports the literature that adolescents delay their bedtimes and rise times with increasing age, irrespective of the cultural background. During the school week the early start times of the schools force the adolescents to get up early. As a consequence rise times did not show this delay during the school week, but the delay was evident in the weekend and when the students were asked to give their optimal sleep schedule, irrespective of school timings.
As the adolescents were students in the same high school, the school timings were the same for all cultural groups. Nevertheless there was a strong effect of cultural background on the bed times of the children. During the school week the bedtimes of the Dutch adolescents were earlier than the bedtimes of the Moroccan or Middle Eastern group. This cultural effect was less extreme when the children were asked for their optimal sleep schedule. It was interesting that in the Middle Eastern group there was hardly any difference between the age groups in bedtimes: the group of 12-13 years went to bed as late as the oldest age group.
During the school week the rise times were dictated by the school timings. As a consequence during the school week the sleep periods were shortened. This was especially the case for the youngest Middle Eastern children. Shorter sleep periods had a negative effect on sleep quality and mood. Parental influence on the bedtimes of the adolescents was most pronounced in the Dutch group and less pronounced in the Middle Eastern group and resulted in earlier bedtimes than in the other groups.
It can be concluded that changes in sleep times during puberty are not only related to hormonal changes and changes in the social setting, but also to cultural background.

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HEART RATE VARIABILITY BIOFEEDBACK AS SOLO TREATMENT METHOD FOR CHRONIC INSOMNIA IN ADULTS: A PILOT STUDY.

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INTRODUCTION

Insomnia is a growing worldwide health problem. It has severe consequences not only for the individual but for society as a whole, therefore it is surprising this disorder remains under recognized, under diagnosed and under treated.[1, 2] Currently, insomnia can be treated both pharmacologically as well al non-pharmacologically. Pharmacological treatment however has downsides: it is not suited for everyone, it can cause unpleasant side effects and it is contra-indicated for treatment of chronic insomnia due to risk of tolerance and dependence.[3] Non-pharmacological treatments have less downsides but some do not sufficiently benefit from it.[4] Additional treatment methods are therefore needed. Biofeedback, a treatment method in which bodily processes are measured and depicted on a computer-screen in real time, may be an effective and recommended treatment method for insomnia.[5] Persons can learn to recognise and control physiological activities and bodily signals, in order to prevent or reduce symptoms. There are many types of biofeedback focussed at different bodily processes. Considering the pathophysiology of insomnia, in which somatic over-arousal and a disbalance in the autonomic nervous system (ANS) are thought to play a central role, heart rate variability (HRV) biofeedback seems useful. Sympathetic and parasympathetic branches of the ANS influence the sinus node of the heart, thereby modulating heart rate. Therefore, HRV analysis provides a window through which ANS functions can be monitored[6]. Mental and emotional stages affect ANS activity and HRV waveforms. For instance, anger tends to cause disorder in HRV waveforms and appreciations tends to cause harmony (or coherent) waveforms. HRV biofeedback aims at increasing coherent HRV waveforms. Several studies have been performed to test the effectiveness of HRV biofeedback on stress relief, most of which seem positive.[7-13] However, no studies have been performed with regard to HRV biofeedback as treatment method for insomnia. This pilot-study is therefore aimed at examining if HRV biofeedback is an effective solo treatment method for chronic insomnia in adults.

METHODS

Participants were recruited from the basic population registered for treatment for insomnia. The pilot study was conducted in the wait period for regular treatment. Individuals had to be 18 years or older, fulfill the criteria of chronic insomnia and sign an informed consent form in order to be included. Exclusion criteria were: severe psychiatric disorder, acute severe or unstable medical illness, disorders characterized by unstable functions of the ANS or the metabolism. Furthermore, those actively involved in treatment of insomnia and those started on psychoactive medication in the month prior to the start of the study were excluded. The total sample consisted of 19 individuals who were randomly assigned to 2 groups. Eight

participants were allotted to the wait control group. Once the study period had passed they were offered HRV biofeedback training. The remaining 11 participants received a 5 sessions lasting individual HRV biofeedback training, using the emWave PC of the HearthMath Institute. Heart rate was measured using a fingertip or earlobe sensor. After analysis of the heart rate patterns the emWave PC calculated a coherence ratio which was fed back in an accumulated score. The training was focussed at synchronising the ANS (establishing a balance between the parasympathetic and sympathetic nervous system) and maximising psychophysiological coherence, indicated by an increase in high coherence ratio. Sessions took about 1 hour and were given on a weekly basis. During sessions participants were taught to breathe calmly and regularly, as if the breath is coming in through the heart and out through the solar plexus. This was combined with exercises in calling up and holding on to positive feelings. After each session participants were asked to practise learned techniques at home during 10 minutes for at least 2 times a day. Furthermore, they received some home-assignments for practising breathing techniques as well as calling up and holding on to positive feelings.

Several measurements were performed prior to and at the end of the study period. Primary outcome measure was subjective sleep measured using sleep logs (7 days). From these sleep logs sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakening (EMA), total wake time (TWT), time in bed (TIB), total sleep time (TST) and sleep efficiency (SE) were calculated. Furthermore, psychological parameters were measured using following questionnaires: the Depression Anxiety Stress Scales, the brief version of the World Health Quality of Health Questionnaire and the Checklist Individual strength. In order to check if HRV training would lead to an increase in high coherence ratio, a 5 minute measurement of coherence ratio was performed in the intervention group in the first and last session.

Data was statistically analysed using SAS version 9.1. Characteristics of both groups were compared using a Fisher exact test and described as numbers and percentages. Given the small sample size, parameters were compared non-parametrically. Before a comparison between the control group and the intervention group was made, the difference between pre and post scores was calculated for each parameter. To test the differences between pre and post in the control and the intervention group a nonparametric paired test was used (Wilcoxon signed-rank test). All tests were two sided.

RESULTS

Average age of the sample was 51 (minimum 23 and maximum 72 years). Mean body mass index (BMI) was 26. Of the sample 15.79% smoked (cigarettes), 47,37% took hypnotics (benzodiazepines), 21.05% used antidepressants and 26.32% took another kind of psychoactive medication. Analysis revealed no significant between group differences at baseline except for depression ($p=0.03$), quality of psychological health ($p=0.01$) and quality of environment ($p=0.01$). The treatment group scored higher on depression while the control group scored higher on both quality of environment en psychological health.

No significant difference in effect was found between treatment group and control group (pre compared to post) for all sleep parameters and psychological parameters. With regard to subjective sleep, no significant pre compared to post changes were found in both groups. Comparison of pre compared to post scores on all three questionnaires showed only a modest significant difference for anxiety in the control group ($p=0.04$). Finally, a comparison of pre and post training measurement of coherence ratio, as performed in the intervention group, showed the coherence ratio increased significantly. See Table 1 for an overview.

Table 1. Parameters pre as well as post for treatment group and control group.

	Control group			*Treatment group*			*Over all*
	Pre M (IQR)	*Post M(IQR)*	*p**	*Pre M (IQR)*	*Post MIQR)*	*P**	*p* [a]
SOL	33.2 (20.4-67.5)	23.6 (17.1-83.6)	0.22	47.1 (21.4-51.4)	51.4 (0.0-130.7)	0.30	0.10
TST	316 (228-332)	298 (227-416)	0.37	313 (287-366)	347 (291-390)	0.57	0.65
SE	62.3 (45.3-70.4)	60.5 (53.3-71.1)	0.22	62.2 (59.2-78.6)	69.3(55.1-78.5)	0.41	0.37
DASS							
Dep.	3.0 (1.5-8.0)	2.5 (0.0-8.5)	0.44	8.0 (8.0-25.0)	11.0 (4.0-17.0)	0.23	0.48
Anx.	3.5 (2.0-5.0)	1.6 (0.0-4.0)	0.04	3.0 (1.0-22.0)	3.0 (1.0-6.0)	0.55	0.40
Stress	7.0 (5.0-11.0)	4.5 (1.5-10.0)	0.15	9.0 (5.5-26.0)	10.0 (5.0-17.0)	0.16	0.97
WHOQOL-bref.							
Qol.	7.0 (6.0-8.0)	7.5 (6.0-8.0)	0.99	7.0 (5.0-8.0)	7.0 (5.0-8.0)	0.07	0.16
Qoph.	15.3 (14.7-17.0)	16.3 (14.7-16.7)	0.99	12.0 (9.3-14.0)	12.0 (10.7-16.0)	0.15	0.38
CIS							
Total	80.5 (70.0-91.5)	78.5 (49.5-91.5)	0.38	89.5 (65.0-122.0)	89.0 (72.0-100.0)	0.41	0.97
Coh.				36.0 (8.0-60.0)	87.0 (58.0-100.0)	0.01	

Note: SOL= sleep onset latency; TST=total sleep time in minutes; SE=sleep efficiency; DASS=depression anxiety stress scales; Dep.=depression; Anx.=anxiety; WHOQOL-bref= World Health Organisation Quality of Life Questionnaire-brief version; Qol=quality of life; Qoph=quality of psychological health; CIS=checklist individual strength; Coh.= high coherence ratio; M=median; IQR=inter quartile range (25-75%); *= paired test (Wilcoxon singed-rank test); [a]=based on difference between pre and post of both groups.

DISCUSSION

Although the coherence ratio improved significantly after treatment, the results of this pilot study provided no evidence to suggest that HRV biofeedback training is an effective solo treatment method for chronic insomnia in adults. During and after treatment positive effects such as feeling more relaxed and confident were reported, but this did not lead to significant improvements in the outcome measures. Since this is, as far as known, the first study done on HRV biofeedback as treatment method for insomnia no comparison with other studies can be made. However, it must be mentioned that the findings are contrary to studies on HRV biofeedback in other populations (mostly non-clinical) in which similar parameters were measured as (side) effect. [7, 11-13] Several reasons can be considered as to why no effect was found.

First of all, the limited time span of the pilot study has to be considered. No clear uniform guidelines are available yet as to how many sessions of applied biofeedback are necessary to treat insomnia. Some suggest biofeedback treatment focused at relaxation and aimed at improving sleep may require 30 to 90 sessions. [14] Five sessions may therefore not have been sufficient to obtain and maximise therapeutic effect. In addition one has to consider the possibility HRV biofeedback may have delayed effect. Relaxation techniques take some time to learn, moreover, they have to be incorporated into daily life. Considering this it may take several weeks before techniques for relaxation are used effectively. [15] It therefore seems plausible that post measurements were conducted too early to see effects. One can furthermore, argue that the protocol used in the current pilot study was too limited in content to achieve results. Focus of the protocol was primarily on breathing techniques in combination with calling-up, reliving and holding on to positive thoughts and sincere feelings of love and appreciation. Little attention was paid to aspects such as how emotions

and thoughts activate both our hormonal system (cortisol and DHEA) and our autonomic nerve system (sympathetic and parasympathetic). Perhaps significant effects would have been found if a more elaborate protocol was used. It can also be argued HRV biofeedback did not yield positive effects, because it was not the best suited treatment for some of the participants. In order to promote sleep, biofeedback treatments have to be appropriate for specific deficiencies of the person in question otherwise improvements are not likely to occur. [16] HRV biofeedback is primarily focused at promoting relaxation and limiting stress as well as arousal. Some insomniacs however do not suffer from heightened arousal, tension or psychological anxiety. [17, 18] Participants were not tested on arousal or tension as part of the inclusion process. This could have been done by a 24- hours ambulatory Holter recording, frontalis electromyogram or measurement of DHEA and cortisol. If participants were sufficiently relaxed and did not experience heightened arousal or tension there would be no added value for them to relax further. This could explain why HRV biofeedback had no effect in these patients. Finally, insomnia is a multidimensional problem, caused and maintained by multiple factors. In the sample signs of cognitive arousal as well as inadequate sleep behavior were seen, indicating that various sleep impeding factors were involved. It could therefore be argued that focussing therapy at one element was simply not sufficient. Considering this and the fact that multicomponent therapies seem to become the standard procedure for treatment of chronic insomnia [19], HRV biofeedback may better be used not as solo treatment but as one element of a multi component therapy. It could for example be integrated into cognitive behavioral therapy.
This pilot study has several restraints such as its small sample size, the limited time span, the limited protocol and the fact that sessions were performed by a certified though inexperienced therapist. Due to these limitations generalisation of the results of this study is not advisable.

CONCLUSIONS

We conclude that successful training of coherence does not lead to improvements of sleep in this small group of patients. Therefore, HRV biofeedback as solo treatment is not an effective treatment method for chronic insomnia in adults. Future research should focus at a more imbedded use of HRV biofeedback. A comparison between a multi-component therapy or treatment as usual, with and without HRV may be interesting in high aroused subjects.

ACKNOWLEDGEMENT
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A CALIBRATED SNORING SOUND SENSOR

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INTRODUCTION

Common polysomnographic equipment measures the sound of snoring on the trachea, in the nasal cannula, or in some cases through an ambient microphone. However, a tracheal sensor hardly senses nasal snoring, and vice versa. An ambient microphone is not reliable in ambulatory settings and has variable orientation and distance to the snorer. Therefore, none of those methods can produce a calibrated sound level. As a consequence, common PSG equipment can not assess snoring and its therapy in a quantitative manner. This study aimed at a simple solution of this limitation.

METHODS

Snoring sound is caused by obstructions in the airway that enhance and amplitude-modulate the intensity of breathing sound. Sound frequencies depend on the type and location of the obstructions and range from 50-2000Hz[1]. This full frequency spectrum is recorded by a tiny (10x6x4mm) WL93 microphone, which is placed on the forehead in order to have a fixed and fairly equal distance to nose and mouth openings. An envelope detector in the electronic circuit (figure 1) constantly tracks the power of this signal, i.e. sound intensity. The bandwidth of the envelope detector is DC-75Hz, so that it also tracks slow modulations caused by snoring. The physiological perception of different sound frequencies is approximated by an A-weighting filter that attenuates frequencies away from 1000Hz. By comparing the system to a professional dBA probe, the circuit was accurately calibrated from 30 till 90 dBA sound levels, i.e. from very light till very heavy snoring. Power consumption is only 2mW.

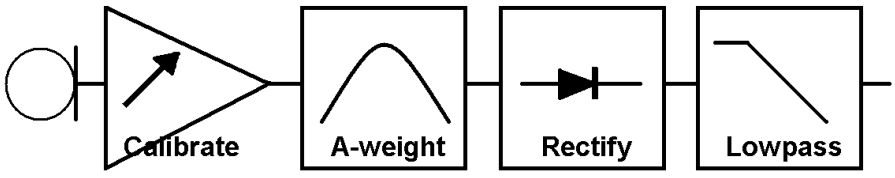

Figure 1. Electronic processing of the microphone signal (left): pre-amplifier with gain calibration, A-weighting filter, and envelope detector consisting of full-wave rectifier and low-pass filter.

RESULTS AND DISCUSSION

The microphone has been applied in routine ambulatory PSG for half a year now, without specific problems. It measures absolute sound levels and is less sensitive to artifacts

compared to tracheal and nasal sensors. Like the other sensors, it also measures the sound of heavy breathing.
The location of the microphone on the forehead is a clear advantage. For instance, figure 2 shows 12 minutes in which a healthy snorer (having sufficient flow) develops an obstruction that both reduces flow (top trace) and increases absolute sound level (trace 4). This sound increase is hardly noticed by the tracheal sensor (trace 3) and certainly not by the nasal sensor (trace 2).

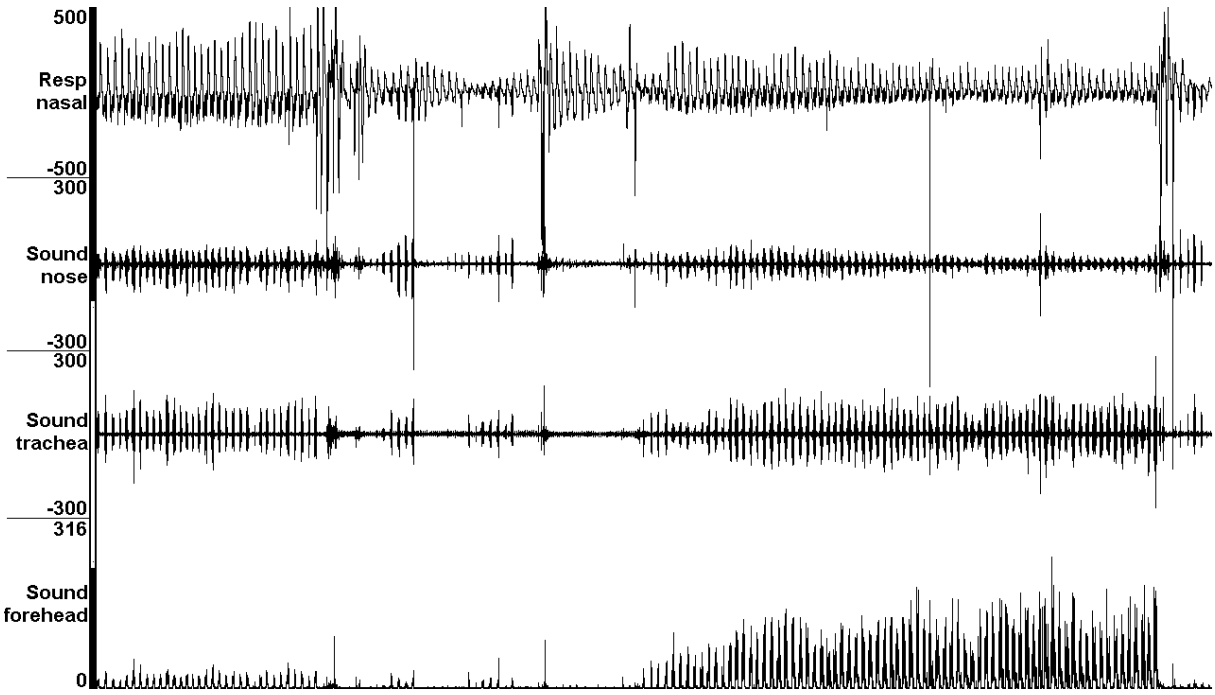

Figure 2. 12 minutes of flow and sound. From top to bottom nasal flow and sound as recorded by nasal, tracheal and forehead sensor. Note the developing obstruction in the last 6 minutes which is accompanied by increasing snoring sound.

In contrast to the commonly applied direct sampling of tracheal and nasal sensor signals, the envelope detector rectifies the signal, corresponding to sound intensity being always greater than (or equal to) zero. The detector also reduces the bandwidth of the signal such that the commonly applied 200Hz sampling is now sufficient to track snoring intensity. Because the signal is calibrated, it can also be displayed on a logarithmic dBA scale. Such a scale better reflects the physiological perception of different sound intensities: it easily shows sound levels down to 0.03 % of 90dBA, i.e. 20dBA (light breathing). The applied envelope detector is a low-power approximation of the squarer that is theoretically required to compute power. Because of the described calibration procedure, the approximation error is less than 10% (i.e. 1dBA) for sinusoidal and noisy signals.
The method measures the intensity of speech and other sounds, not actual speech frequencies. In fact, speech can not be distinguished from many other sounds, and can certainly not be understood. Therefore, the privacy of the patient is assured. The present implementation also smoothes sound intensity modulations that are faster than 75Hz. Therefore, the method can not distinguish different types of snoring[1].

Because the microphone is very sensitive, has a HiFi frequency characteristic, and is located on the forehead, it also picks up external sounds that are potentially sleep-disturbing. Those external sounds are monitored better than the other sensors can (figure 3). Still, they can easily be distinguished from snoring sound because the latter is synchronized to respiration and has a different waveform shape.

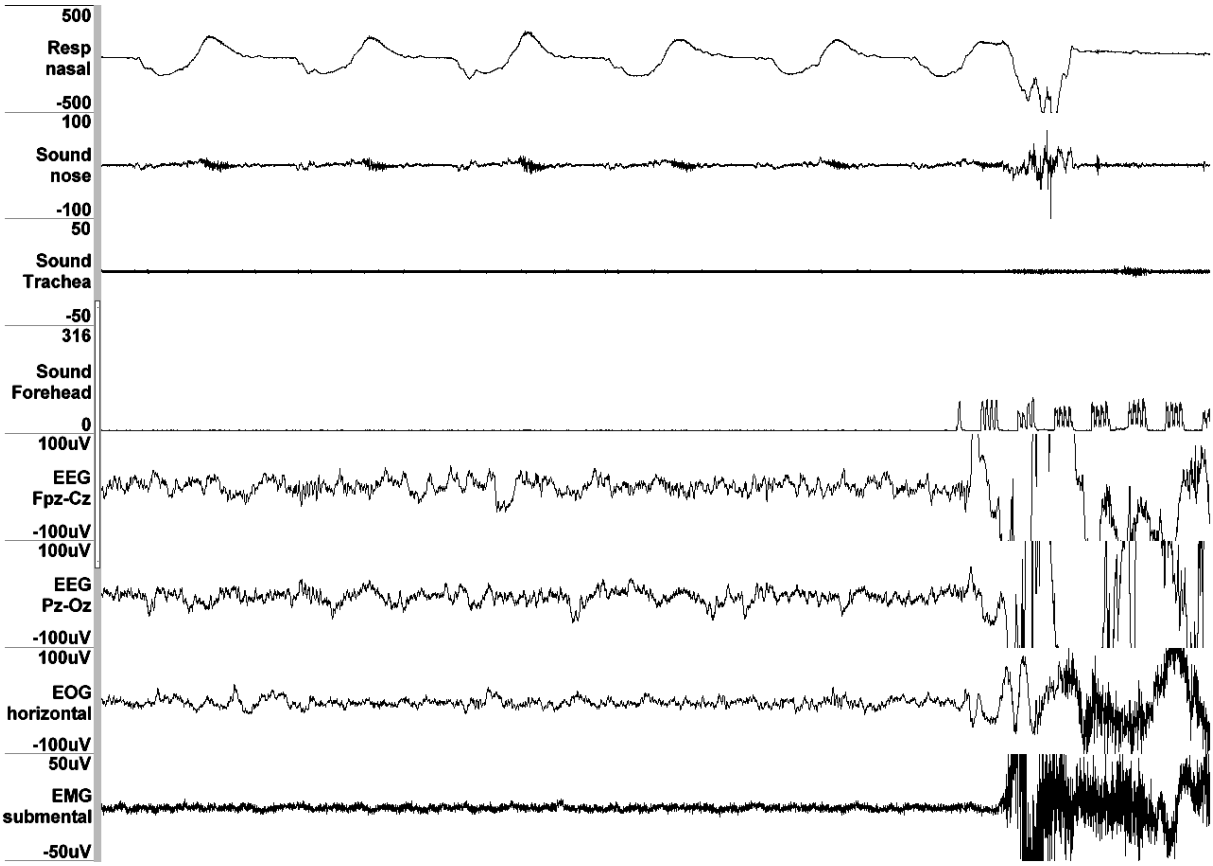

Figure 3. 30s PSG with (from top to bottom) respiration, 3 x sound, EEG, EOG and EMG during light sleep. Despite enhanced sensitivity of the other sensors, only the forehead microphone shows the alarm sound that caused the K-complex and subsequent awakening.

CONCLUSIONS

The described forehead snoring sensor is a reliable and practical system for measuring absolute snoring sound intensity, both in ambulatory and clinical settings. Environmental sounds are also picked up and are a valuable addition for the diagnosis of sleep disorders.

ACKNOWLEDGEMENTS

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NATIONAL SLEEP DAY 2008 IN THE NETHERLANDS: RESULTS OF A WEB QUESTIONNAIRE ON SLEEP PROBLEMS IN CHILDREN

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INTRODUCTION

Each year since 2006, the Dutch Society for Sleep- Wake Research (NSWO) organizes the National Sleep Day in The Netherlands. 'Sleep Problems in Children' was chosen as the theme for 2008 because of growing interest on an international level in pediatric sleep regulation and sleep disturbances. It is quite remarkable that very little is known, especially in the Netherlands, on prevalence of sleep disturbances in children. More insight could provide useful information for focusing new Dutch sleep research. Research on sleep disturbances in children is an important area and deserves more attention, as it affects not only them but also their parents and siblings, but also because the effects of sleep disturbances on daytime functioning are especially important in children, as it may affect not only their present, but also for their future performance.

From recent studies it is known that sleep deprivation can cause sleepiness and fatigue, but also cognitive problems [1]. In children these problems may lead to attention problems at school, behavioral problems, and also in memory deficits and assessment problems of the consequences of their own behavior.

METHODS

Data acquisition

In November 2007, the PR committee of the NSWO launched a web-based questionnaire about sleep problems in children. The questionnaire contained 17 items, using a 5 point-rating from never to always, regarding sleep structure and subsequent daytime effects: sleep onset times/problems, sleep maintenance problems, wake up times/problems, daytime sleepiness, and daytime functioning. Several items were included on possible sleep disorders: snoring, sleep disordered breathing, parasomnia, insomnia, hypersomnia, circadian rhythm sleep disorders, Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD). A few demographic items were included: birthday, gender, length, weight and postal code. The last two items (yes-no-not applicable) focused on parental concern: whether parents worry about the negative consequences of sleep loss for their child and whether they've been searching for treatment.

Through direct mail and telephone contacts, schools and day care facilities were asked to inform parents about the questionnaire. In addition all members of the NSWO were asked to inform family and friends and to ask them to complete the questionnaire.

Subjects

After three months, 899 completed questionnaires could be used for analyses. Of these 899 questionnaires 450 concerned boys (50.6%) and 439 (49.4%) concerned girls with an average age of 5.4 years (sd=4.04), distributed as shown in figure 1.

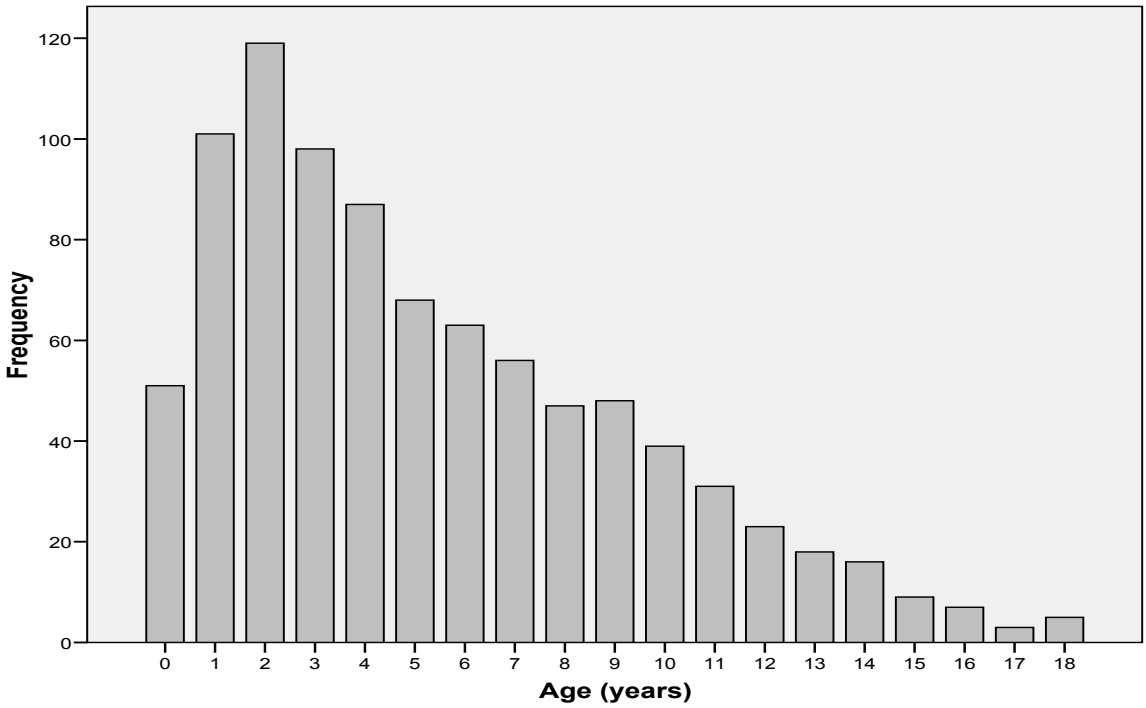

Figure 1. Age distribution for complete sample.

Analysis

In view of the age distribution of the sample we assumed that the majority of the questionnaires were completed by parents. All analyses were done using SPSS 15.0. Age was deduced from Birthday and date of completion of the questionnaire. Estimated Sleep Duration (ESD) was calculated from bed-time and final waking up time. ESD was categorized in 4 groups (see table 1) based on critical sleep length according to the recommendations of the National Sleep Foundation in the USA[2]. All children were categorized in three age groups, 0-4, 5-10 and 11-18 years based roughly on the developmental stages baby-preschool, young-primary school and adolescent. Descriptive statistics in SPSS were used for general parameters. Non parametric tests (Chi square and Mann-Whitney U test) were used to estimate significance. (α =0.05).

Table 1. Sleep amount per age group in Poor and Good Sleeper groups. Number indicates percentage of children in that ESD group. Significant difference Poor versus Good Sleeper group printed bold (Mann-Whitney, Z=-6.65; p=0.000)

	N	*Estimated Sleep Duration*			
Age	*Poor/Good sleepers*	*0-6 hours*	*6-8 hours*	*8-10 hours*	*10+ hours*
0-4	145 / 325	1.4 / 0.3	2.8 / 1.5	17.9 / 8.3	77.9 / 89.9
5-10	81 / 226	1.2 / 0.4	2.5 / 0.9	**56.8 / 23.0**	39.5 / 75.7
11-18	40 / 72	**5.0 / 0.0**	**40.0 / 11.1**	52.5 / 72.2	2.5 / 16.7

RESULTS

In this sample, 266 (29.9%) children were reported to have sleep problems according to their parents. In the group of Poor Sleepers (n=266), the sex distribution (139 / 52.3% boys versus 127 / 47.7% girls) did not significantly differ from the total population while the average group age was 5.7 years (sd=4.34). The remaining group of Good Sleepers consisted of 311 boys (49.9%) and 312 girls (50.1%) with an average age of 5.2 years (sd=3.9). In each age group the most prevalent sleep problems were related to sleep onset and sleep maintenance. All reported sleep problems are shown in figure 2 per age group.

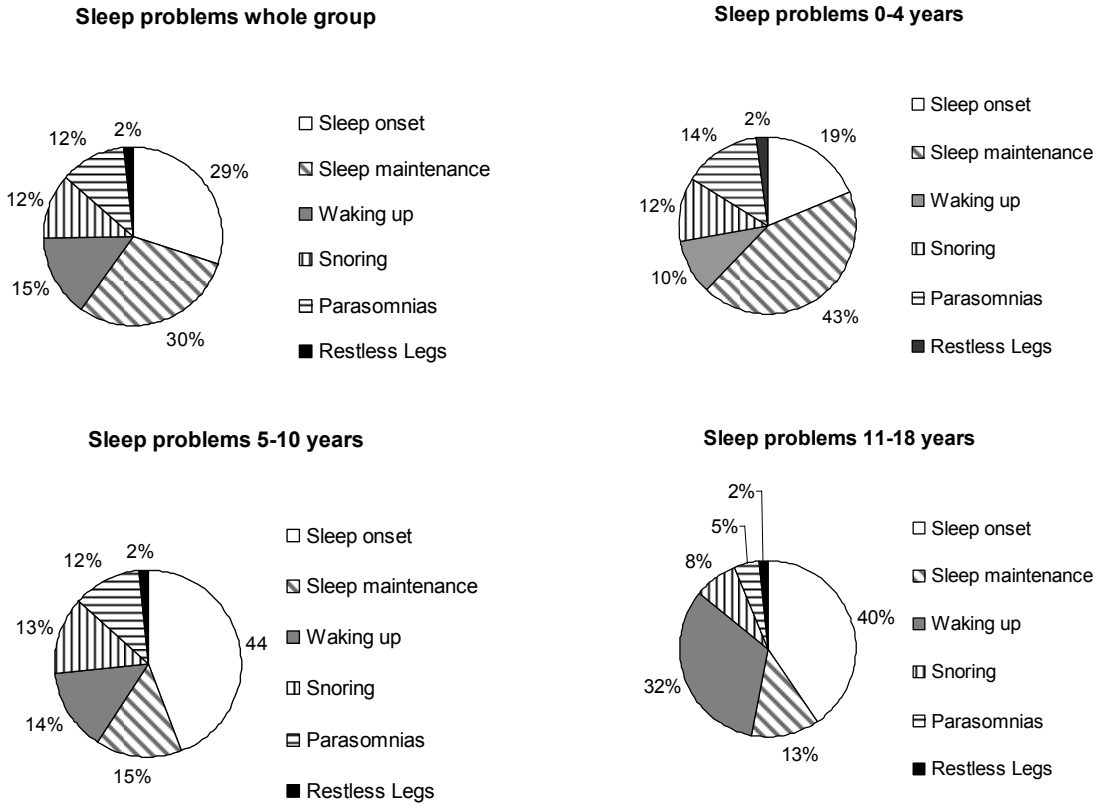

Figure 2. Sleep problems per age group.

Especially sleep duration is affected by the sleep problems reported. The amount of sleep per night is less in the Poor Sleepers than in the Good Sleepers for all age groups (see table 1).

DISCUSSION

In this web based questionnaire we found that a relatively large proportion (29.9%) of the parents reported sleep problems in their children. This high number may reflect a selection; the parents that complete this kind of questionnaire may already be experiencing sleep problems in their child and may be more willing to cooperate. Also those parents searching the internet looking for sleep tips may have come upon this questionnaire. The reliability of web-based questionnaires is still a matter of debate and the prevalence number in this study must not be interpreted as coming from a reliable selection of the Dutch population. Nevertheless it indicated that sleep disturbances in children are clearly present and it is

interesting to search within this group for the type of sleep problems being mentioned as well as the relationship between sleep problems and age.
Also the age distribution of the children in the database may reflect a selection bias as we have tried to contact daycare facilities and primary and secondary schools. This resulted in a large amount of sleep data for children under the age of 10. Parents of teenagers are probably also less aware of the sleep habits and possible daytime effects of sleep deprivation of their teenager and thus may underreport problems in this area[3]. Fortunately the number of completed questionnaires is high enough to eliminate certain chance effects.
A sleep duration of less than 8 hours per night is considered to be critical for children of all ages. We found 5% of teenagers between ages 11 and 18 to sleep a maximum of 6 hours per night and 45 % sleeping no more than 8 hours per night, which is in agreement with NSF polls in the USA[3]. This may reflect the natural variation of short sleepers and long sleepers for this age group, but considering the fact that parents reported a sleep problem for these teenagers, it should be taken seriously. Interestingly, the parents that report this amount of sleep in their child, only seem to be aware of sleep onset problems and problems awakening in the morning and do not report any daytime problems. It remains to be seen whether this reflects less awareness of parents about daytime functioning of their teenager or whether these problems just do not exist. Further research on the reliability of reports by parents concerning the sleep of their child, especially in this age group, seems necessary.
Sleep is very important for physical and mental functioning. In recent studies it is shown that sleep deprivation in children has definite negative consequences for higher cognitive functioning, for which it is thought that the prefrontal cortex plays a crucial role[1,4]. Sleep has a specific function in memory consolidation and therefore it deserves a lot of attention, in particular in children, for whom the whole day consists of learning and memory.

CONCLUSIONS

A number of interesting conclusions could be drawn from this pilot project with a web based questionnaire. The study provides a first preliminary estimate of the prevalence of sleep problems in children in The Netherlands. Although the number of 30% of children showing some kind of sleep problem may be overestimated due to a selection bias, it is remarkable that this number corresponds to prevalence numbers in the USA. If it is overestimated by 100%, this still means that at least one out of six children suffers from sleep problems that may affect his or her daytime functioning. In this group sleep duration is clearly reduced, which could result in impairments in learning and memory.

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THE EFFECTS OF MELATONIN ON SLEEP-WAKE RHYTHM OF DAYTIME HEMODIALYSIS PATIENTS: A RANDOMIZED PLACEBO-CONTROLLED CROSS-OVER STUDY (EMSCAP STUDY)

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INTRODUCTION

End-stage renal disease (ESRD) is associated with an increased prevalence of sleep disturbances, which have a major influence on quality of life and mortality.[1] In this patient group circadian rhythmicity, defining periods of low and high sleep propensity[2], can be negatively affected due to pathology of ESRD[1] and the dialysis process, causing daytime sleepiness and insomnia.[1]
The pineal hormone melatonin plays an important role in the synchronization of circadian sleep-wake rhythm. In normal conditions, melatonin is secreted only during the night[3]. The onset of the evening rise in endogenous melatonin is called the Dim Light Melatonin Onset (DLMO) and can be calculated as the first interpolated point above 4 pg/ml in saliva after which the endogenous melatonin concentration continues to rise.[4] This increase in endogenous melatonin level in the evening correlates in normal circumstances with the increase in evening sleep propensity.[5]
An absence of the nocturnal rise in melatonin concentration in daytime hemodialysis patients has been described earlier.[6] Administration of exogenous melatonin might compensate for this absent melatonin rhythm. This has been confirmed for other patient groups like Delayed sleep phase syndrome (DSPS) patients, but not for patients with ESRD such as hemodialysis patients. Therefore, the present study set out to investigate the effects of exogenous melatonin on the sleep-wake rhythm of hemodialysis patients, as measured by sleep quality and the endogenous melatonin rhythm.

METHODS

The study design is a randomized double-blind placebo-controlled cross-over study. The Medical-Ethical Committee approved the protocol of the study (ClinicalTrials.gov: NCT00404456), and informed consent was obtained from all patients. The study lasted 3 periods of 6 weeks. In the first study period, melatonin 3 mg tablets (Pharmanord ®, Vejle, Denmark) or placebo tablets (Pharmanord ®, Vejle, Denmark) were administered at 22:00 every night. In the second period, placebo and melatonin tablets were reversed. All patients received melatonin 3 mg tablets during the last period. At baseline, daytime hemodialysis patients were asked to fill out a sleep questionnaire and to wear an actometer for seven

consecutive days. In addition, melatonin concentrations in saliva were measured during the night after daytime hemodialysis and during the consecutive night. When the median sleep onset latency, measured by means of the actometer was longer than 15 minutes and melatonin concentration was below 4 pg/ml in saliva during the night (inclusion criteria), patients could be included in the study.
The actometer was placed on the wrist of the arm without graft or fistula. The following parameters were calculated, according to standardized methods[7]: Actual Sleep Time Actual Awake Time, Sleep Efficiency, Sleep Onset Latency and Fragmentation Index. The latter was calculated as the total number of wake bouts (defined as a wake period by the algorithm of the software) divided by the total sleep time in hours. Actigraphy was carried out during the baseline week and during the last week of the first and second study period.
Melatonin concentrations in saliva were measured the night after daytime hemodialysis and the subsequent night without daytime hemodialysis at 21:00 h, 23:00 h, 1:00 h, 7:00 h and 9:00 at baseline. These measurements were repeated during the last week of the third study period. To measure endogenous melatonin, exogenous melatonin was not administered during days of sampling of melatonin in saliva. Patients were asked to slowly move a cotton plug (Salivetten ®, Sarstedt Numbrecht Germany ©) in their mouth for one minute. Melatonin levels were measured by the commercially available RIA kit (Bühlmann Laboratories). Saliva samples were kept at - 18 degrees Celsius until analyzed; then they were centrifuged (1000g, 2 minutes). Aliquots of 400 microliter of saliva sample were added directly in assay tubes. The detection limit was 0.5 pg/ml.
Sleep-wake characteristics were derived from the validated Dutch sleep disorders questionnaire.[8] Patients were asked to keep a log of their sleep-wake schedule for 7 consecutive days at baseline and during the last week of the first and second study period.
If the patients had a regime of Monday-Wednesday-Friday hemodialysis all measurements were started during the study on a Monday. If patients had a regime of Tuesday-Thursday-Saturday hemodialysis all measurements were during the study started on a Tuesday.
Median values and interquartile differences of the sleep questionnaire and actigraphy on dialysis days and non-dialysis days were calculated during the double-blind cross-over period. The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 14 was employed for all statistical analysis. All parameters were tested by Wilcoxon (2-tailed) to find significant differences ($p < 0.05$) between before and after treatment. Plots were made of melatonin concentrations before and after treatment. The melatonin concentrations were analyzed by means of paired comparison per measuring point by Wilcoxon signed-ranks test analysis.

RESULTS AND DISCUSSION

Twenty patients (14 male, 6 female) completed the 18 week investigation period. The general characteristics of the patients were similar to the main characteristics of the general Dutch dialysis population.[9]
As is shown in Table I, the median sleep onset latency on the night after dialysis significantly reduced after melatonin treatment. Patients needed a median of 30 minutes to fall asleep before melatonin treatment, which reduced to a median of 15 minutes ($Z = -2.20$, $p = 0.03$) after melatonin treatment. The median fragmentation index reduced from 3.9 to 3.1 wake bouts per hour of sleep ($Z = -2.41$, $p = 0.02$), indicating less fragmented sleep.

Table I. Results of the actometer on the night after daytime dialysis (displayed as median and interquartile difference) after 5 or 11 weeks (depending on the placebo-melatonin period)

Parameters	*Median [Interquartile difference] Before treatment*	*Median [Interquartile difference] After treatment*
Sleep onset latency (min.)	29.9 [44.3]**	15.5 [27.8]**
Sleep efficiency (%)	69.5 [19.3]	73.1 [27.5]
Actual Awake time (%)	22.4 [19.4]	19.4 [13.6]
Actual Sleep Time (min.)	368.0 [134.4]	387.5 [155.6]
Fragmention index	3.9 [1.3]**	3.1 [0.7]**

**p < 0.05

The sleep questionnaire results showed that the patients reported less time needed to fall asleep (Z = -1.96, p = 0.05), an increase in sleep time (Z = -2.73, p = 0.02) and a trend towards less daytime napping (Z = -1.74, p = 0.08) after melatonin treatment. Furthermore, an improvement in feeling well-rested in the morning was noticed with melatonin (Z = -2.13, p = 0.03). Their perception on sleep quality and daytime function did not change significantly after treatment with melatonin.

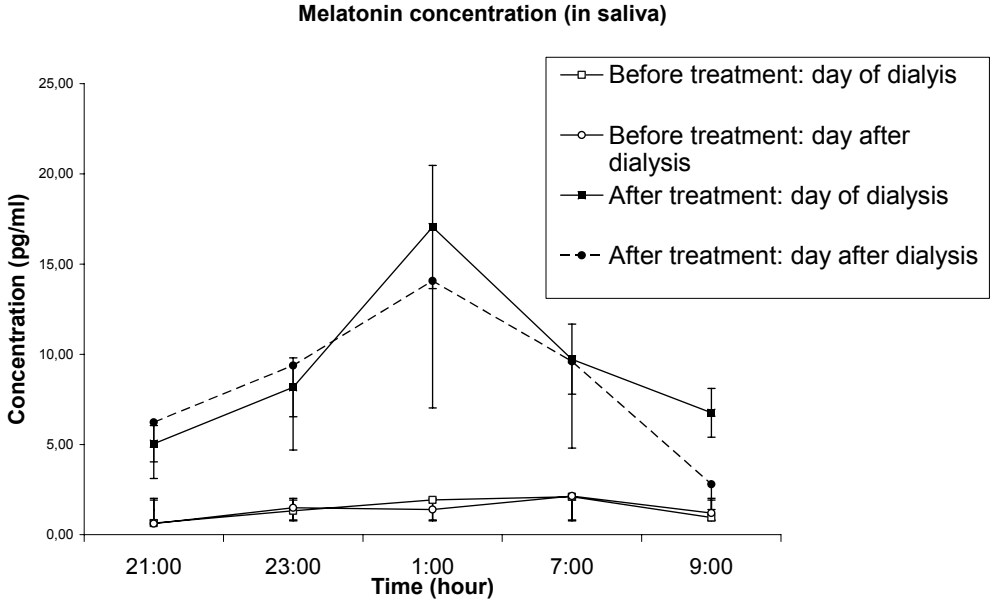

Figure I. displays the mean melatonin concentration measured in saliva on the day of dialysis and the consecutive day. The horizontal axis reflects the time of day in hours and the vertical axis reflects the melatonin concentration in saliva in pg/ml. The lines with open bullets represent the measures before treatment. The lines with closed bullets represent the measures after treatment. The vertical lines at the measuring points represent the standard deviation error bars.

Before treatment, as is shown in Figure I, the nocturnal melatonin rise was absent. After treatment the average melatonin concentration increased well above the DLMO set point of 4 pg/ml in saliva at night. Endogenous melatonin concentration was significantly increased after treatment in comparison with before treatment (p < 0.05, Wilcoxon tested) at all measuring points. The melatonin curve was lower after treatment on the following night without daytime dialysis, as is shown in Figure I.

The results of baseline measurements from the present study confirm previous observations of an absence of a nocturnal melatonin rise in patients suffering from ESRD.[6] This apparent disturbance of the circadian melatonin rhythm may be explained by several mechanisms: Dialysis and its sleep inducing effects result in a disturbance of the sleep-wake rhythm.[1] This disturbance is expressed in the absence of a normal onset of melatonin production.[1] Secondly, betablockers, frequently used in haemodialysis patients, have been shown to depress nocturnal melatonin production[3]. Furthermore, the decline in melatonin levels is due to impairment in beta adrenoreceptor mediated responsiveness in renal insufficiency.[10] The adrenergic system plays an important role in the synthesis of serotonin N-acetyltransferase (NAT), the key enzyme in melatonin biosynthesis[3]. Exogenous melatonin bypasses the enzyme NAT and therefore may allow a recuperation of the enzymatic activity of NAT. Consequently, after a period of melatonin administration, this enzymatic activity may have been sensitized.[3] This would facilitate the triggering of the synthesis and release of endogenous melatonin, which was observed in this study (Figure I). The melatonin curve was significantly lower on the following night without daytime dialysis. Possibly, sensitized enzyme activity of NAT dropped after two days without exogenous melatonin as this was not administered during days of saliva sampling.

CONCLUSIONS

Melatonin administration in daytime dialysis patients has very promising effects on the endogenous melatonin rhythm. As a follow-up on the positive results of this small and short-term study, the so-called MELODY study was recently initiated. The results of this larger long-term (one year) multi-center placebo-controlled study on the effects of exogenous melatonin on sleep and quality of life might confirm the beneficiary role of melatonin in this population.

ACKNOWLEDGEMENTS

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RELATION BETWEEN SLEEP DURATION AND BODY MASS INDEX IN ELDERLY MEN

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INTRODUCTION

World-wide, the prevalence of overweight and obesity has taken on epidemic proportions. So far in the study of etiology of obesity, attention has been focused primarily on food intake and physical activity, but recent evidence suggests that sleep may also play a role. Cross-sectional studies across different age groups have repeatedly found an association between reduced sleep and higher prevalence of overweight and obesity[1-6]. This relationship is also confirmed in prospective studies, which identified an association between short sleep duration and future weight gain[7-13].
Fifty-seven percent of Dutch elderly men (≥65 years) has overweight (BMI ≥25), including 11 percent with obesity (BMI ≥30)[14]. Interestingly, the prevalence of sleep disorders also tends to increase with age[15]. Few studies have focused on the elderly, with different results. Therefore, the aim of this study was to examine the cross-sectional and longitudinal association between sleep duration and BMI in a sample of men who participated in the Zutphen Elderly Study. We hypothesized that short sleep duration is related to overweight/obesity and weight gain over time in elderly men.

METHODS

The Zutphen Elderly Study is a population-based cohort study on diet, risk factors for chronic diseases, and health in elderly men born between 1900 and 1920. Additional information has been described elsewhere[16]. Self-reported sleep duration, anthropometric measurements, life-style factors including physical activity and energy intake, and presence of chronic diseases were determined in a sample of 408 men, all aged ≥69 years and not taking medication affecting sleep or body weight. Sleep duration was asked by questionnaire and classified into the subgroups ≤6, 7, 8 and ≥9 hours of sleep during the night.
Multiple linear regression analysis was used to estimate the cross-sectional and longitudinal association between sleep duration and BMI. Data obtained in 1985 were used for cross-sectional analysis and additional follow-up measurements of 1990 were used for longitudinal analysis. Since the prevalence of overweight and obesity is high, odds ratios do not reflect a proper estimate of the prevalence ratio. Therefore, proportional hazard regression analysis, taking time equal to 1 and using the robust variance estimator, was performed to evaluate the strength of a cross-sectional relationship between sleeping hours and the prevalence of overweight and obesity. Participants were classified into normal weight (BMI 17.4-25 kg/m^2), overweight (BMI 25-30 kg/m^2) and obese (BMI 30-38.7 kg/m^2).

RESULTS AND DISCUSSION

Mean age of the men was 74.9 years (SD: 4.6). Fifteen percent of the men reported ≤6 hours of sleep, 25.2 percent slept 7 hours, 43.1 percent slept 8 hours, and 16.7 percent slept ≥ 9 hours. In general, short sleepers spent fewer minutes on medium physical activity, were less likely to smoke, felt less healthy and were more likely to have diabetes compared to the other sleep duration categories. Men who slept ≥9 hours consumed more caffeine, had a lower mental score and were more likely to have cancer compared to men who slept <9 hours. Socio-economic status was highest among men who slept 7 or 8 hours. Interestingly, men who slept ≤6 hours were more likely to be obese, but less likely to be overweight.
Multiple regression models are shown in Table 1. Sleep duration of ≥9 hours per night was chosen as the reference category since men in this category had the lowest BMI. There was no statistically significant association between duration of sleep and BMI without adjustments (model 1) or adjusted for age (model 2). After adjustment for age, presence of diabetes, energy intake and physical activity, men sleeping 7 hours had on average a 1.09 kg/m^2 higher BMI compared to men sleeping ≥9 hours (95 percent CI: 0.19, 1.99) (model 3), and the test for linear trend was statistically significant. This was also true when the prevalence of obesity was analysed as outcome, but not for the outcome overweight. Men sleeping 8 hours had the lowest BMI and lowest prevalence of obesity.

Table 1. Mean BMI difference and prevalence ratio of overweight and obesity vs. normal weight for each sleep duration category relative to those sleeping ≥9 hours: Zutphen Elderly Study, 1990.

		Sleep duration (hours/night)							
		≤6		*7*		*8*		*≥9*	*P for trend*[b]
		Mean	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	
Model 1[a] (n = 408)		0.75	-0.27, 1.78	0.85	-0.06, 1.76	0.61	-0.22, 1.44	0.00	0.12
Model 2[a] (n = 408)		0.83	-0.19, 1.85	0.79	-0.19, 1.69	0.59	-0.24, 1.41	0.00	0.10
Model 3[a] (n = 400)		0.93	-0.09, 1.94	1.09	0.19, 1.99	0.77	-0.05, 1.59	0.00	0.05
		PR[c]	95% CI	PR[c]	95% CI	PR[c]	95% CI	PR[c]	
Model 1[a]	OW[c]	0.88	0.58, 1.35	1.18	0.85, 1.66	1.27	0.93, 1.72	1.00	0.42
	OB[c]	2.23	0.81, 6.16	1.06	0.36, 3.09	0.38	0.21, 1.82	1.00	0.05
Model 2[a]	OW[c]	0.92	0.60, 1.40	1.16	0.83, 1.61	2.10	0.92, 1.70	1.00	0.50
	OB[c]	2.25	0.81, 6.24	1.05	0.36, 3.09	0.62	0.21, 1.82	1.00	0.05
Model 3[a]	OW[c]	0.90	0.58, 1.39	1.22	0.87, 1.71	1.27	0.94, 1.73	1.00	0.54
	OB[c]	2.32	0.73, 7.38	1.23	0.35, 4.33	0.62	0.17, 2.27	1.00	0.04

[a] Model 1: crude model; model 2: adjusted for age; addition to model 3 (fully adjusted model): adjustment for diabetes, energy intake, high intensity of physical activity (tertiles) and medium intensity of physical activity (quartiles).
[b] The *P* for trend refers to a linear trend in regression coefficients across increasing categories of sleep duration by treating the median of each category as a categorical variable.
[c] OW: prevalence ratio (PR) of overweight; OB: prevalence ratio (PR) of obesity.

We tested for effect modification by age and chronic diseases (Table 2). Men who were >74 years of age had a significantly higher BMI when sleeping 7 or 8 hours and a borderline significantly higher BMI when sleeping ≤6 hours. Also men without chronic diseases who slept ≤6, 7 or 8 hours had a significant higher BMI than men who slept ≥9 hours. There was a linear trend indicating a higher prevalence of obesity with decreasing sleep duration among men >74 years of age (*P* for trend = 0.05), and among men without chronic diseases (*P* for trend = 0.05), and a borderline significant trend for men ≤74 years or age (*P* for trend =

0.08). However, since the numbers of subjects in the subgroups were small, the prevalence ratio's itself were not significantly different from 1.

Table 2. Mean BMI difference and prevalence ratio of overweight and obesity vs. normal weight by age and presence of chronic diseases applied with model 3[a]: Zutphen Elderly Study, 1990.

		Sleep duration (hours/night)							
		≤6		*7*		*8*		*≥9*	*P for trend[b]*
		Mean	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	
≤74 years		0.29	-1.33, 1.92	0.52	-0.77, 1.81	-0.14	-1.33, 1.05	0.00	0.41
>74 years		1.34	-0.01, 2.70	1.62	0.34, 2.90	1.47	0.33, 2.61	0.00	0.06
CD[c]		0.10	-1.13, 1.33	0.58	-0.58, 1.71	0.23	-0.81, 1.27	0.00	0.67
No CD[c]		2.46	0.62, 4.31	1.79	0.26, 3.31	1.74	0.36, 3.12	0.00	0.02
		PR[d]	95% CI	PR[d]	95% CI	PR[d]	95% CI	PR[d]	
≤74 years	OW[d]	0.71	0.35, 1.45	1.30	0.85, 1.99	1.21	0.82, 1.80	1.00	0.64
	OB[d]	2.26	0.71, 7.20	0.69	0.16, 2.97	0.18	0.02, 1.39	1.00	0.08
>74 years	OW[d]	0.98	0.54, 1.77	1.20	0.72, 2.01	1.40	0.87, 2.26	1.00	0.63
	OB[d]	4.50	0.42, 48.66	2.79	0.20, 39.51	1.89	0.14, 25.49	1.00	0.05
CD[c]	OW[d]	0.88	0.51, 1.51	1.30	0.86, 1.98	1.28	0.86, 1.90	1.00	0.63
	OB[d]	1.13	0.36, 3.54	0.60	0.15, 2.43	0.30	0.07, 1.29	1.00	0.41
No CD[c]	OW[d]	1.09	0.52, 2.27	1.22	0.67, 2.21	1.35	0.79, 2.32	1.00	0.90
	OB[d]	5.80	0.68, 49.83	2.59	0.32, 21.13	1.65	0.21, 12.85	1.00	0.05

[a] Model 3: adjusted for age, diabetes, energy intake, high intensity of physical activity (tertiles) and medium intensity of physical activity (quartiles).
[b] The *P* for trend refers to a linear trend in regression coefficients across increasing categories of sleep duration by treating the median of each category as a categorical variable.
[c] Chronic Diseases (CD): baseline prevalence of angina pectoris, claudicatio intermittens, TIA, stroke, high blood pressure, diabetes, CARA, myocardial infarction, cancer, decompensatio cordis, rheumatism and osteoporosis.
[d] OW: prevalence ratio (PR) of overweight; OB: prevalence ratio (PR) of obesity.

From longitudinal analysis we found a weak inverse association between sleep duration and body weight change compared to our cross-sectional results, since men sleeping less lost weight. After classifying according to prevalence of chronic diseases, fewer sleep after five years was associated with weight loss among men with chronic diseases and was associated with weight gain among men without chronic diseases. However, these results were not statistically significant.

CONCLUSIONS

The results of the present study support earlier findings, which show that the relationship between sleep duration and BMI decreases with age. This study adds to the scientific evidence that this decreasing relationship with age may be explained by the higher prevalence of chronic diseases among elderly. More longitudinal and experimental research is needed to prove a cause-effect relationship between sleep duration and BMI. Also, the confounding affect of age and chronic diseases on longitudinal level should be studied in a larger population.

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THE USEFULNESS OF ACTIGRAPHY IN FORENSIC PSYCHIATRY

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INTRODUCTION

The Division of Forensic Psychiatry (GGZ Drenthe; DFP) treats people who suffer from one or more mental disorders and who have (nearly) committed an offence. The main treatment objective is to alleviate their mental disorder(s), thereby reducing the risk of recidivism. The DFP consists of a Forensic Psychiatric Hospital dealing with inpatient treatment and various forensic community outpatient services.
Many forensic psychiatric patients experience sleep problems due to a variety of factors. It is well established that various psychiatric disturbances, such as schizophrenia, depression, and post-traumatic stress disorders are associated with sleep disturbances[1]. The medications prescribed for mental health illnesses may elicit or exacerbate sleep disturbances[1]. A high percentage of our patients have a history of substance abuse. While drugs of abuse may induce sleep problems by themselves, drug withdrawal is also often associated with a disruption of sleep for longer periods of time[1]. Additionally, living within the structure and conditions of a prison and/or a forensic psychiatric hospital stimulates poor sleep habits, such as spending excessive amounts of time in bed and increasing non-sleep related behaviors in/on the bed[2].
Poor sleep is generally believed to be associated with emotional instability and has recently been shown to relate to increased overall aggression, impulsivity and hostility in young offenders[2]. Therefore, a correct diagnosis and effective treatment of sleep-wake disturbances may be of special importance in this patient population. In order to obtain an objective diagnosis for our patients, we started to employ actigraphy and found the results, often, highly informative. By means of two case studies we would like to illustrate the usefulness of actigraphy in Forensic Mental Health.

METHODS

For diagnostic reasons patients who complain about their sleep and/or daytime sleepiness are interviewed to obtain details concerning their sleep complaints, the history of the complaints, prior treatment, sleep habits, psychopathology, medication etc. In addition they complete a number of sleep questionnaires, including the Pittsburgh Sleep Quality Index[3] (PSQI) and the Slaap Diagnose Lijst[4] (SDL). During at least two weeks the patients complete a sleep diary and continuously wear an activity monitor (Cambridge Neurotechnology Ltd, Cambridge, UK) on the non-dominant wrist. This device counts the number of supra-threshold arm movements for each 1 min epoch. Actigraphy provides useful and reliable measures of sleep-wake organisation and sleep quality[5]. The actiwatch® Software from Cambridge Neurotechnology Ltd is used for data analysis and graphical presentation.

RESULTS AND DISCUSSION

Case example 1:
Patient A is a 21-year-old man with Aspergers disorder of the negative type, a history of cannabis abuse (in forced remission). Citalopram (20 mg/day) is prescribed. He has been admitted to our hospital for the last 18 months. His treatment progressed so well that he has been referred to the probation and parole services to be supported. He has already found a suitable job in the community. At this point his serious sleeping problem was identified by the investigator. Patient A usually goes to bed late at night, wakes up late in the morning and is unable to arise earlier. He was earlier investigated and assessed at a Sleep Disorders Center for similar symptoms. The treatment recommendations were to take melatonin (1 mg) at 20:00 hr to procure a phase advance, to adhere to strict bedtimes and to make sure that there is light in the morning (by opening curtains or putting on the lights). This is a common treatment strategy for Delayed Sleep Phase Syndrome (DSPS) and it was odd why it was not effective anymore. From the interview and sleep questionnaires patient A appeared to keep regular bedtimes (from 24:00 to 09:00 hr) and was satisfied with the quantity and quality of his sleep. However, actigraphy revealed actual bedtimes were rather irregular and much later than reported by the patient (Fig. 1), which was interpreted as a sign of DSPS. Confronted with these observations, the patient communicated that he recently started taking melatonin later at night, between 23 and 24 hr, because of the hypnotic effects he experiences by then.

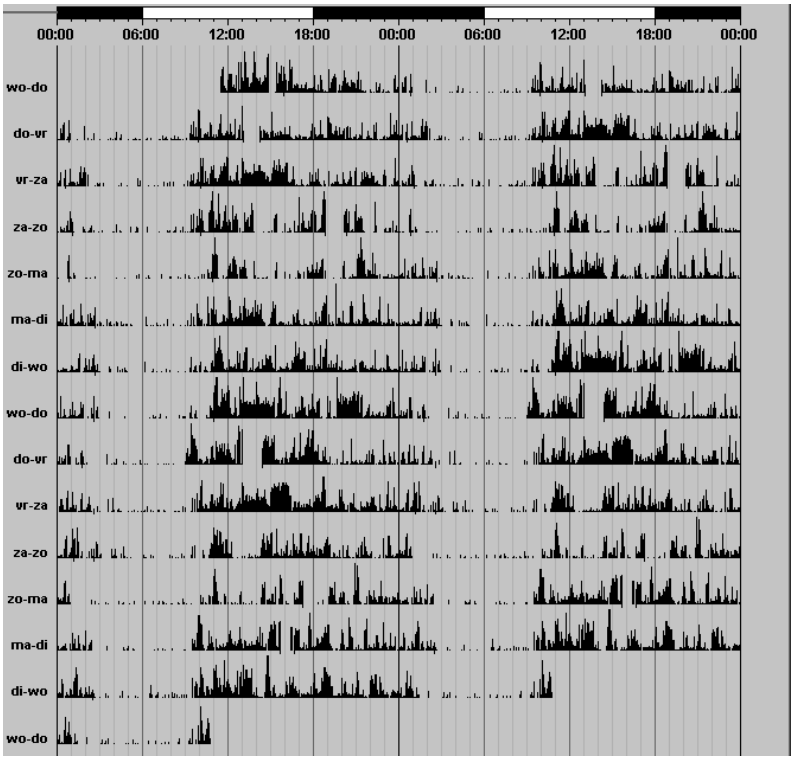

Figure 1. Double plotted actigraph (consecutive days next and beneath each other) of patient A, whose rest-activity pattern shows delayed rest and activity onsets. Horizontal line=time of day, vertical=days.

We explained to him that the time of melatonin intake is crucial in view of its phase advancing action. He then started taking melatonin regularly at 21:00 hr, which enabled him to go to bed earlier (on average from 01:43 to 00:30 hr, see Fig. 2), fall asleep earlier and to rise in time, as soon as he started working.

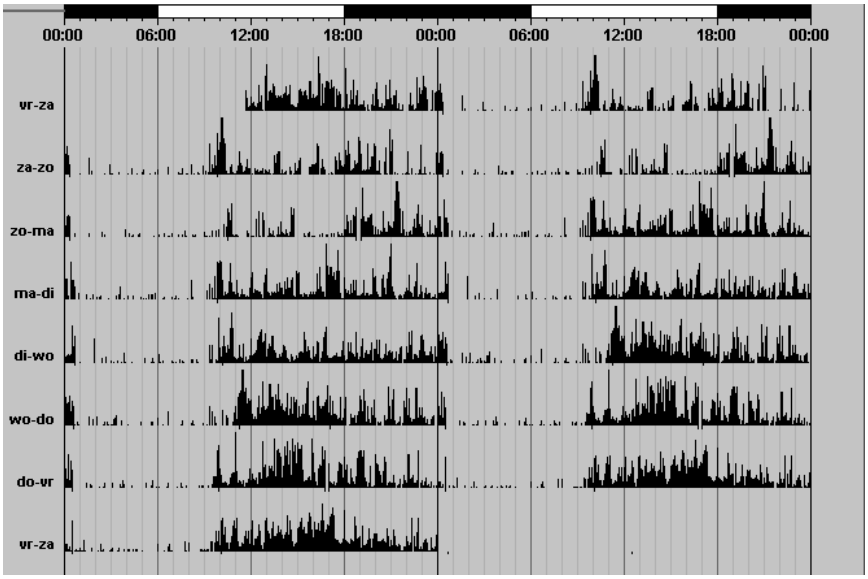

Figure 2. Double plotted actigraph of patient A after advancing the time of melatonin intake from 23:00-24:00 to 21:00 hr.

Case example 2:
Patient B is a single woman of 40 years with dissociative identity disorder, ADHD, borderline personality disorder and a history of poly-drug abuse. She resides in the community and receives comprehensive, individualized and long term care from our Forensic Assertive Community Treatment (For-ACT) team[6]. For medication she takes methylphenidate (3 x 80 mg/day), risperidone (20 mg/2 weeks, i.m.), levomepromazine (2 x 50 mg/day), oxazepam (3 x 25 mg/day) and venlafaxine (225 mg/day). She complains about sleep disturbances that are so severe that she is unable to function normally. The psychiatrist of the For-ACT team approached us with the request to investigate what her sleeping problems were. We did not meet her personally. The filled-in sleep questionnaires that we received revealed insomnia associated with major problems in trying to fall and stay asleep as well as high levels of daytime sleepiness. Furthermore, the sleep disturbances were related to her psychiatric problems. Actigraphy showed a highly irregular rest-activity pattern, with occasionally exceedingly long activity as well as rest phases most likely indicating the use of amphetamines. From these observations the psychiatrist concluded that his patient did not suffer primarily from a sleep disturbance, but from the disruptive impact of stimulant abuse (amphetamine, cocaine and excessive non-prescribed doses of methylphenidate) on her sleep and wake behavior.

CONCLUSIONS

In our experience actigraphy provides useful measures in forensic psychiatric populations, which often help in the diagnosis of sleep disorders and/or sleep-schedule disorders,

including assessment of effects of intervention, even though the reliability and validity of this methodology has not been studied in these populations.

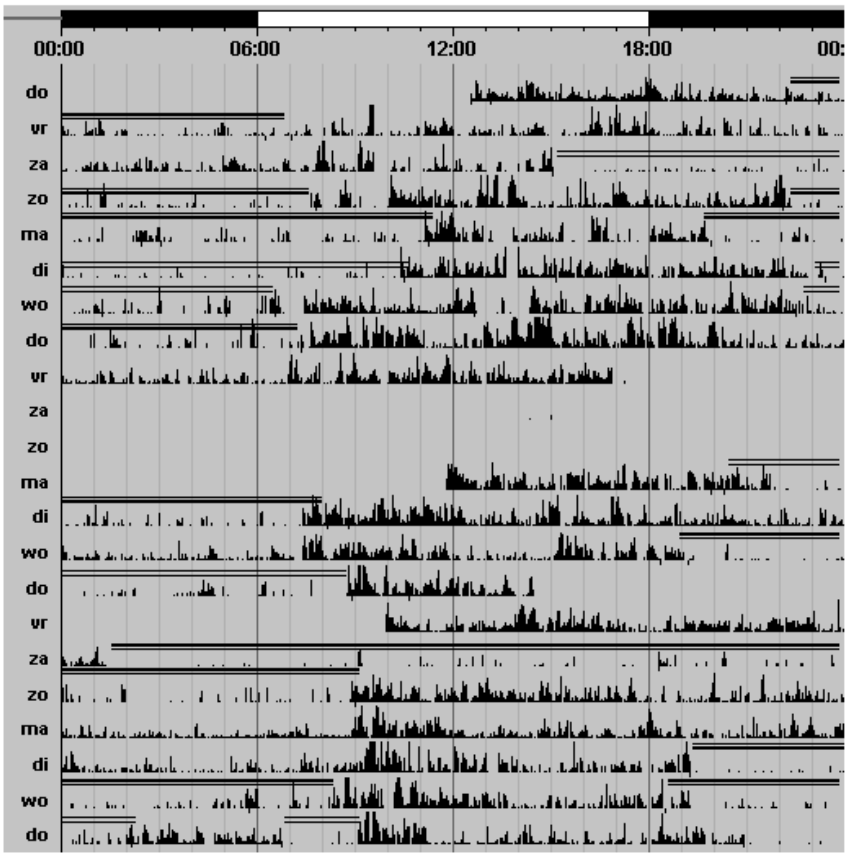

Figure 3. Actigraph of patient B, whose rest-activity pattern is very irregular and shows some exceptionally prolonged rest and activity periods. On some days data are missing, because wrist monitor was not used. Bars above the activity curves indicate times when the patient was in bed.

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RESIDUAL EFFECTS OF GABOXADOL ON HIGHWAY DRIVING AND COGNITIVE PERFORMANCE OF HEALTHY VOLUNTEERS

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INTRODUCTION

Residual sedation the morning after use of hypnotics is a major problem with respect to traffic safety. Gaboxadol is a GABA-agonist, binding primarily to benzodiazepine-insensitive extrasynaptic $\alpha_4\beta_3\delta$-, and $\alpha_6\beta_3\delta$-containing $GABA_A$ receptors, involved in tonic inhibition.[1-3] After oral doses it is rapidly absorbed and eliminated (half-life 1.5-2.0 hrs).[4] Clinical trials did not reveal residual effects on cognitive functioning of bedtime doses up to 20 mg.[5-11] The aim of the present study was to determine whether gaboxadol would have residual effects on car driving the morning after ingestion at bedtime or later in the night.

METHODS

Subjects

Twenty-five healthy subjects (13 males, 12 females) aged between 22-44 years completed the study.

Design and treatments

The study was conducted according to a double blind, 5-way crossover design. On treatment nights subjects ingested capsules twice; once before initiating sleep at 11 pm and again during brief awakening at 4 am. They arose at 7 am. Treatments were: placebo at both times, gaboxadol 15 mg or zopiclone 7.5 mg at 11 pm followed by placebo at 4 am, and placebo at 11 pm followed by gaboxadol 15 mg or zolpidem 10 mg at 4 am. Zopiclone and zolpidem were included as active controls to demonstrate sensitivity of the tests and procedures. Zopiclone 7.5 mg was selected as an active control for the bedtime dose of gaboxadol, because the former was repeatedly found to have moderate impairing effects on driving the morning after bedtime administration.[12,13] Zopiclone's effects on driving after middle of the night dose were severe, however.[12] Therefore, zolpidem 10 mg was selected as an active control for the middle of the night dose of gaboxadol, because its effects on driving were previously found to be significant, but much milder than those of zopiclone.[14]

Tests and procedures

Residual effects were assessed using a battery of laboratory tests, a highway driving test and subjective rating scales, all of which have been previously found sensitive to the residual effects of hypnotics[12-16] and low doses of alcohol.[13,17] The laboratory tests were chosen to measure residual drug effects on skills related to driving and were conducted between 7:30 and 8:15 am. The standardized highway driving test was performed from approximately 9 to

10 am, i.e. 10-11 hrs after evening ingestion of the medication or 5-6 hrs after middle-of-the-night ingestion.
In the Standardized Highway Driving Test[18] the subject operates a specially instrumented vehicle over a 100 km (61 mi) primary highway circuit, accompanied by a licensed driving instructor having access to dual controls. The subject's task is to maintain a constant speed of 95 km/h (58 mi/h) and a steady lateral position between the delineated boundaries of the slower traffic lane. The vehicle speed and lateral position are continuously recorded. These signals are edited off line to remove data recorded during overtaking maneuvers or disturbances caused by roadway or traffic situations. The remaining data are then used to calculate means and standard deviations of lateral position and speed. Standard deviation of lateral position (SDLP in centimeters) is the primary outcome variable. SDLP is a measure of road tracking error or "weaving". The test duration is approximately 1 hour.

RESULTS AND DISCUSSION

Results showed that evening doses of gaboxadol tended to increase SDLP but the effects were only marginally significant. In addition it had minor but significant effects on speed variability and performance in a divided attention test. In contrast, evening doses of zopiclone significantly impaired performance in every test, except tracking. Following middle-of-the-night doses, gaboxadol had significant effects on driving and psychomotor performance, but not memory. Performance after middle-of-the-night doses of zolpidem was impaired in every test.

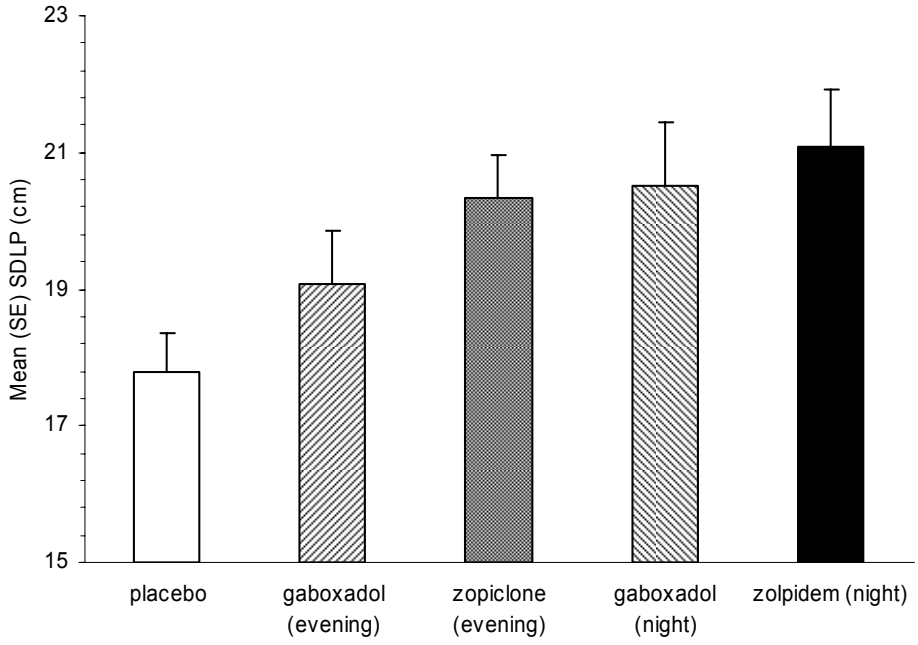

Figure 1. Mean ± SE SDLP in each treatment condition.

CONCLUSIONS

It was concluded that gaboxadol 15 mg can produce minor residual effects on driving between 10 and 11 hrs after evening administration. Sensitive individuals may occasionally experience impairment. Administration later at night is associated with moderately impairing residual effects on driving and psychomotor performance, but not on memory.

ACKNOWLEDGEMENTS

This study was financially supported by H. Lundbeck a/s, Copenhagen, Denmark. The authors like to thank Jesper Lund and Marjan Vontenie for initiating the study and their help in preparing the protocol and monitoring the study; and Henk Brauers and Willy Jeurissen for ensuring the safety of the subjects during driving; and Irma Brauers for the logistic work.

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LACK OF AGE DIFFERENCES IN RESIDUAL EFFECTS OF ZOPICLONE 7.5 MG ON MEMORY, ATTENTION AND PSYCHOMOTOR PERFORMANCE

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INTRODUCTION

The prevalence of insomnia increases with age close to 50% of persons older than 65 years. Parallel to this heightened prevalence, use of hypnotic drugs is increased as well in older patients.[1] Besides sleep enhancement, most hypnotics are known to impair next day cognitive and psychomotor functioning.[2] Experimental studies have shown that the duration and severity of these residual effects differ between hypnotics and depend on the dose used.[3,4] Moreover, some studies of age effects on the pharmacokinetics and pharmacodynamics of benzodiazepines have shown that elderly may respond more strongly, as a result of higher plasma concentrations, increased sensitivity or a combination of the two.[5-7] In contrast, other studies have not found significant differences between young and elderly in pharmacokinetics and performance effects of hypnotics.[8,9]
The objective of the present study was to compare the residual effects of a frequently prescribed hypnotic, zopiclone 7.5 mg, on memory, attention and motor performance between elderly and young healthy volunteers.

METHODS

Subjects
Eighteen healthy older volunteers (10 females; 8 males) with a mean age of 64.3 ± 1.0 years and 25 healthy younger volunteers (12 females; 13 males) with a mean age ± SE of 31.4 ± 1.5 years participated in the study.

Design and treatments
Both groups were treated with zopiclone 7.5 mg and placebo according to a double-blind, two-way crossover design. Treatments were administered in identical looking capsules and ingested immediately before retiring to bed at 23:00 hrs.

Tests and procedures
Residual effects on memory, attention and psychomotor functioning were assessed between 7:45 and 8:30 hrs, i.e. between 8:45 and 9:30 hrs after administration. Memory performance was measured using the 15 Word Learning Test[10], attention was assessed by the Divided Attention Task[11] and motor performance was assessed by means of the Critical Tracking Task[12].

RESULTS AND DISCUSSION

Memory performance

Overall analyses revealed that both immediate recall and delayed recall were significantly impaired following zopiclone administration in both groups ($F_{1,41}$=5.45, p<0.05; $F_{1,41}$=17.0, p<0.001, respectively). There were, however, no Age or Drug by Age effects for immediate (figure 1) and delayed recall.

Attention performance

Zopiclone impaired performance on the tracking subtask of the Divided Attention Task in both groups, as revealed by a significant overall effect ($F_{1,41}$=14.61, p<0.001). No effect of Age or Drug by Age were found (figure 2).

The target detection subtask of the Divided Attention Task was significantly impaired in both groups after zopiclone intake as was shown by an increased reaction time ($F_{1,41}$=5.32, p<0.05). There were no differences in performance between the two groups. In addition, no interaction effect was revealed (figure 3).

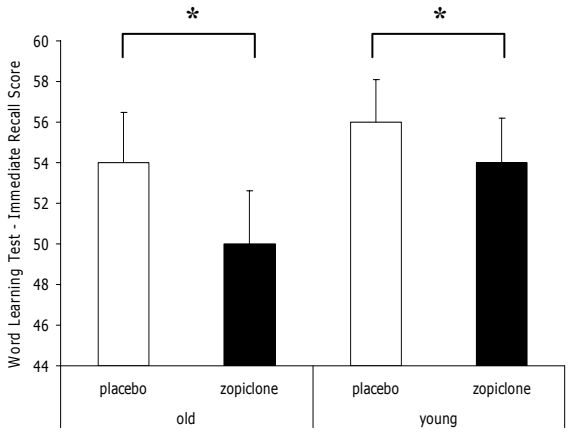

Figure 1. Mean ± SE Immediate Recall Score at 8:45 hrs after administration (* p<0.05).

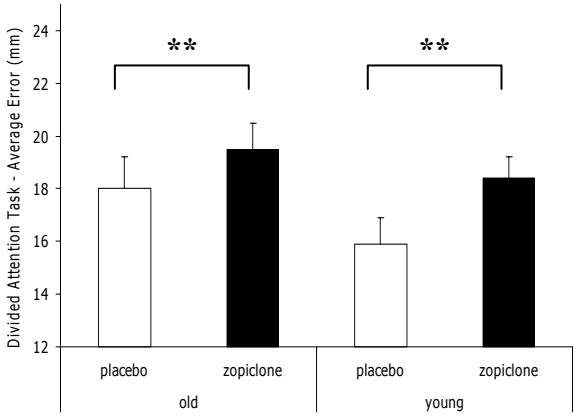

Figure 2. Mean ± SE Average Error (in mm) at 8:45 hrs after administration (** p<0.001).

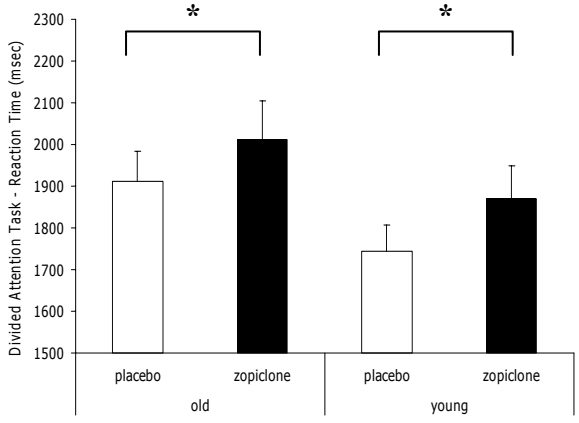

Figure 3. Mean ± SE Reaction time (in ms) at 8:45 after administration (* p<0.05).

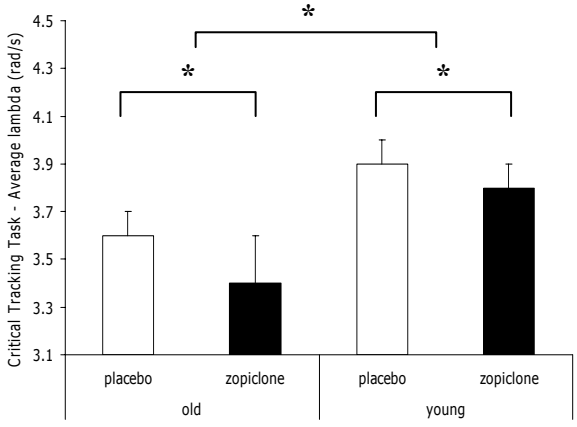

Figure 4. Mean ± SE Average lambda (in rad/sec) at 8:45 after admin. (* p<0.05)

Motor performance

Zopiclone significantly impaired tracking performance, as assessed by the Critical Tracking Task (overall effect: $F_{1,41}=5.56$, $p<0.05$). In addition, the older subjects performed overall significantly worse than the younger subjects ($F_{1,41}=4.33$, $p<0.001$). Yet, there was no interaction effect between Age and Drug (figure 4).

CONCLUSIONS

Zopiclone 7.5 mg significantly impairs memory and psychomotor performance the next morning between 8:45 and 9:30 hours after evening administration in both younger and older volunteers. Results of the present study do not show an increased sensitivity to the residual effects of zopiclone 7.5 mg in healthy elderly individuals.

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INTER-INDIVIDUAL DIFFERENCES IN PERFORMANCE ON A LETTER VERBAL FLUENCY TASK DURING SLEEP DEPRIVATION

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INTRODUCTION

Trait-like inter-individual differences have been observed in several aspects of cognitive performance during sleep deprivation.[1] The expression of these inter-individual differences varies across tasks.[1] Thus far, no systematic research has been reported on inter-individual differences during sleep deprivation on executive function tasks. We explored this issue through a Letter Verbal Fluency (LVF) task, which measures phonemic fluency, and is thought to reflect the executive function of divergent thinking.[2]

The LVF task is of particular interest because laboratory studies have documented inconsistent findings for the group-average effects of sleep deprivation on LVF performance, with results ranging from impairment[3] to no effect[4] and even improvement[5] in the primary outcome variable, i.e., number of words generated. An explanation for these mixed findings could be that the studies at hand, which had small to moderate sample sizes, may have been confounded by large inter-individual differences. We therefore specifically investigated the inter-individual differences in LVF performance as observed during a laboratory sleep deprivation experiment.[5]

METHODS

As part of a larger study, 12 carefully screened, healthy adults (ages 22–37, 5 females) spent six nights and seven days in a controlled laboratory environment. Subjects were allowed to sleep the first two nights and the last two nights, while they stayed awake during the intervening third and fourth nights for a total of 62 hours of sleep deprivation.

All subjects completed three iterations of a cognitive test battery, which, among other tasks, contained the LVF task. The test battery was completed after the second night (at baseline), after the fourth night (during sleep deprivation), and after the sixth night (post-recovery). When the test battery after the fourth night was taken, subjects had been awake for 51 hours. The clock time of test administration was fixed at 11:00 to keep circadian influences constant.

In each trial of the LVF task, subjects were asked to name as many words as they could in a one-minute period, starting with a specific letter. Each LVF test session consisted of three trials with different start letters. Three equivalent versions of the task,[6] involving alternative sets of start letters, were administered in randomized order across the three test sessions. The first trial of each LVF test session was considered a practice trial and was omitted from the analyses.

The number of words generated and the number of switches between phonemic clusters were extracted as measures of task performance. Although number of words generated is typically used as the primary outcome variable, switches between phonemic clusters are believed to be a purer measure of executive functioning.[7] Therefore, we considered both variables.

For the analysis of inter-individual differences in executive functioning, the data from the baseline, sleep deprivation and recovery sessions were first analyzed separately. We applied mixed-effects ANOVAs across the second and third start letters to separate within-subjects variance from between-subjects variance, controlling for task version. The intra-class correlation coefficient (ICC)[8] was calculated, as the ratio of the between-subjects variance to the total variance, to evaluate systematic inter-individual differences.

If significant systematic inter-individual differences were observed, the data from the second and third start letter in each session where averaged within subjects. Correlations among subjects between performance during sleep deprivation and performance at baseline were then calculated to assess whether the inter-individual differences at baseline predicted responses during sleep deprivation. Correlations between performance during sleep deprivation and performance after recovery were also calculated.

RESULTS AND DISCUSSION

Significant inter-individual differences were found for the number of words generated on the LVF task at baseline ($Z=1.92$, $P=0.027$) and after recovery ($Z=1.90$, $P=0.029$), and a trend was observed during sleep deprivation ($Z=1.50$, $P=0.067$). Figure 1 (left) shows the between-subjects variance in each of the three test sessions. The ICC was 0.84 at baseline, 0.58 during sleep deprivation, and 0.91 after recovery, indicating that systematic inter-individual differences in number of words explained more than 50% of the variance in all phases of the study.

Significant inter-individual differences were also found for the number of switches between phonemic clusters on the LVF task during sleep deprivation ($Z=1.74$, $P=0.041$), and trends were observed at baseline ($Z=1.60$, $P=0.054$) and after recovery ($Z=1.41$, $P=0.079$). Figure 1 (right) shows the between-subjects variance in the three test sessions. The ICC was 0.63 at baseline, 0.71 during sleep deprivation, and 0.58 after recovery, indicating that for number of switches, systematic inter-individual differences were able to explain more than 50% of the variance in all phases of the study as well.

The range of the systematic inter-individual differences for number of words was 11.4 at baseline, 7.2 during sleep deprivation, and 8.6 after recovery. Considering that the overall range in responses was 22, these inter-individual differences may be considered substantial. The range of the systematic inter-individual differences for number of switches was 6.6 at baseline, 5.8 during sleep deprivation and 5.1 after recovery. As the overall range in number of switches was 14, the systematic inter-individual differences in switches may also be considered substantial. Inter-individual differences were largest at baseline (see Figure 1)—a practice effect reduced the difference between the poorest performers and the best performers in the later sessions.

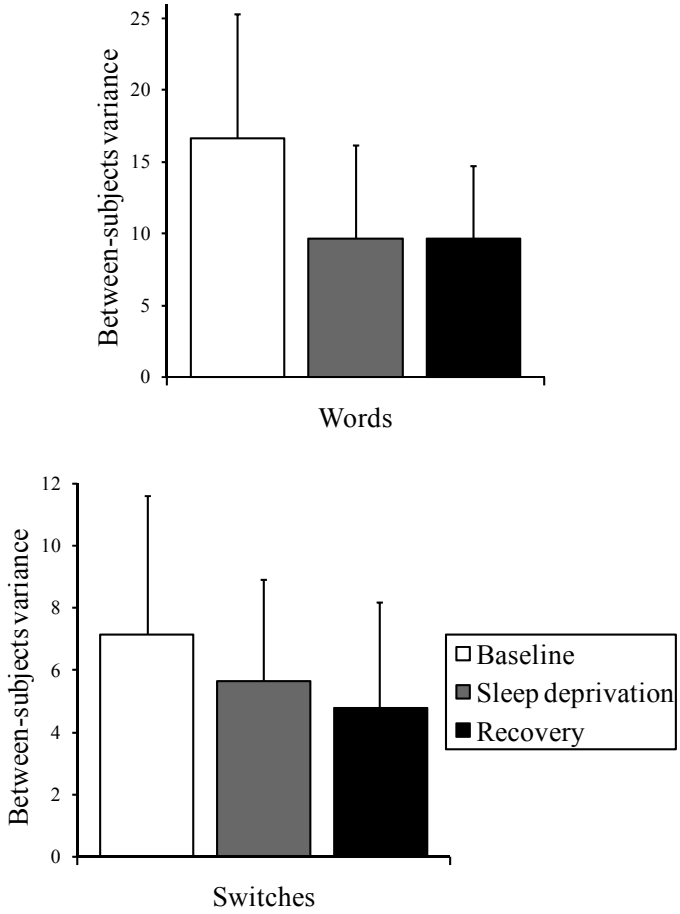

Figure 1. Magnitude (with standard error) of between-subjects variance for number of words generated (left panel) and number of switches made between phonemic clusters (right panel) on a LVF task.

There were relatively strong correlations for number of words generated during sleep deprivation with performance at baseline ($r=0.72$, $P<0.001$) and with performance after recovery ($r=0.84$, $P<0.001$). This indicates that the inter-individual differences during sleep deprivation were in large part predictable by inter-individual differences in performance when rested.

There was a more moderate correlation for number of switches made during sleep deprivation with performance at baseline ($r=0.49$, $P=0.01$), while the correlation with performance after recovery was not significant ($r=0.06$, $P=0.76$). This implies that for the number of switches between phonemic clusters, the inter-individual differences during sleep deprivation could not be predicted well by performance when rested.

CONCLUSIONS

Substantial inter-individual differences were observed for number of words generated and for number of switches made between phonemic clusters in the LVF task after 51 hours of total sleep deprivation. This suggests that there were systematic inter-individual differences in executive functioning during sleep deprivation. Inter-individual differences were also observed at baseline and after recovery. The inter-individual differences in number of words generated during sleep deprivation could be explained in large part by the differences in

rested performance at baseline and after recovery. However, the inter-individual differences in number of switches made between phonemic clusters during sleep deprivation were not readily explained by the differences in performance in the rested state.

The finding that inter-individual differences in number of words generated on the LVF task are preserved across rested and sleep-deprived states implies that the group-average performance responses across sessions are representative of the response trajectories within the individual subjects. As such, main effects and interactions in mixed-effects ANOVA and regression analyses performed on LVF number of words outcomes are not likely to be confounded by inter-individual differences. Low statistical power may be an issue because of inter-individual differences if traditional (non-mixed-effects) ANOVAs and regression techniques are used.[8] Nevertheless, the present findings imply that the inconsistencies in the results among studies for the group-average effects of sleep deprivation on number of words generated in the LVF task[3–5] cannot likely be accounted for merely by confounding influences from inter-individual differences.

Our observation that inter-individual differences in number of words generated in sleep-deprived LVF performance are predicted by differences in performance when rested contrasts with earlier findings in a study of performance on less complex cognitive tasks during sleep deprivation,[1] as well as with the present result for switches between phonemic clusters in the LVF task. In these cases, baseline performance explained only a minor portion of the between-subjects variance observed during sleep deprivation. It has recently been reported that inter-individual differences in baseline executive functioning are genetically determined.[9] Whether or not such baseline inter-individual differences in performance are preserved during sleep deprivation, however, appears to depend not only on the nature of the cognitive performance task at hand, but also on the specific outcome measure used.

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SYSTEMATIC INTER-INDIVIDUAL DIFFERENCES IN POLYSOMNOGRAPHIC SLEEP VARIABLES

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INTRODUCTION

Several studies[1–4] have reported inter-individual differences in the sleep physiology of healthy young adults as measured by means of nocturnal polysomnography (PSG). In a recent study involving repeated exposure to 36 hours of sleep deprivation, these inter-individual differences in sleep variables were shown to be stable across sleep periods and preserved from baseline to recovery sleep.[4] In the present study, we examined the stability and robustness of inter-individual differences in nocturnal PSG sleep variables in a study design involving 62 hours of total sleep deprivation.

METHODS

As part of a larger study, 23 carefully screened, healthy adults (ages 22–38, 11 females) spent six nights and seven days in a controlled laboratory environment. Subjects were randomized to a sleep deprivation condition (n=12) or a control condition (n=11). Subjects in the sleep deprivation condition were allowed to sleep the first two nights (baseline) and the last two nights (recovery). They stayed awake during the intervening third and fourth nights for a total of 62 hours of sleep deprivation. Subjects in the control condition were allowed to sleep all six nights. Sleep periods involved 10 hours time in bed between 22:00 and 08:00.

All sleep periods were polysomnographically recorded (Nihon Kohden digital equipment). The recordings included frontal (Fz), central (C3, C4) and occipital (Oz) electroencephalography (EEG) derivations referenced against M1/M2, bilateral electrooculography (EOG), submental electromyography (EMG), and electrocardiography (ECG). PSG recordings were manually scored using the criteria of the American Academy of Sleep Medicine (AASM)[5] to assess the durations of the various sleep stages and their latencies.

The following sleep variables were extracted from the PSG records: total sleep time, sleep efficiency, duration of the non-REM sleep stages N1, N2 and N3, duration of REM, wake after sleep onset (WASO), sleep latency (time from lights out to any sleep stage), latency to N2 and N3, REM latency, number of non-REM/REM sleep cycles, and transition index (average number of sleep stage transitions per hour). Stage N3 incorporates stages S3 and S4 as defined by the criteria of Rechtschaffen and Kales[6] and is also known as slow wave sleep. In order to remain compatible with our earlier study,[4] for WASO we counted only wakefulness between sleep onset and final awakening, thereby deviating from the AASM definition of WASO[5] (which incorporates all wakefulness from sleep onset until lights on).

For the analysis of trait-like inter-individual differences in sleep variables, mixed-effects ANOVAs—in which we controlled for the expected condition by night interaction—were used to separate the within-subjects variance across repeated recordings from the systematic between-subjects variance. To evaluate inter-individual differences, the intraclass correlation

coefficient (ICC) was calculated as the ratio of the between-subjects variance to the sum of the between- and within-subjects variances.[7]
A principal components analysis of the raw data was performed to see which variables clustered together and to reduce the dimensionality of the data set. Only the data of sleep variables with a significant ICC were used for this analysis. The number of dimensions was determined by inspection of the scree plot. A varimax rotation was performed to facilitate the interpretation of the dimensions. Because of the relatively small sample size, only sleep variables with a minimum absolute loading of 0.6 were used for interpretation.

RESULTS AND DISCUSSION

Statistically significant ICC values were found for 11 of the 13 PSG sleep variables—see table 1. ICC values ranged from 0.21 to 0.76. Thus, among most of the sleep variables, a modest to substantial portion of the overall variance was explained by systematic between-subjects variability. The highest value was observed for stage N3 (slow wave sleep).

Table 1. Intraclass correlation coefficients for systematic inter-individual differences in sleep variables.

Sleep variable	*ICC*	*P-value*
Total sleep time	0.21	0.050
Sleep efficiency	0.23	0.048
Stage N1	0.64	0.002
Stage N2	0.38	0.012
Stage N3	0.76	0.001
REM sleep	0.45	0.007
Wake after sleep onset	-	0.10
Sleep latency	0.42	0.008
Latency to N2	0.42	0.008
Latency to N3	0.46	0.007
REM latency	-	0.09
Non-REM/REM cycles	0.30	0.022
Transition index	0.67	0.002

Principal components analysis suggested the data clustered in 3 dimensions—see table 2. Dimension 1 explained 37.5% of the overall variance in the dataset and had high loadings for the variables total sleep time, sleep efficiency, sleep latency (negative loading), and latency to N2 (negative loading). These variables all seemed to be related to the duration of sleep. Dimension 2 explained 23.9% of the overall variance and had high loadings for latency to N3, and the durations of stages N1, N2 and N3 (N3 with negative loading). These variables seemed to be associated with sleep intensity—a long latency to N3, and long durations of N1 and N2 affect the amount of N3 negatively. Dimension 3 explained 12.5% of the overall variance and had high loadings for non-REM/REM cycles and the transition index. This dimension seemed to primarily reflect transitions between sleep stages. REM sleep duration did not load substantially on any of the dimensions, but loaded modestly on all three dimensions.

Table 2. Results of principal components analysis. Factor loadings ≥ 0.6 or ≤ −0.6 (underlined) were used for interpretation.

Sleep variable	*Dimension 1*	*Dimension 2*	*Dimension 3*
Total sleep time	0.94	−0.09	0.06
Sleep efficiency	0.94	−0.09	−0.06
Sleep latency	−0.83	−0.02	−0.00
Latency to N2	−0.83	0.04	0.01
Latency to N3	−0.06	0.88	−0.03
Stage N1	−0.06	0.69	0.45
Stage N2	0.53	0.60	−0.01
Stage N3	0.18	−0.88	0.05
Non-REM/REM cycles	0.41	−0.28	0.71
Transition index	−0.53	0.21	0.67
REM sleep	0.45	−0.32	−0.45

CONCLUSIONS

Modest to substantial degrees of systematic inter-individual variability were found on 11 out of 13 PSG-assessed sleep variables. Replicating our previous finding,[4] we observed systematic inter-individual variability for total sleep time, sleep efficiency, duration of stages N1, N2 and N3, duration of REM, sleep latency, latency to stages N2 and N3, number of non-REM/REM cycles, and the transition index. In addition, we found systematic inter-individual differences in the latency to stage N3, which was not seen in our previous study.[4] Systematic inter-individual differences in WASO and REM latency did not reach statistical significance. Nevertheless, the combined evidence of the present study and our previous study suggests that systematic inter-individual differences play an important role in the sleep structure of healthy adults.

A principal components analysis suggested that sleep variables clustered in three independent dimensions, which appeared to reflect the duration of sleep, sleep intensity, and stage transitions. This in part replicates previous results, with sleep duration and sleep intensity emerging as independent dimensions in our earlier study as well.[4] The third dimension in the earlier study was believed to reflect discontinuity, which is related but not identical to the present third dimension. In both studies the transition index loaded on the third dimension; but in the present study non-REM/REM cycles also loaded on this dimension, while the previous study found loadings for movement time (excluded by AASM scoring rules[5] and therefore not used here), S1 (named N1 using AASM scoring rules[5]), and REM sleep.

Taken together, our findings in the present study and in our previous study[4] indicate that across nocturnal baseline sleep and nocturnal recovery sleep following total sleep deprivation, inter-individual differences in PSG-assessed sleep variables are modestly-to-highly stable and robust. With regard to these inter-individual differences, the sleep variables cluster into independent dimensions of sleep duration and sleep intensity, and a third dimension that requires further investigation.

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SYMPTOM SEVERITY IN RELATION TO NOCTURNAL MOTOR ACTIVITY IN ADULT ADHD AND TOURETTE'S SYNDROME

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INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) and Tourette's Syndrome (TS) are comorbid neuropsychiatric disorders that frequently present with sleep problems, particularly problems with initiating and maintaining sleep[1,2]. Since disturbances in sleep may be reflected in the appearance and severity of daytime symptoms, and vice versa, they are of influence in the psychopathology of ADHD and TS.
Both ADHD and TS are characterized by a disinhibition and dysfunction in the regulation of motor functions. Yet, objective quantification of motor activity during sleep is scarce in adult patients, and adults with ADHD or TS have never been studied in relation to each other regarding behavioral parameters. Furthermore, comorbidity between both disorders is usually ignored.
In order to clarify if overt motor activity during sleep plays a role in the reported sleep disturbances and daytime severity of symptoms in adults with ADHD or TS, we performed a study in the habitual environment of adult patients with ADHD but without TS comorbidity, and adult TS patients without ADHD comorbidity. Motor activity was quantified by means of ambulatory accelerometry[3,4].
Previously, we reported on the increased nocturnal body motility in both disorders, as quantified by means of ambulatory accelerometry[5]. In this paper, we focus on the relationships between nocturnal behavior and daytime symptom severity.

METHODS

Participants: Fifteen adults with ADHD (6 males; mean age: 33.8 years, SD: 9.1; 3) and 17 with TS (14 males; mean age: 41.0 years, SD: 11.1) participated in an ambulatory study in their home environment. The diagnosis ADHD or TS was made by a senior psychiatrist based on the DSM-IV criteria, as assessed by means of the Structured Clinical Interview for DSM-IV axis I and II disorders (SCID-I and SCID-II). Specific exclusion criteria for the patients were: a) comorbidity of TS in ADHD patients or vice versa, b) neurological or physical disorders that could possibly influence motor activity, arousal or mood, c) pregnancy, and d) alcohol or drugs abuse or dependence in the last six months. All patients were drug-free at the time of the study.
Procedure: Ambulatory recordings of daily physical activities, in addition to keeping a daily log, were made during weekdays for a consecutive period of two days in the habitual environment of the subjects. The daily log included brief questionnaires regarding subjective sleep quality (SSQ; scoring range: 1 - 11)[6] to be filled in after waking up in the morning, and

severity of ADHD and TS symptoms, to be filled in at 13.00 hrs, 18.00 hrs, and before sleep. The subjects were instructed to perform their normal daily activities during the measurement period, to keep a regular sleep-wake pattern and to avoid abnormal physical and mental exertions. The motor activity parameters of the first sleep period were studied in relation to morning SSQ score and the clinical parameters of the previous and following day.

Clinical symptoms: ADHD symptoms: the DSM-IV criteria regarding ADHD hyperactivity/impulsivity symptoms were quantified by means of selected items of a Dutch self-report questionnaire for ADHD[7], which were filled in by both ADHD and TS patients. The items were rated on a 4-point scale (never/seldom, sometimes, frequent, highly frequent), and reflected the hyperactivity/impulsivity severity of the previous period (morning, afternoon, or evening). The item scores were summed per period (scoring range: 0-36); averaged values of the three periods were calculated. Motor Tics: for each period of the day (morning, afternoon, or evening), the patient filled in 3 items regarding presence and frequency of tics and impairment by tics. If tics did occur, frequency of tics was assessed on a 6-point scale: no tics, once per 45 minutes or less, once per 15-45 minutes, once per 5-14 minutes, once per 1-4 minutes, once per minute or more frequent (based on the 'Yale tic scale, interviewers version')[8]. General impairment by tics was assessed on a 5-point scale, ranging from minimal to severe impairment (based on item "G" from the 'Yale Global Tic Severity Scale')[8]. Frequency and impairment scores were averaged over the three daytime periods.

Accelerometry: Motor activity during the sleep was measured by five accelerometers. Three accelerometers were attached in the midline of the sternum in the sagittal, coronal, and transversal planes. Two accelerometers were attached at the lateral side of both upper legs in the coronal plane. The signals were recorded on a Vitaport2 ™ digital portable recorder, at a sample rate of 64 Hz, and were analyzed with a kinematic software package[3,4]. The following output measures were computed: Time in Bed (TIB; the period from lying down in bed until getting up from bed in the morning), static positions (proportion of TIB spent in the static postures lying, sitting and standing), lying position (proportion of TIB spent in lying back, lying side, lying prone), dynamic activities (proportion of TIB that was interrupted by performing dynamic activities such as walking and general non-specific movements), and transitions per hour (the number of transitions between lying positions, back, prone and side, per hour during TIB). In addition, for each accelerometer signal, the variability or 'acceleration energy' was computed as an index of motility, reflecting the overall level of physical activity during a specific measurement period. On the basis of these analyses, the following parameters were also studied: motility static positions (motility index of the time spent lying, sitting and standing during TIB), motility lying position (motility index of the time spent lying back, lying side, lying prone during TIB), and motility dynamic activities (motility index of the time spent walking and making general non-specific movements during TIB). The mean of the motility values of the trunk sensors was used to reflect total trunk motility. In addition, the motility index of static positions, lying position and dynamic activities was also computed for the legs, as the mean motility value of the two leg sensors.

Statistical analyses: Differences between ADHD and TS patients regarding daytime self-reported hyperactivity/impulsivity severity were evaluated by means of T-tests. Correlations between self-report scores of sleep quality and severity of symptoms within a patient group were analyzed by means of linear regression analyses with gender and age entered as covariates.

RESULTS

Daytime Symptom Severity: As expected, the ADHD patients scored significantly higher regarding self-reported daytime hyperactivity/impulsivity scores during both the previous and following day, in comparison with the TS patients ($t=2.5$, $p=.02$, and $t=2.2$, $p<.05$, respectively), and tics were absent in the ADHD patients (table 1).

Table 1. The Mean (SD) values of the activity and tics severity scores during the previous and following day, as well as relevant motor activity parameters, for the ADHD and TS group separately.

		ADHD *Mean (SD)*	*TS* *Mean (SD)*
Clinical severity			
Activity score	previous day	10.4 (6.8)	5.3 (4.4)
	following day	8.6 (6.6)	4.6 (4.0)
Impairment Tics	previous day		1.4 (1.2)
	following day		1.6 (1.3)
Frequency of Tics	previous day		3.2 (1.6)
	following day		2.9 (1.9)
Subjective Sleep Quality score		6.6 (2.7)	6.9 (3.2)
Motor activity			
Lying position (%)		99.4 (0.4)	97.8 (2.9)
Dynamic activities (%)		0.5 (0.2)	0.7 (0.6)
Transitions while lying (n/hr)		2.4 (1.0)	1.4 (1.0)
Leg motility lying position (a.u.)		2.1 (0.29)	2.1 (0.59)

ns: non significant; a.u.: arbitrary units; n/hr: number per hour

Nighttime motor activity in relation to subjective sleep quality and daytime symptom severity:
ADHD: Only a trend-effect was observed: self-reported severity of hyperactivity symptoms of the previous day was positively correlated with the nighttime leg motility during lying postures ($\beta=0.46$, $p=0.08$).
TS: Self-reported tic frequency during the previous day as well as the following day was negatively correlated with TIB ($\beta=-0.60$, $p<.05$ and $\beta=-0.50$, $p=0.07$, respectively) and was negatively correlated with the number of transitions from one to another lying position ($\beta=-0.51$, $p=0.05$ and $\beta=-0.43$, $p=0.08$, for the previous and the following day, respectively). In addition, the SSQ scores correlated positively with the time spent in the lying posture ($\beta=0.61$, $p=0.02$) and negatively with the time spent doing dynamic activities at night ($\beta=-0.49$, $p=0.08$). Self-reported severity of hyperactivity symptoms during the following day correlated negatively with the percentage of time spent in the lying position during the night ($\beta=-0.73$, $p<.01$).

DISCUSSION AND CONCLUSION

Sleep disturbances may be reflected in the appearance and severity of daytime symptoms, and vice versa. In order to clarify if nocturnal motor activity in ADHD and TS is related to symptom severity during the previous and following day, we conducted an ambulatory study

in the natural environment of the patients. Special attention was paid to comorbid conditions of ADHD and TS. Our findings show different results for ADHD and TS patients.
For the ADHD patients, only one positive trend effect was observed: increasing severity of hyperactivity complaints of the previous day correlated with higher nocturnal leg motility/restlessness. Several studies have reported that sleep disruption associated with primary sleep disorders such as Restless Leg Syndrome or Periodic Limb Movements in Sleep may mimic daytime symptoms of ADHD[9,10]. Our findings underline the need to further clarify nocturnal restlessness and daytime complaints in ADHD in relation to these sleep disorders.
In TS patients, we found no relationships with nocturnal motility, but with behavioral parameters not reflecting motor tics. More daytime tics correlated with reduced TIB and less postural transitions while lying; higher subjective sleep quality correlated with increased percentage of time spent in the lying position and subsequently correlated negatively with percentage of time spent doing dynamic activities. In addition, increased severity of daytime hyperactivity correlated with reduced percentage of time spent in the lying position. The fact that we did not separately quantify presence of nocturnal motor tics may have contributed to the lack of a relationship between daytime symptom severity and nocturnal motility.
Our findings illustrate that it is essential to control for comorbid conditions regarding TS and ADHD in order to fully understand the relationships between daytime functioning and nocturnal sleep complaints. We conclude that daytime symptom severity is related to nighttime behavioral parameters in adults with ADHD, but more so in adults with TS, underlining the relevance of objective quantification of motor activity during sleep.

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THE IMPACT OF LUMINANCE AND COLOUR ON PSYCHOMOTOR VIGILANCE AND WELL-BEING

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INTRODUCTION

It has been known for some time that ambient illumination affects the vigilant state. [1-3] Nonetheless, lighting conditions in most buildings are often inadequate with regard to the biological need of light.[4] Most studies have focused on exposure to different levels of luminance. Some studies have shown that exposure to high luminance levels during daytime improves vigor, performance, and alertness. In a study by Phipps-Nelson et al.[5], conducted under constant routine conditions, the negative impact of sleepiness on performance was weakened when subjects were exposed to bright light (1000 lux at eye level) relative to dim light conditions (<5 lux at eye level). This was confirmed by Rüger et al.[6] who exposed subjects to 5000 lux during daytime and reported a reduction in daytime sleepiness and fatigue as compared to dim light exposure (<10 lux). Yet, other studies are more skeptical about the beneficial direct effects of bright light on daytime performance. These studies propose the suppression of melatonin secretion during nighttime after bright light exposure as being the key mechanism in enhancing daytime performance.[7,8] Thus, it remains unclear whether luminance level can positively affect the attentional state during daytime.
Little is known about the acute daytime impact of colour lighting on the attentional state. Chronobiological research has shown some alerting effects of monochromatic light during nighttime. In a study by Cajochen et al.[9] subjects were exposed to two hours of either monochromatic light at 450 nm ("blue light"), monochromatic light at 550 nm ("green/yellow light"), or no light while under strictly controlled conditions. The results showed that short wavelength light was more effective in suppressing sleepiness than the longer wavelength light. These findings are in agreement with a study by Gordijn et al.[10] who showed relatively more suppression of melatonin and sleepiness when subjects were exposed for six hours to blue light (460 nm) as compared to red light (620 nm) during nighttime. Yet, a study by Lavoie et al.[11] did not find any effects of bright white light (3000 lux) as compared to dim red light (<15 lux) on alertness and vigilance during nighttime. Blue light with a sufficient luminance level is thus expected to be beneficial as compared to colours without a blue component. Daytime studies on the impact of colour light on the attentional state are virtually non-existent. In the present exploratory study it was attempted to determine the potential facilitatory effect of colour lighting with two different luminance levels on attentional state.

METHODS

Subjects
Thirty-seven healthy students from the TU Delft (19 male, 18 female; age 21.3 ± 2.6 [SD] years, range 17-27 years) were included in this study. Participants with a personal or family history of psychopathology and/or cardiovascular disorders were excluded from the study.

All participants were paid for participation, and were required to give written consent. The study was approved by the Ethics Committee of the TU Delft.

Lighting

For the present experiment two LED bars (LED Pixel Track MKII, Showtec Inc., USA) were included. Light of the LED bars was emitted on a reflective screen providing a bright area of app. 0.9mx0.7m (h.x w.) on a surface of app. 1.4mx1.1m (Figure 1). Although the luminance levels discussed in the Introduction section are rather extreme for practical use, some studies have suggested that it is possible to affect nonvisual processes under typical ambient lighting conditions, i.e. 100-180 lux at eye level.[12,13] In the present study, the low luminance group received app. 45 lux in the direction of gaze, while the high luminance group received app. 195 lux. Light levels were measured with an Elvos LM-1010 photometer. For practical purposes, participants were randomly exposed to four different Red-Green-Blue (RGB) lighting combinations: RG, RB, GB, and RGB. At all times during the experiment a fluorescent bar (white light) fixed in an overhead luminaire was turned on (app. 20 lux).

Figure 1. Setup of the experiment.

Performance & Questionnaires

Vigilance was assessed using a 7 minute vigilance detection task, requiring both sustained attention and high-rate responses.[14] Colour perception was measured by means of 3 items (stimulating, potent, vivid) on a 7-point Likert scale. Four well-being parameters were assessed (fatigue, sleepiness, boredom, motivation) on a five-point Likert scale (1=very little–5=very much). Perceived arousal and valence were measured with a computerized version of the self-assessment manikin (SAM).[15]

Experimental Procedures

The study was conducted at the Studio Home/Office laboratory of the TU Delft, Department of Industrial Design Engineering. Upon arrival in the laboratory the subject engaged in a 10-min adaptation period. Next, they commenced with a 5-min baseline measurement while sitting quietly in front of the computer screen in an upright position (in 20 lux white light), after which they had to fill out three short questionnaires (well-being, perception, SAM). This was followed by the first 12-min test bout, consisting of a dual task (5min, not reported) and the vigilance task (7min). Finally, the individuals were allowed a 5-min rest period. The results for the dual task and rest are not described in this paper. The participants were assigned randomly to a low luminance or a high luminance condition, and exposed to all colour combinations. Measurements were taken during daytime between 09:00 – 19:00h.

Analyses

Individual baseline values were subtracted from values obtained during the experimental protocol. All parameters were subjected to mixed-model analysis of variance (mmANOVA) to test for effects across colours and luminance level, with Colour (4 levels) and Group (2 levels) set as fixed effects, and Participants set as a random effect. A fixed Intercept effect was included to test against baseline. Planned contrasts (t-tests) were implemented to detect differences on a specific level. SPSS 14.0 (SPSS Inc., Chicago, Illinois) was used for statistical testing and significance level was set at 0.05.

RESULTS AND DISCUSSION

Overall, the mmANOVAs showed no effects of lighting on vigilance performance (see Table 1). Significant interaction effects were found in most of the well-being parameters, and are depicted in Figure 1. The graphs show a more negative effect of lighting in the high luminance group, in particular when exposed to RB and GB colour combinations. Colour perception was somewhat affected by colour lighting, but not by luminance level, with higher values for the RG and RB colour combinations as compared to GB and RGB combinations.

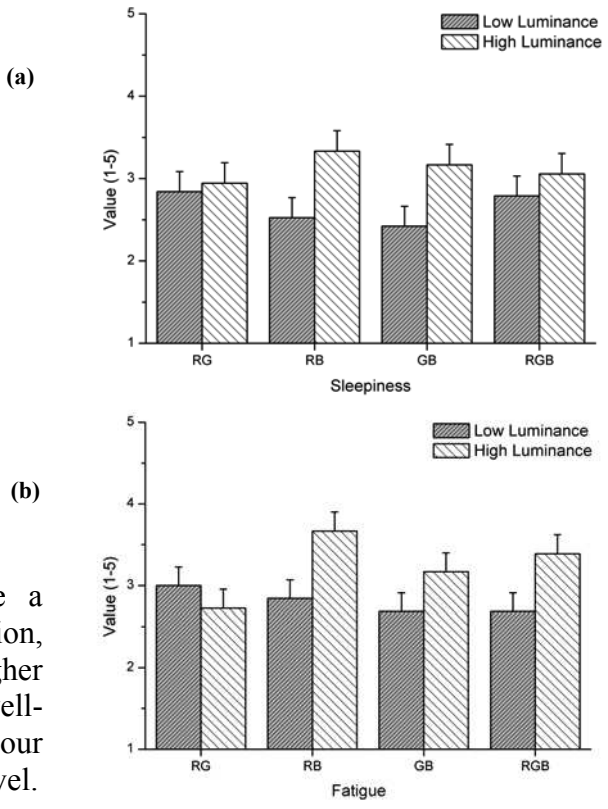
Lighting exposure had no effect on psychomotor vigilance, in line with the results of some previous studies.[8] This could imply that the effects of lighting on vigilance are primarily mediated by melatonin secretion or suppression,[7] although other studies have found daytime effects on vigilance.[5] Surprisingly, the individuals exposed to the higher level of luminance reported higher levels of fatigue and sleep than the individuals exposed to a low level of luminance in three of the four colours. Only the red/green combination appeared to be beneficial for the high luminance group. This could entail that although performance is not affected, blueish light could induce sleepiness, probably related to the simultaneous increase of reported fatigue, in particular with higher luminance levels. In general, the literature has shown relatively more vigilance-promoting effects of blue light, both in laboratory and field studies. An alternative explanation might be that exposure to luminance levels of 195 lux, while sufficient to induce fatigue, is insufficient to positively affect vigilance and well-being. Thus, the expectation by Cajochen et al.[13] that 100-200 lux at eye level would be sufficient to enhance alertness, was presently not confirmed. Possible limitations to the current study might be the duration of lighting exposure, duration of the vigilance task, and the use of colour combinations instead of monochromatic light.

Table 1. Results of the mmANOVA analyses on colour lighting and luminance level.

	Colour	*Group*	*CxG*
Performance			
Response latency (ms)	0.1	0.3	0.7
Accuracy (%)	0.7	0.0	0.2
Well-being			
Fatigue (1-5)	2.8	2.1	4.6*
Sleepiness (1-5)	0.4	2.6	3.1*
Boredom (1-5)	0.8	0.1	4.4*
Motivation (1-5)	2.0	1.2	3.0*
Arousal (1-9)	0.5	0.5	0.5
Valence (1-9)	1.0	0.2	0.6
Colour Perception			
Stimulating (1-7)	1.7	2.3	0.7
Vivid (1-7)	4.9*	2.8	1.4
Annoying (1-7)	12.0**	0.2	1.2

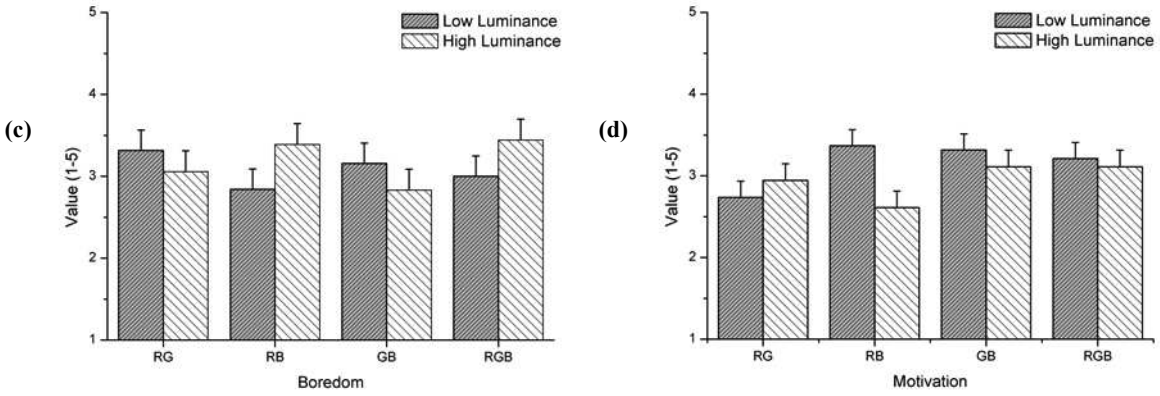
** p<0.001, * p<0.05

Figure 1. Means and SEMs for (a) Fatigue, (b) Sleepiness, (c) Boredom, and (d) Motivation for the low luminance (N=19) and high luminance (N18) groups.



CONCLUSIONS

Colour and luminance seemed to have a limited effect on well-being and perception, but not on psychomotor vigilance. A higher luminance level negatively affected well-being in most but not all colours, while colour perception was unaffected by luminance level.



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NOCTURNAL ENERGY EXPENDITURE, HEAT FLUX AND GALVANIC SKIN RESPONSE IN MILD AND MODERATE-TO- SEVERE OBSTRUCTIVE SLEEP APNEA (OSA)

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INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder, associated with important comorbidity. Severe OSA is treated with CPAP (continuous positive airway pressure) therapy, in which room air under positive pressure is applied through the nose upon the upper airways. 85% of the cases are characterized by overweight and obesity. The development of OSA is mostly preceded by weight gain, while unexplained weight gain can also occur during CPAP therapy. Changes in energy expenditure could contribute to weight changes. In OSA different mechanisms could have an impact on metabolism during sleep, like the frequent arousals which characterize OSA[1], increased respiratory effort against an obstructed airway, and hypoxemia, which can suppress energy expenditure[2]. Although metabolic processes have been studied extensively in OSA, data on nocturnal energy expenditure (NEE) are scarce[3,4]. It is also unclear whether sleep stages influence NEE[5] and the effect of CPAP on NEE in OSA was only studied in a small series of patients[3]. Traditionally, NEE is measured in a metabolic room ("ventilated hood"), using Weir's formula, based on the difference in oxygen content between inspired and expired air[6]. This method is cumbersome and parallel polysomnography is unpractical. Recently, a new system called SenseWear Pro2 Armband (SWA) has been developed and validated[7,8]. It uses sensors that continuously gather data (heatflux, skin temperature, near body temperature, galvanic skin response), estimating the wearer's caloric expenditure. Parallel application of SWA during polysomnography makes it able to evaluate thoroughly NEE related to sleep stages and to the occurrence of apneas and hypopneas, in different patient categories. We hypothesized that NEE and thermogenesis are increased due to repetitive apneas, compared to nonapneic snoring controls. Moreover, we hypothesized that NEE increases at night in OSA, with acute changes in NEE after an apnea, and with more changes related to increasing OSA severity.

METHODS

Patients:
61 patients were evaluated with SWA during a routine polysomnography. They were referred to the Sleep Disorders Center of the Antwerp University Hospital due to suspicion of sleep related breathing disorder. We did not use any other inclusion- or exclusion criteria. After analysis patients were divided into 3 groups: Group 1 were nonapneic snorers (AHI<5), Group 2 with mild OSA (AHI 5-20) and Group 3 with moderate-to-severe OSA (AHI > 20). Measurements were performed in 2006 and 2007.

Methods:
Metabolic monitoring: the Sensewear PRO_2 Armband (SWA, Bodymedia Inc., Pittsburgh, USA) is worn on the upper arm at the level of the triceps muscle and measures the following parameters by means of sensors: arm movements with an inbuilt accelerometer; heatflux by means of a heatflux sensor (a marker of thermogenesis); skin temperature, near skin temperature; galvanic skin response by means of a sensor with 2 hypoallergenic electrodes, evaluating electrical conductance. Consequently, information can be obtained on energy expenditure, physical activity and sleep/wake state (based on an inbuilt algorithm using absence of movement as a marker of sleep). In this study we focused on energy expenditure and thermogenesis.

RESULTS AND DISCUSSION

Overall, 61 patients were evaluated: 30 simple snorers, 16 mild OSA and 15 moderate-to-severe OSA. Patients characteristics are summarized in Table 1. Monitored parameters with the SWA during a complete night are shown in Table 2. No significant differences could be observed between the 3 study groups.

Table 1. Patients characteristics

	Overall	*Simple snorers*	*Mild OSA*	*Moderat-to-severe OSA*	*p*
Age (years), males/females	49±11, 38/23	47±12, 16/14	50±8, 10/6	53±12, 12/3	0.16
Body mass index (kg/m^2)	29±7	27±6	29±6	32±9	0.08
PaO_2 (mmHg)	92±13	91±15	94±11	92±10	0.95
FEV_1 (% predicted)[a]	105±15	104±15	100±15	111±16	0.23
TLC (% predicted)[b]	102±12	102±12	100±10	101±16	0.71
AHI (#/h)	12±14	2±2	10±3	34±12	<0.01

[a]FEV_1: forced expiratory volume in one second
[b]TLC: total lung capapcity
Mean±SD.

Table 2. Monitored parameters with the SenseWear Pro 2 Armband during a complete night

	Overall	*Simple snorers*	*Mild OSA*	*Moderat-to-severe OSA*	*p*
Heatflux ($Watt/m^2$)	65±018	67±018	63±016	65±20	0.74
Skin temperature (°C)	33±1	33±1	33±1	33±1	0.91
Near body temperature (°C)	33±1	33±1	33±1	33±1	0.86
Galvanic Skin Response (S)	0.4±0.4	0.3±0.3	0.5±0.7	0.4±0.3	0.51
Energy expenditure (kcal)	660±191	617±152	657±227	746±200	0.11

A subanalysis according to sleep stage did also not show any significant differences between the study groups (Table 3). To evaluate the impact of an apnea on metabolic parameters, a subanalysis was performed before and after 10 apneas in the beginning and at the end of the night (Table 4). No statistically significant changes could be found between and within the study groups.

Table 3. Monitored parameters with the SenseWear Pro 2 Armband according to sleep stage

	Overall	*Simple snorers*	*Mild OSA*	*Moderat-to-severe OSA*	*p*
AWAKE					
Heatflux (Watt/m²)	71±20	73±20	67±16	70±23	0.50
Skin temperature (°C)	34±7	33±1	32±1	36±14	0.40
Near body temperature (°C)	32±4	33±1	32±1	30±8	0.46
Galvanic Skin Response (S)	0.4±0.4	0.3±0.4	0.5±0.6	0.3±0.2	0.39
Active EE (kcal/min)	1,4±0.3	1.3±0.2	1.5±0.5	1.4±0.3	0.29
Stage 1					
Heatflux (Watt/m²)	65±21	64±20	61±18	69±26	0.71
Skin temperature (°C)	34±7	33±1	33±1	36±14	0.85
Near body temperature (°C)	32±4	33±1	32±1	31±8	0.73
Galvanic Skin Response (S)	0.4±0.5	0.4±0.5	0.5±0.6	0.4±0.4	0.35
Active EE (kcal/min)	1.3±0.3	1.3±0.2	1.4±0.5	1.4±0.3	0.17
Stage 2					
Heatflux (Watt/m²)	62±20	63±19	58±18	63±23	0.54
Skin temperature (°C)	34±7	33±1	33±1	36±13	0.87
Near body temperature (°C)	32±4	33±1	33±1	31±4	0.85
Galvanic Skin Response (S)	0.4±0.5	0.3±0.3	0.6±0.7	0.4±0.4	0.42
Active EE (kcal/min)	1.3±0.3	1.2±0.2	1.4±0.5	1.3±0.3	0.23
Stage 3,4					
Heatflux (Watt/m²)	67±24	67±26	60±21	72±24	0.37
Skin temperature (°C)	40±20	40±21	33±1	45±26	0.28
Near body temperature (°C)	38±20	40±21	33±1	39±26	0.46
Galvanic Skin Response (S)	9±28	10±31	0.6±0.9	13±34	0.77
Active EE (kcal/min)	9±28	11±30	1.4±0.5	14±34	0.48
Stage REM					
Heatflux (Watt/m²)	63±24	64±21	60±20	63±33	0.86
Skin temperature (°C)	35±11	33±1	33±1	40±20	0.47
Near body temperature (°C)	33±10	33±1	33±1	35±20	0.62
Galvanic Skin Response (S)	2±13	0.4±0.4	0.5±0.7	6.6±25.2	0.67
Active EE (kcal/min)	3.0±12.8	11.3±0.3	1.4±0.5	7.6±24.9	0.23

Active EE: active energy expenditure (measured during one minute)

Table 4. Monitored parameters with the SenseWear Pro 2 Armband before and after apnea

	Mild OSA		*Moderate-to-severe OSA*	
	Night start	End of the night	Night start	End of the night
Before apnea				
Heatflux (Watt/m²)	61±18	59±23	65±26	68±29
Skin temperature (°C)	33±1	33±1	33±1	37±17
Near body temperature (°C)	33±1	33±1	33±1	37±17
Galvanic Skin Response (S)	0.7±0.9	0.5±0.5	0.3±0.3	6.7±25.2
Active EE (kcal/min)	1.4±0.5	1.4±0.5	1.4±0.3	7.7±24.9
After arousal				
Heatflux (Watt/m²)	61±18	60±24	65±26	68±29
Skin temperature (°C)	33±1	33±1	33±1	37±17
Near body temperature (°C)	33±1	33±1	33±1	37±17
Galvanic Skin Response (S)	0.7±0.9	0.5±0.5	0.3±0.3	6.7±25.2
Active EE (kcal/min)	1.4±0.5	1.4±0.5	1.4±0.3	7.7±24.9

CONCLUSIONS

This study clearly demonstrated that OSA is not associated with an altered NEE, skin impedance (based on galvanic skin response) or heat flux, compared to controls. Moreover, an increase in OSA severity has no impact on NEE or thermogenesis. We could also demonstrate that no acute changes can be induced by change in sleep stage, by the occurrence of apneas, or according to the night time, and argues against a progressive increase of NEE in OSA at night. However, this does not rule out an impact of CPAP on NEE, but has to be studied yet.

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OCCULAR PERFUSION PRESSURE IS DECREASED DURING CPAP THERAPY IN OBSTRUCTIVE SLEEP APNEA

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INTRODUCTION

An association between glaucoma and obstructive sleep apnea (OSA) has been reported in several studies. Mojon et al[1] evaluated 69 patients with OSA and found a 7.2% prevalence of glaucoma, which is significantly higher than the 2% expected in a healthy population. Glaucoma is defined as a chronic progressive optical neuropathy with irreversible visual field defects and excavation of the optic nerve head. Elevated intraocular pressure (IOP) and cardiovascular disease are the main risk factors in the development and progression of glaucoma. In a preliminary study, we reported a firm tendency towards increased IOP at night in OSA, with further progression when CPAP is applied. The ocular perfusion pressure (OPP) is the pressure that forces blood to flow through the ocular vascular bed and is equal to the difference between the mean arterial pressure and the venous pressure at the exit point. The venous pressure in the eye is approximately equal to the IOP. Studying the OPP could lead to more insight in the observed IOP course in OSA patients.

METHODS

During a 24 hour hospitalization blood pressure, pulse and IOP were measured every 2 hours in newly diagnosed OSA patients. During the daytime, patients were asked to lie down during the measurements in order to evaluate IOP with a Perkins handheld applanation tonometer (Clement Clarke, Harlow, UK), after instillation of an anesthetic oxybuprocaine hydrochloride 0.4% eye drop (Unicaïne; Thea, Schaffhausen, Germany) followed by fluorescein staining. At night, patients remained in bed and were briefly woken every two hours. After one month CPAP therapy, the measurements were repeated. The CPAP mask was applied during the overnight measurements.
The OPP was calculated based on IOP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), according to ophthalmodynamometric studies (subtracting the IOP [as a substitute for venous pressure], from two thirds of the mean arterial pressure [result of DHP plus one third of the difference between SBP and DBP].[2]

$$OPP = 2/3\ [DBP + 1/3(SBP-DBP)] - IOP$$

A paired sample t-test was used for statistical evaluation.

RESULTS AND DISCUSSION

Patient characteristics are shown in Table 1.

Table 1. Patient characteristics.

	OSA patients
N	21
Age (y)	57 ±2
BMI (kg/m2)	31±2
FEV_1 (%Pred)	97±11
Neck circumference (cm)	43±1
Diabetes (% of total group)	19
Epworth sleepiness scale score	12±1
AHI (#/h)	48±5
CPAP pressure (cm H2O)	6±1
AHI during CPAP titration night (#/h)	8±3
Corneal thickness (μm)	541±8

(Mean±SEM)

The average 24-hour IOP graph at baseline showed a cyclic course, with a statistically significant nocturnal IOP elevation ($p<0.05$) (Figure 1). One month after onset of CPAP therapy, the average IOP was significantly higher than baseline at 2, 4, 6 and 8 AM ($p<0.05$)

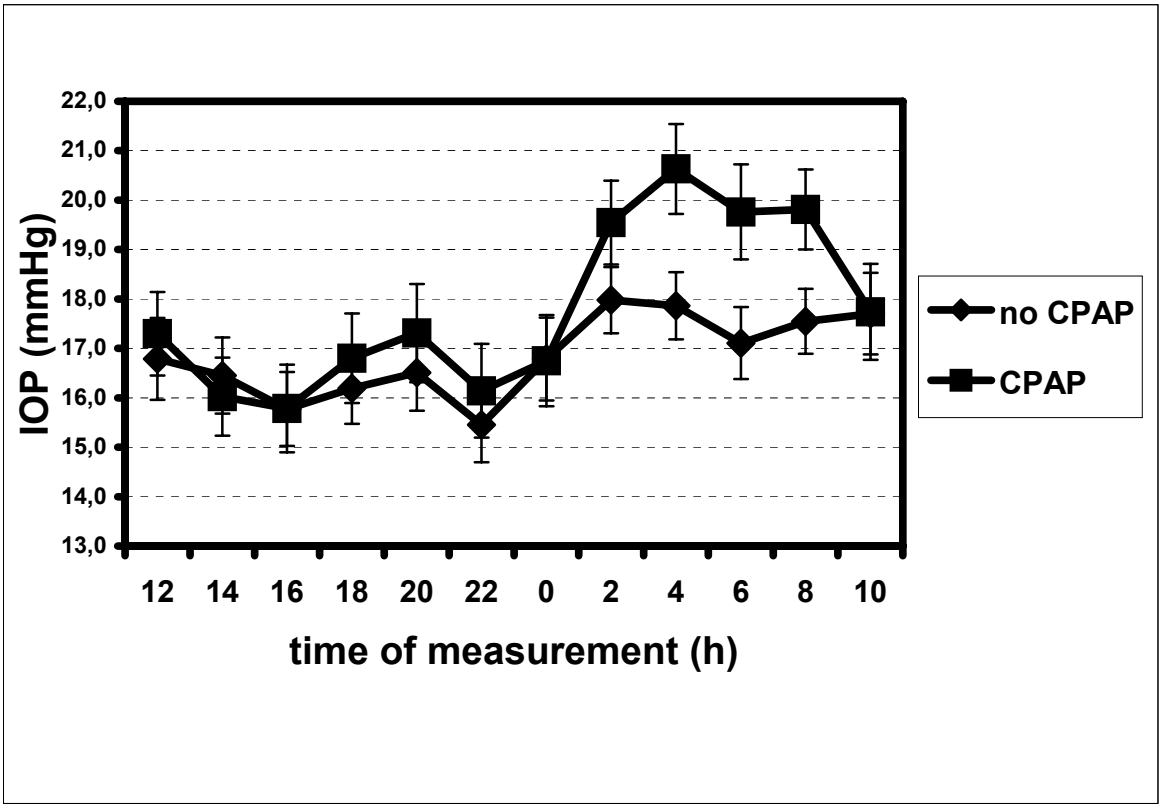

Figure 1. Intraocular pressure before and after one month CPAP therapy (during the daytime measurements were performed without CPAP application) (Mean±SEM).

No significant variations were found in SBP at baseline, nor during CPAP therapy. A statistically significant difference in DBP was observed during CPAP therapy, compared with baseline. Significant fluctuations of pulse rate during the nychthemeron were found. Pulse rate was significantly lower at midnight, 2, 4, 6, and 8 AM. CPAP did not influence the pulse rate significantly. There was a statistically significant decrease in mean OPP during CPAP therapy, compared to baseline, at 2, 4, 6 and 8 AM ($p<0.05$) (Figure 2, Table 2).

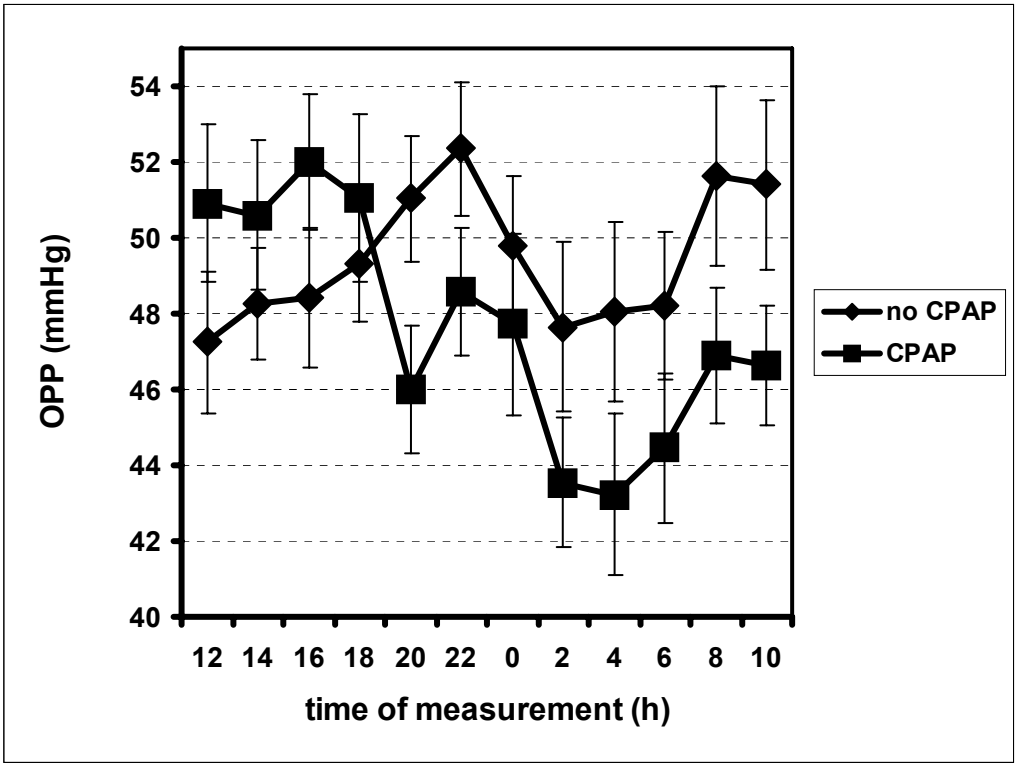

Figure 2. Calculated Ocular perfusion pressure before and after one month CPAP therapy (Mean±SEM).

Table 2. Mean Ocular Perfusion Pressures at baseline and after one month CPAP therapy.

Time of measurement (h)	*Baseline (mmHg)*	*One month CPAP (mmHg)*
12	47 ± 2	51 ± 2
14	48 ± 1	51 ± 2
16	48 ± 2	52 ± 2
18	49 ± 2	51 ± 2
20	51 ± 2	46 ± 2
22	52 ± 2	49 ± 2
0	50 ± 2	48 ± 2
2	48 ± 2	44 ± 2 *
4	48 ± 2	43 ± 2 *
6	48 ± 2	44 ± 2 *
8	52 ± 2	47 ± 2 *
10	51 ± 2	47 ± 2

* $p<0.05$, Mean±SEM

In concordance with earlier findings, we could demonstrate a pressure-raising effect of CPAP.[3] Moreover, we could demonstrate a decrease of OPP, which is related to hemodynamical changes and to IOP and indicates a lower flow through the ocular vascular bed. Why CPAP causes a decrease in OPP is not yet understood. One could speculate that CPAP leads to an elevated intrathoracic pressure, which in turn gives a pressure elevation in the venous circulation, which may reduce the aqueous humor outflow through the episcleral veins and inherently decreases OPP.[4] The interaction among various physiological parameters, ocular perfusion pressure, outflow facility in sleep position, and circulating hormones while asleep could also be involved. Moreover, cardiovascular complications are reported more frequently in OSA, as coronaropathy, heart failure, heart rhythm disturbances, cerebrovascular accidents and pulmonary hypertension. These cardiovascular risk factors could make OSA patients more vulnerable for low tension glaucoma (glaucomatous damage even with 'normal' IOP), and hence, lower OPP. As CPAP is known to have a beneficial effect on hemodynamic parameters in OSA, one might expect a beneficial effect of CPAP on glaucomatous progression by decreasing the risk for vascular perfusion damage. However, this study revealed a decrease in OPP (associated with a raise in overnight IOP) at night during CPAP application compared to baseline OPP. These results are in contrast with OPP findings in healthy subjects, as Liu et al reported that the nocturnal OPP in supine position was significantly higher than the diurnal OPP in the sitting position.[5] OSA patients have vascular endothelial dysfunction. This endothelial dysfunction could reduce the ability to auto-regulate blood flow when OPP changes occur and may lead to unstable ocular perfusion. Although the effects of periodically reduced OPP on blood flow to the optic nerve head remain to be determined, it has been cautiously speculated that a reduction in OPP could lead to ischemia of the ocular tissues followed by reperfusion damage. A decrease in OPP could result in further glaucomatous damage in subjects predisposed to glaucoma who are treated with CPAP.

CONCLUSIONS

An overnight decrease in OPP is present in patients with OSA. During CPAP therapy, nocturnal OPP decreases even more prominently and reflects an increase in IOP and hemodynamical changes. This could explain the higher prevalence of glaucoma in this population. Follow up is warranted, but single IOP and OPP evaluation during office hours do not permit the identification of patients who may present nychthemeral IOP spikes.

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SEVERITY BUT NOT PREVALENCE OF RLS IS HIGHER IN CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY

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INTRODUCTION

Several studies have reported an increased prevalence of restless legs syndrome (RLS) in patients with various forms of polyneuropathy [1,2]. As the underlying condition causing the polyneuropathy may interact with the occurrence of RLS[3], we investigated the prevalence and severity of RLS in a cohort of patients with chronic idiopathic axonal polyneuropathy (CIAP). Since in CIAP various causes of polyneuropathy have been excluded, there are no known (metabolic) factors that can interact with the occurrence of RLS [4].

METHODS

Patients were identified from databases from the University Medical Center Utrecht and the St. Antonius Hospital Nieuwegein. CIAP patients have a chronic sensory or sensorimotor axonal polyneuropathy. There is a male predominance and the mean age of onset is 57 years [4]. CIAP was diagnosed if no cause for the polyneuropathy was found after extensive clinical and laboratory evaluation including search for monoclonal proteins, metabolic, endocrine and malignant or auto immune diseases, exposure to toxic agents or hereditary causes. Age and sex matched healthy subjects served as controls. Exclusion criteria for controls were polyneuropathy, clinical disorders or medication known to be associated with polyneuropathy or RLS. The diagnosis of RLS was established when all four International RLS Study Group criteria were met[5]. A telephone diagnostic interview was performed by a trained interviewer, conform the validated John Hopkins telephone diagnostic interview for restless legs [6]. To establish if there was a circadian pattern, special attention was paid to the presence of complaints when sitting during morning hours and the lack of relief by movements, as these features were considered to be associated with polyneuropathy. If a participant met al four essential RLS criteria the severity of symptoms was evaluated using the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome (IRLS)[7]. Differences between groups were tested using the Independent *t*-test and Chi-square test. A p-value below 0.05 was considered significant.

RESULTS AND DISCUSSION

100 patients with CIAP and 65 age and sex matched controls were included. The prevalence of RLS in CIAP (n = 16, 16.0%) patients was comparable (p = 0.7) to the prevalence of RLS in control subjects (n = 12, 18.5%). CIAP patients scored an average of 6.5 points higher on the IRLS severity scale (p = 0.025). The age of onset of RLS was similar in CIAP patients and controls. Seven patients used gabapentin and four used pregabalin compared to none in the control group. After excluding these patients from the statistical analysis, the prevelance of RLS in CIAP patients remained the same (14 out of 89, 15.7%). The use of gabapentin and pregabalin had no significant influence on either prevalence (p = 0.9) or severity (p = 0.5) of RLS.

Table 1. Patient characteristics, RLS prevalence and RLS severity of CIAP patients and controls.

	CIAP patients (n = 100)	*controls (n = 65)*	*p-value*
age, y	69.5 ± 8.9	68.3 ± 8.8	0.4
Male : female, %	71 : 29	72 : 28	0.9
age of onset CIAP, y	60.6 ± 8.5		
RLS[a]-prevalence, n (%)	16 (16.0)	12 (18.5)	0.7
age of onset RLS, y	60.9 ± 13.2	60.3 ± 13.9	0.9
IRLS[b] score	17.4 ± 8.5	10.9 ± 4.9	0.03
IRLS > 15, n (%)	8 (8.0)	3 (4.6)	0.2
RLS frequency >1 day/week, n (%)	10 (10.0)	6 (9.2)	0.9
RLS causing sleep problems, n (%)	8 (8.0)	2 (3.1)	0.2

Data are presented as mean ± SD unless otherwise indicated
[a]RLS = restless legs syndrome; [b]IRLS = International Restless Legs Syndrome Study Group rating scale

CONCLUSIONS

In contrast to other studies, we did not find an increased prevalence of RLS in patients with polyneuropathy. There was however a significant difference in RLS severity between patients with CIAP and controls. Polyneuropathy symptoms possibly amplify the RLS complaints. Previous studies included patients with polyneuropathy caused by various metabolic disorders as diabetes and renal failure, which are already associated with an increased prevalence of RLS[1,2]. Using telephone interviews instead of paper questionnaires may have helped to avoid attributing polyneuropathy symptoms to RLS, a special attention was paid to the absence of a circadian pattern and the lack of relief by movements. Our study results support the central dopaminergic deficit hypothesis, since we found no association between peripheral neuropathy and RLS.

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CORONARY ARTERY CALCIUM SCORE (CACS) IN MODERATE TO SEVERE OSA PATIENTS WITHOUT SYMPTOMATIC CARDIOVASCULAR DISEASE (CAD) AND EFFECT OF LONG-TERM CPAP TREATMENT

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder which occurs in 4% of males and 2% of females. The repetitive apneic events of OSA, pharyngeal collapse during sleep that leads to markedly reduced (hypopnea) or absent airflow (apnea), disturbs the normal physiologic interactions between sleep and the cardiovascular system. Sleep fragmentation caused by OSA has several consequences like increased sympathetic activity, vascular endothelial dysfunction, increased oxidative stress, inflammation, increased platelet agreability, metabolic dysregulation, and may be implicated in the initiation and progression of cardiovascular disease. It has been shown that OSA is associated with hypertension, arrhytmias, stroke, myocardial infarction and congestive heart failure (CHF). OSA has also been linked with subclinical atherosclerosis. Therefore, multislice computed tomography (MSCT) is used to quantify the magnitude of coronary artery calcification (CAC). CAC is a marker of subclinical atherosclerotic burden and is associated with coronary events and asymptomatic myocardial ischemia. Recently, Sorajja et al found an association between the coronary artery calcification score (CACS) and increasing OSA severity[1]. The aim of the present study was to look at the CACS in moderate to severe OSA patients (AHI>20), without history of coronary artery disease or present symptoms of CAD, at baseline and after 6 months of CPAP treatment.

METHODS

Study Population:

Twenty eight (25 males) moderate to severe OSA patients (AHI>20) were included. Moderate OSA was defined as AHI ≥20 to AHI≤ 30, severe OSA as AHI >30 to 50 and very severe OSA as AHI >50. All of them were free from confounding factors for cardiovascular disease (CAD), like smoking, hypertension, diabetes and hypercholesterolemia, which were exclusion criteria. Hypertension was defined as systolic BP>140 mmHg, diastolic BP>90 mmHg, or use of antihypertensive medication. Diabetes was defined as a fasting blood glucose level >126 mg/dL and/or use of antidiabetic medication. Hypercholesterolemia was defined as total cholesterol >240 mg/dL, HDL<35 mg/dL, LDL >160 mg/dL and/or use of lipid-lowering medication. All patients got a baseline cardial MSCT, a full polysomnography and CPAP titration night in the sleep laboratorium. After 6 months of CPAP treatment, the minimum time to detect changes in plaques, a re-evaluation took place in twelve patients.

Multislice Computed Tomography (MSCT):
MSCT imaging was performed using the VCT Lightspeed 64 (General Electric, Milwaukee, USA) with a 0.625 mm slice thickness extending from the carina to the diaphragm. The CT-scan was triggered through ECG. Images from the R-R interval during end-diastole were used. CACS was calculated using the Agatston Quantification algorithm, which is based on the area and the density of the calcified plaques and also adjusts for age and gender[2]. These adjustments are necessary to calculate the according percentiles, compairing a healthy, gender and age matched population, since men develop calcifications about 10 to 15 years earlier than women, and can be detected in the majority of healthy asymptomatic men over 55 years of age and women over 65 years of age. These data have been used to create the tables that compare the amount of calcium of an individual to a group of people with similar age and gender (percentiles).

RESULTS AND DISCUSSION

Included patients had a mean AHI 53 ± 27 (range 22-97), mean age 50 ± 11 y (range 28-76), 57% were obese (BMI>30), 39% were overweight (BMI>25), 4% had a normal body weight (BMI<25). Mean BMI was 32 ± 5 kg/m². Patients characteristics before and after 6 months CPAP treatment are shown in Table 1. At baseline, thirteen (43%) of the twenty eight patients had CACS=0, eight (29%) had a CACS between 0 and 80, 3 (11%) had a CACS between 80 and 400, and one (4%) patient had a CACS higher than 400. A test was considered to be negative if no calcifications were detectable (CACS=0) within the coronary arteries. Although this does not absolutely exclude the presence of atherosclerotic deposits, it indicates that there is a low likelihood of advanced coronary atherosclerosis and a low risk of adverse coronary events over the next 2 to 5 years. A negative predictive value of 90-100% for a >50% stenosis of a coronary artery has been reported.
According to Greenland and Gaziano a calcium score of less than 80 significantly reduces the risk of a coronary event within 10 years in an intermediate-risk group to less than 5% and, thus, to no need for preventive risk measures, whereas a calcium score of more than 80 significantly increases the risk in an inter-mediate-risk group to >20% and, thus, to a category of individuals where preventive measures are warranted[3]. Six patients (21%) in our population had a CACS higher than eighty and therefore need adequate preventive measures. A calcium score higher than 400 means that significant narrowing is possible with a high probability of CAD (>90%). One patient had a CACS>400. Shaw et al[4] reported a 5-years overall mortality among 10377 asymptomatic individuals who had undergone coronary calcium screening: CACS>400 and particularly those with CACS>1000 had a significantly higher mortality versus subjects with calcium score of <10.
After adjustment of the CACS for age and sex, we calculated the according percentiles. We found 13 (46%) patients in the CACS range <25 percentile, 3 (11%) in the 25 percentile, 6 (21%) in the 50 percentile, 2 (7%) in the 75 percentile and 4 (14%) in the 90 percentile (see Figure 1) . This means that the patients in the 75 percentile group (21% of the study population) are at higher risk than the normal gender and age matched population[5]. After six months of CPAP treatment the CACS remained equal (CACS before: 68 ± 85, after: 71 ± 91) (p=0.44) .

Table 1. Clinical characteristics at baseline and after 6 months CPAP treatment (mean ± SD)

	Baseline (n=28)	*6M CPAP (n=12)*	*P=*
Age (years), males/females	50 ±11, 25/28	-	-
Body mass index (kg/m^2)	32 ± 5	31 ± 6	0,89
Apnea hypopnea index (AHI) (#/h)	53 ± 27	9,1 ± 5,8	<0.01
Heart rate (per minute)	79 ± 13	78 ± 13	0,9
CPAP compliance (hours/night)	-	5,3 ± 1,5	-
Systolic/Diastolic Blood Pressure (mmHg)	131 ± 15 / 78 ±11	119 ± 6 / 67 ± 7	0,06
Total cholesterol (mg/dL)	200 ± 39	167 ± 28	0,18
HDL (mg/dL)	52 ±16	47 ±9	0,52
LDL (mg/dL)	131 ± 38	107 ± 32	0,25
CACS	68 ± 85	71 ±91	0,44

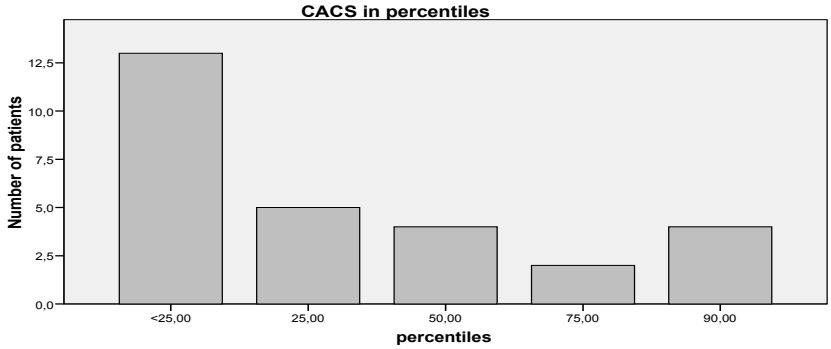

Figure 1. Distribution of CACS based on percentiles (<25, 25, 50, 75, 90) in untreated OSA patients

Since OSA is associated with CAD and also because coronary atherosclerosis is the most important cause of morbidity and mortality in individuals with cardiovascular risk factors, we performed a study looking at CAD, based on CACS. However, risk factor assessment to identify high-risk subgroups is neither highly sensitive nor highly specific. Most methods for cardiovascular risk stratification are invasive, such as angiography and intravascular ultrasound (IVUS), and not ethically recommended to approach an asymptomatic OSA population without any traditional risk factors for CAD. Many individuals, considered to be at high risk for coronary events will not develop myocardial infarction or sudden cardiac death, while others, considered to be at low-risk or no risk, will suffer from a coronary event and have not been evaluated for CAD. In our study population 7% had a CACS in the 75 percentile and 14% had a CACS in the 90 percentile. These findings indicate that these 'healthy' OSA patients have a higher risk to develop a cardiovascular incident in the near future and need to be followed up. The exact risk augmentation in not yet available.
CACS is a non-invasive evaluation of coronary calcification with MSCT. This strategy is based on the close histopathological correlation between coronary calcium deposits and the total amount of coronary atherosclerosis. Detection of subclinical CAC is important for risk stratification and treatment decisions. Traditional cardiovascular risk factors have been shown to correlate with the severity of CAC. The presence of coronary calcium is a predictor of adverse coronary events. However, calcification is neither a marker for plaque vulnerability nor for plaque stability and thus should not be performed as a 'stand-alone' test. However, the greater the overall calcium burden, which correlates with a greater overall coronary plaque burden, the greater is the likelihood of a further adverse coronary event. So, we must interprete these results with prudence, because calcification of a plaque is the last phase of atherosclerosis and the most calcificated plaques are not the culprits.

The data about the independent prognostic value of calcium, in addition to the traditional risk factors, yield conflicting evidence. The MSCT-scan quality varies from scan to scan, which can cause an over- or underestimation of the CACS. In this study the MSCT quality was confirmed by an experienced radiologist, quantifying each CT.
CACS scoring is a potential useful tool for monitoring progression of coronary atherosclerosis.
Studies indicate that the annual progression of coronary calcium varies between 25% to 50% in symptomatic and asymptomatic non-treated high risk individuals. In patients treated with lipid-lowering medication, the progression of CACS varies between 0 to 20%.
After 6 months of CPAP treatment the CACS in our population remained equal. We can speculate that the study period is too short to develop changes in the CACS or that CPAP treatment has no effect on calcified plaques. In previous studies it has been shown that 6 months is the minimal treatment period to observe changes in the vascular wall. A longer follow up period could be considered. However it must be stressed that calcified plaques are not the only factor predicting coronary atherosclerosis. Vulnerable plaques may or may not be calcified, thus complicating the determination of cardiac risk by screening for calcification. Plaque composition, morphology and expansive coronary wall remodelling may be more important predictors of plaque vulnerability and clinical behavior than the degree of coronary stenosis[6]. Hence, we cannot make definite conclusions regarding treatment effects on non-calcified plaques, since this was behind the scope of our study.

CONCLUSIONS

Our study showed that moderate to severe asymptomatic healthy OSA patients are at increased risk to develop CAD according to their CACS, a marker of CAD. However, CACS should not be performed as a 'stand-alone' test, but should be integrated into risk assessment with well recognized risk factors for asymptomatic intermediate-risk cohorts, such as moderate to severe OSA patients. The additional use of other non-invasive techniques, such as the carotid intima media thickness measurement (IMT), which has the ability to follow the progression of plaques, is advised. Long-term CPAP treatment has however no impact on the CACS.

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RESTLESS LEGS SYNDROME IN CHILDREN, A SURVEY IN THE NETHERLANDS

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INTRODUCTION

The International Classification of Sleep Disorders (ICSD 2,[1]) defines Restless Legs Syndrome (RLS) according to the guidelines coined during a National Institutes of Health meeting[2]. In short: 1) there is an urge to move the legs accompanied or caused by unpleasant feelings in the legs, 2) the urge or feelings start at rest, 3) they are (partially) relieved by movement, 4) are worse in the evening or night and 5) are not better explained by another disorder. This description is the gold standard for adults. In pediatric patients the diagnosis is more difficult and the criteria have been adapted for this age category. The text in the ICSD 2 is as follows:
A. The child meets all four criteria for RLS as listed for adults and relates a description in his own words that is consistent with leg discomfort or
B. The child meets all four adult criteria, but does not relate such a description and has at least two of the three following findings: 1) a sleep disturbance for age, 2) a biological parent or sib with definite RLS, 3) a polysomnographically (PSG) documented periodic limb movement index (PLMI) of 5 or more per hour of sleep. Although these criteria look well delineated and two recent papers have tried to list early manifestations[3,4], in many suspected cases uncertainties remain.
The prevalence of RLS in children is described in one publication only and estimated at approximately 2%[5]. It is clear that RLS occurs in children, even in toddlers and in young adolescents. Therapy of the disorder is thought to be similar to that in adult cases and has probably a high success rate.
We envisage a Europe wide survey of clinical, PSG and therapeutic aspects of RLS in children and young teenagers as so many details are still unknown. The results for The Netherlands are already analysed and are reported in this short communication.

METHODS

A questionnaire was sent out in the autumn of 2007 to all general (i.e. not limited to one disorder, for example sleep apnea syndrome) sleepcenters in The Netherlands. The list was taken from the inventory by the NSWO published end of 2006. The persons addressed were asked to contact also the pediatricians in the same hospital whether they had children suspected of RLS on file. The questionnaire asked for retrospective data on children with RLS, in case such patients were seen in that particular sleepcenter. For each child, personal data, history of the sleepdisorder, PSG data and choice of therapy and its success, were asked. Participation was limited to children 15 years of age or younger at the moment of diagnosis of RLS. They had to meet the criteria for children as mentioned above and PSG

had to be performed. Four major sleepcenters in The Netherlands have sent in their data; the others answered that they or pediatricians in their hospital did not see children with sleepdisorders in a systematic way.
The data were tabulated and described using simple statistics (median, range)

RESULTS AND DISCUSSION

An illustrative case history will be given first:
Boy, born in 2000. He is sleepy during daytime since 2004. He falls asleep at all moments during the day, even during his favorite soccer match. The patient is in bed from 7 pm to 7.30 am. He is often awake and noisy and complains about pain in the legs during the night. The latter was diagnosed as "growing pains" by the general physician. His mother and her father have RLS. PSG showed a sleep efficiency index of 94%, total sleep time 664 min., wake after sleep onset 41 min., normal REM (25%) and deep sleep (30%), 2.4 apneas/hr and 100 leg movements in sequences leading to a PLMI of 6/hr. Improvement of sleephygiene and counseling of the parents gave little improvement. Gabapentine 300 mg in the evening was given as medication in 2005. The growing pains subsided, subjective sleep improved, and the boy was no longer sleepy during the day. These results remained so up to the end of 2007.
In total, the data of 13 patients were obtained (8 boys). The age at onset of the complaints was 1-15 years, median 6 years. RLS was prevalent in the family for four of the patients. Ten children suffered from other disorders as well: (well regulated) epilepsy in 3, slight psychomotor retardation in 1, ADHD in 2, PDD-NOS/Asperger syndrome in 2, migraine in 1 and spina bifida occulta in 1 of the children. Co-medication was: antiepileptic drugs, methylphenidate or zolpidem as thought previously appropriate for the concurrent disorders.
The main findings of the survey are given in the table and regard the presenting symptoms, PSG and actigraphy data. The iron status was assessed in only a few patients and was normal in all. Therapy was given in different ways depending on local preferences. Dopamine agonists (N=5), Clonazepam (N=4), Gabapentin (N=3), Iron (N=1) were given. Only two patients were not actively treated. The results of treatment were satisfactory. Sleep improved and daytime symptoms and growing pains disappeared in 9 of the patients, including the boy with the spina bifida. In the other 4 patients the results were classified as moderate, i.e. some symptoms remained partially. In this limited survey no best treatment option emerged.

This study gives some insight in clinical aspects and PSG data in a selection of children with RLS. The study should not be considered as an epidemiological survey. Although the prevalence of RLS may be lower in children when compared to adults, the complaints can be very bothersome in children which makes awareness of the symptoms by sleep specialists and pediatricians necessary. As can be expected in young children, the adult criteria for RLS with emphasis on what the sufferer feels and how he reacts, do not fit for patients who still can not fully express themselves. It was a major step forward when criteria for RLS in children were formulated, which in contrast to the adult rules, accept all strange or painful feelings as diagnostic, but also make confirmation of the disorder by PSG often necessary. Thus, periodic limb movements which are only additional prove in adults, are strong evidence in children. This is obviously only true when the history and other clinical data are in line with the diagnosis as well. When doubts remain, a short try-out with medication may even be warranted, although such procedure should be limited as much as possible.
The main differential diagnosis in children exists of (acute) polyneuropathies and psychogenic disorders. Venous insufficiency is possible, but not very likely in this age category. In adults medication may precipitate RLS. This is in particular known for anti-

depressants, a form of medication only sparsely used in children. Furthermore, iron deficiency may contribute to RLS in adults and children as well. We recommend to look for this anomaly which is easily treated and often has spectacular influence on RLS. Finally, all spinal and radicular disorders can give RLS. This holds for children also and makes a detailed neurological history and examination obligatory. In the survey two patients were included with ADHD as co-morbidity. In the literature ADHD and RLS in children and adolescents are described as interrelated more than expected from chance alone[6]. The underlying mechanism is not known yet, but if both disorders are indeed connected, RLS in childhood may become of major interest. This is another reason to make the disorder more known to all workers in the field of sleepdisorders including pediatricians.
Most clinicians are reluctant to give dopamine agonists, which is now therapy of first choice in adult RLS, to children. As young patients react well to other approaches for example gabapentin or clonazepam, this is justified to some extent, but should not lead to denial of the possibilities of dopamine agonists even in young children[7]. In the survey, this medication was used as a last resort and was succesfull in 4 out of the 5 cases who were treated. Although applicable for only one patient in the survey, we want to emphasize the importance of suppletion of iron in cases with low iron reserves and its success even in the long run.

Table 1. Presenting symptoms and polygraphy data

Presenting symptoms	*N*	*Median (range)*
Bad sleep (initiating and maintaining sleep, DIMS)	13	
Tired during the day	13	
Sleepy during the day (EDS)	3	
Growing pains in the legs	4	
Nightmares	3	
"Adult" criteria of RLS	1	
PSG and actigraphy (summary)		
Frequent arousals and awakenings	13	
Sleep latency, wake after sleep onset prolonged	13	
Deep sleep, REM normal	13	
Short sleeper	1	
Aberrant sleep hygiene	2	
Naps during the day	4	
Apneas and hypopneas/hour < 2.5	13	
Periodic limb movement index (PLMI)		10 (6-25)

CONCLUSIONS

This survey is limited to a small group of patients, but already provides guidelines what to ask and what to look for when RLS is suspected in a child or adolescent. The European branch of the International RLS Study Group has decided to enlarge the survey to as many as possible other sleepcenters in Europe. Up to now the response is encouraging, but more patients are welcome in order to delineate the disorder more exactly.

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NSWO OVERVIEW 2008

SURVEY OF SLEEP WAKE RESEARCH IN THE NETHERLANDS

Gé S.F. Ruigt

NV Organon, Oss

This is the 2008 survey of Sleep-Wake Research in The Netherlands. Research institutes and centres engaged in sleep-wake research are mentioned in alphabetical order including the scientists, who are working at the various institutes with the principal investigator / contact person being underlined.

AMERSFOORT: MEANDER MC, SLEEP AND DIALYIS

The Department of Neurology and Clinical Neurophysiology is the location of the Centre for sleep and wake disorders in Amersfoort. Clinical whole night sleep studies, and 'multi sleep latency tests' form the main basis for diagnosis and treatment of sleep apneu syndroom, restless legs syndrome and periodic leg movement disorder, narcolepsy, insomnia and other disturbances of night time sleep and excessive daytime sleepiness. In a multidisciplinairy setting called the Morpheus study group difficult clinical problems are discussed and tried to be solved. In the Morpheus group a neurologist, lung specialist, ENT specialist and a oral surgeon are presented.
Additionally in 2004 a multidisciplinary study started on the sleep disturbances of dialysis patients. Emphases of this study are the role of nocturnal dialysis and exogenous melatonin and sleep problems in this population. The Dutch Kidney Foundation sponsors this research project.

Reseachers: JBS Boringa, neurologist, JE Nagtegaal, hospital pharmacist and BCP Koch, resident pharmacist and principal investigator.

AMSTERDAM: AMSTERDAM CENTER FOR SLEEP-WAKE DISORDERS, at the SLOTERVAARTZIEKENHUIS www.slaapkliniek.nl

The Amsterdam Centre for Sleep and Wake Disorders has its base at the Slotervaart general hospital in Amsterdam. This sleep centre has an outpatient facility which is served by 2 neurologists and one Physician Assistant (in training). There outpatient department for children with sleep-wake disorders is served by a pediatrician and a child psychologist. Furthermore the multidisciplinary team comprises of: sleep technicians, psychologists, pulmonologists, ear nose and throat specialists, dentists of the Academic Centre for Dentistry Amsterdam (ACTA) and an Obesitas treatment facility.
Clinical monitored whole night sleep studies in a dedicated department with eight bedrooms and 'multi sleep latency tests' form the main basis for diagnosis and treatment. Our specialties are: OSA (obstructive sleep apnoea syndrome), UARS (upper airway resistance syndrome); Insomnia; Restless legs syndrome; Narcolepsy and other disturbances of night time sleep and excessive daytime sleepiness. We have a special team for children with sleep disorders.

CPAP treatment for OSA is done “in house” concluded with routine PSG check-up after 6 month, which yields a high compliance score.
Research is focused on the treatment of bruxism, the relationship between bruxism and 'periodic leg movements' and the use of 'mandibular advancement/repositioning device' in sleep breathing disorders (both thesis projects). Also drug studies in Insomnia and RLS are performed.

Researchers: Dr. H.L. Hamburger, neurologist; mr. L. Harten, technician;
Prof.dr. F. Lobbezoo, dentist; mrs G.Arab, dentist (MAD); mr J.vd Zaag, dentist (bruxism)

AMSTERDAM: NETHERLANDS INSTITUTE FOR NEUROSCIENCE

Sleep wake research in the Netherlands Institute for Neuroscience (NIN) focuses on sleep and cognition, in health and disease (dementia, insomnia) and in animal models. The institute has expertise in the functional anatomy of the human hypothalamus, in actigraphic assessment and analyses of circadian rhythms and tremor; fMRI, High Density EEG, TMS, MEG (in cooperation with the VUmc and the AMC). A multi-centre clinical trial on the long term effects of daily melatonin gifts and bright light exposure on the development of disturbed sleep, circadian rhythms, behavior, emotion and cognition in demented elderly people has just been completed, which is now followed up by a two-year follow-up study in early dementia. Moreover, the relation of temperature regulation with vigilance and sleep is a main issue and studied in healthy young and old subjects, insomnia, Alzheimer's disease and narcolepsy (in cooperation with the LUMC). Consequences of age-related and insomnia-related disturbances in sleep and circadian rhythms for cognitive performance have become a major topic. fMRI has been used to investigate to what extent age-related sleep disturbances contribute to age-related decrements in executive functioning and memory consolidation. The relation between EEG-synchronization patterns and cognitive processing is a recent interest. Finally, animal models for the effect of sleep deprivation on cognition are now being developed to allow for studies on the involvement of neurotransmitter changes.

Researchers: dr. E. Van Someren, dr. Y. van der Werf, dr. J. Benjamins, dr. M. Feenstra, R. Joosten, dr. C. Valencia, C. Leenaars, drs. E. Altena, drs. N. Romeijn, Drs. R. Schutte, Drs. E. Most, Drs. G. Piantoni.

AMSTERDAM: UNIVERSITY OF AMSTERDAM

The Department of Education is involved in research concerning the relation of sleep duration, sleep quality, and chronic sleep reduction with school performance and behavior problems of children and adolescents. Both cross-sectional and longitudinal studies are undertaken to study these relationships. Recently a Ph.D. project is started concerning the relations between subjective and objective sleep parameters of adolescent boys and girls in periods without and with stress (exams) and to study the differential relations of sleep parameters, and especially chronic sleep reduction, with adolescents’ school functioning and school performance in these periods.Prof. dr. G. Kerkhof is involved in this project.

Researchers: drs. Dewald, J.F. (J.F.Dewald@uva.nl); dr. Meijer, A.M. (A.M.Meijer@uva.nl), dr. Oort, F.J. (F.J.Oort@uva.nl) and dr. Wittenboer, G.L.H. van den

AMSTERDAM: UNIVERSITY OF AMSTERDAM

The Department of Psychology is involved in research on sleep and circadian rhythm.
One project is focusing on biological, social and environmental markers of the shift-work maladaptation syndrome. Measurements are done before the start of a job involving shift-work and during 2 consecutive years after the actual start of the shift-work.
Other projects involve the study of sleep loss. Epidemiological studies are done on insomnia in relation with comorbidities. Also the effect of cognitive behavioral therapy on chronic insomnia is studied. A project on the effect of chronic sleep loss in adolescents focuses on changes in sleep/wake patterns in adolescents living in a multicultural society.
Recently a project has started to study the causal relation between sleep and memory consolidation.

Researchers: dr. S. Drosopoulos, dr. W. Hofman, prof. Dr. G. Kerkhof, dr. L. Talamini

AMSTERDAM: UNIVERSITY HOSPITAL 'VRIJE UNIVERSITEIT'

The centre for sleep disorders located at the Department of Clinical Neurophysiology consists of a multidisciplinary team. It has an outpatient clinic and facilities for ambulatory and clinical sleep registration. Important interests are the influence of sleep on cognition in sleep apnoea syndrome and in insomnia, narcolepsy and the validation of new techniques for signal analysis.

Researchers: dr. A. Boonstra, dr. R. de Bree, prof. dr. C. Stam, dr. E. Van Someren, dr. R. Strijers, dr. D.Waterman, dr. Y. van der Werf

AMSTERDAM: PERSONAL HEALTH INSTITUTE INTERNATIONAL

The research of Personal Health Institute international (PHIi) evolves around inter-twined boundaries of technology, physiology and behavior. The ongoing research on knowledge based modeling of diagnosis and therapy has led to a computational model of a therapist providing Cognitive Behavior Therapy of insomnia. In an international consortium, under construction, this model will be tested for fine tuning of pharmacotherapy and application to teenagers. A research project in Germany has already started.
The diagnostic models and tools to advance sleep medicine is another area of activity. The members of the institute have already obtained a patent for modeling respiratory instability during sleep. PHIi is developing a consortium NEBULA CRUISER that will allow researchers and clinicians to share tools and models of signal and image processing. The membership to this NEBULA CRUISER consortium is open to all who like to focus on their work on signal processing without programming and who like to share ideas and expertise with their colleagues.
PHIi also develops wearable, wireless medical monitoring devices. A prototype of such a device, called CLOCKWATCHER, a wearable and ubiquitous monitor for measuring intrinsic physiological rhythms in humans, is in the validation and testing phase. Development and testing is done in conjunction with the EUCLOCK consortium of the European Union. Another wearable medical device GALAXY will soon be validated and tested in Stockholm for long-term monitoring in real-life situation of children with Prader-Willy Syndrome.

PHIi also undertakes contract research and provides services as CRO. Recently, PHIi worked on the evaluation of a pharmaceutical agent for OSAS and validation of bruxism therapy.

Researchers: ing. W. Ecke, drs. M. Fischer, dr. W.F. Hofman, A. Kumar, MSc (a.kumar@phi-i.com), dr. C. Lijzenga, dr. P. Rao

ARNHEM, SLEEP CENTRE ALYSIS,

Sleep centre Alysis in Arnhem is specialised in diagnosing and treating slaap apnea patients in a quick and patient-friendly manner in amultidicsiplinary team. Most sleep studies are ambulatory and our waiting list is short. Patients meet different specialists in one afternoon. We are also specialised in preventive vasculary risk screening in this patient group and therefore we have a close relationship with the vascular internal specialist. Risk patient are included in a life style program.
In our sleep centre we also diagnose and treat patients with a variety of lung diseases, insomnia, restless legs and snoring.
Research is focused on patients with chronic lung diseases

Dr. PJE Vos (pulmonologist), Drs. P. de Bruijn (pulmonologist), Drs. L. Ferman (ENT), Dr. P.H.E. Hilkens (neurologist), Drs. P.A.G. Rijsemus (dentist).

BREDA / OOSTERHOUT: AMPHIA HOSPITAL, CENTER FOR SLEEP-WAKE DISORDERS

Our center is located in the Amphia hospital on the Pasteurlaan in Oosterhout, region West-Brabant The multidisciplinary team consists of clinical neurophysiology personel, a specialised nurse, neurologist, pneumologist, ENT physician, neuropsychologist and psychiatrist. There are possibilities for clinical and ambulatory sleep research (polygraphy/polysomnography, actigraphy, sleep endoscopy) for diagnosis and treatment of sleep related breathing disorders, RLS/PLMS, circadian rhythm disturbances, sleep and epilepsy and ADHD.

Researchers: A.H.Temmink (neurologist), J.Asin (pneumologist) and E.Janssen (Otolaryngologist).

EDE: CENTRE FOR SLEEP-WAKE DISORDERS AND CHRONOBIOLOGY OF THE GELDERSE VALLEI HOSPITAL

This sleep centre, situated in the midst of the Netherlands, has extensive possibilities to study disorders in out patients as well as in hospitalised patients. Treatments are recommended that can be supervised by the patients' general practitioner. Special interests are circadian rhythm disorders and sleep disorders in children, blind people, autistic patients and in patients with ADHD, chronic whiplash syndrome, chronic fatigue syndrome and intellectual disability. There is a collaboration with the Expertise centre for sleep disturbances in individuals with intellectual disabilities (Maastricht University - Gouverneur Kremers Centre). Effects of melatonin treatment on circadian rhythm disorders are presently evaluated. Patients are asked to complete the "zelftest slaapstoornissen" at www. slaapstoornissen.nl

Researchers: dr. P.H.P. Jansen, dr. M. Majoor, dr. A.J.M. Vos, , dr. M.G. Smits, drs M.Smidt

ENSCHEDE: SLEEP CENTRE OF THE HOSPITAL 'MEDISCH SPECTRUM TWENTE'

This sleep centre located in the east part of The Netherlands is an example of symbiosis between the Clinical Department of Respiratory Medicine and the Department of Clinical Neurophysiology. It fulfils a supra-regional function in the diagnosis of sleep disorders and nightly respiratory disturbances. Currently the research topic is prevalence of sleep disorders in patients with chronic toxic encephalopathy.

Researchers: dr. Duijvenstein, drs. M. Eijsvogel, mr. B. Hilhorst, dr. J. Vliegen, drs. J. Vliegen

GRONINGEN: UNIVERSITY OF GRONINGEN

The Research Group CBN-Chronobiology has a long history of research in the field of causation, function and timing of behavior in animals and humans. Theoretical work on the temporal organisation of sleep-wake behavior in humans goes hand in hand with experimental work in the available 4-subject temporal isolation facility. This facility is used to study the regulation of sleep and performance in humans in relation to environmental light. Non-human research focuses on the generation and function of circadian rhythms and sleep in nocturnal and diurnal rodents, in worms, fungi, and yeast. There is a long-standing tradition of collaboration with various members of the Department of Biological Psychiatry of the Groningen University, which, in collaboration with the Institute of Pharmacology in Zürich, has led to the two-process model of sleep regulation.

Researchers: prof. dr. D. Beersma, drs. A. Boerema, drs. Z. Chen, drs. M. Comas Soberats, prof. dr. S. Daan, dr. M. Gerkema, drs. M. Gimenez, dr. M. Gordijn, dr. R. Hut, prof. dr. M. Merrow, dr. A. Strijkstra, drs M.van de Werken, drs D. Lenssen, dr M. Maas, dr R. Bertossa, dr V. Pilorz

GRONINGEN: UNIVERSITY OF GRONINGEN

Research at the Department of Molecular Neurobiology includes studies on sleep and circadian rhythmicity. Animal models are used to study the function of sleep as well as the consequences of sleep loss, particularly, the role of sleep in neuronal plasticity and cognitive function, the relationship between stress and sleep, and the effects of disrupted or restricted sleep on brain function, stress sensitivity and emotionality. Studies on circadian rhythmicity include regulation of protein expression in the suprachiasmatic nucleus and the role of this biological clock in modulation of cognitive processes.

Researchers: drs. T. Cetin, drs. G. Dagyte, drs. R. Hagewoud, drs. R. Havekes, drs. H. Hulshof, dr. P. Meerlo, drs. A. Novati, dr. E.A. van der Zee

GRONINGEN, UNIVERSITY MEDICAL CENTER: CENTRE FOR SLEEP/WAKE DISORDERS

The Centre for Sleep/Wake Disorders of the UMCG is a multidisciplinary sleep centre for the study, diagnosis and treatment of sleep/wake disorders. Situated within the framework of an Academic Hospital, it is characterized by the close cooperation between all involved disciplines. In its diagnostic activities, the center focuses on ambulatory and clinical long-term recording techniques.
Research focuses on the themes: therapy of OSAS, PLMS, sleep disturbances in cardiac and renal failure, and driving capability in patients with EDS.

Clinicians/researchers: Prof. Dr. L.G.M. de Bont, Prof. Dr. W.H. Brouwer, M.H.J. Doff, Dr. J.W. Elting, M.G. Gremmer, Dr. D.J.. Heersema, Drs. A. Hoekema; Dr. J.H. van der Hoeven (external contacts) , Drs. A.G.W. .Korsten-Meijer; Dr. G.J. Luijckx;; Drs. J.A. Nieuwenhuis, Dr. P.J. Wijkstra

HEEZE: SlEEP MEDICINE CENTRE 'KEMPENHAEGHE'

The Centre for Sleep Medicine 'Kempenhaeghe' is specialised in complex sleep-related breathing disorders, neurological sleep disorders and non-pharmacological treatment of insomnia. These topics are also focus of the clinical research lines of the center. In addition, there is a close collaboration with the department of Neurology of the Radboud University Nijmegen Medical Centre on the diagnosis, treatment and scientific study of sleep disorders in patients with Parkinson's disease.

Prof.dr. D. Pevernagie (director), mrs. N. Duis, dr. M.G. v. Erp, dr. C. Henke, drs. M. van de Laar, mrs. P. van Mierlo, dr. S. Overeem (scientific coordinator), dr. Th. W. Rentmeester, drs. K.E. Schreuder, mrs. A. Teeuwen, Drs. N.L.E. Vandenbussche, dr. H.M.J.C. Verbeek, drs. K. Vleer.

HENGELO, STREEKZIEKENHUIS MIDDEN-TWENTE: CENTRE FOR SLEEP/WAKE DISORDERS.

The centre for sleep/wake disorders of the Ziekenhuisgroep Twente in Hengelo is located at the Department of Neurology and Clinical Neurophysiology. The multidisciplinary team consists of sleep technicians, a neurologist / neurophysiologist, psychiatrists, socialpsychiatric nurses, pulmonologists, orthodontists, EN&T-specialists and pediatricians. Ambulatory sleepstudies, clinical whole night sleep studies, and multi sleep latency tests form the main basis for diagnostics and treatment of respiratory disturbances in the sleep, restless legs syndrome, narcolepsy and other disturbances of nighttime sleep and excessive daytime sleepiness. At this moment research is focussed on chronic primary insomnia (contract research; clinical pharmocotherapeutical study).

Principal researcher / coordinator "Sleep Team": T.J. Tacke, neurologist / clinical neurophysiologist.

‘S-HERTOGENBOSCH: SLEEP-WAKE CENTER, JEROEN BOSCH HOSPITAL

The sleep-wake center ‘s-Hertogenbosch is a multidisciplinairy center with neurologists, pulmonologist and ear nose and throat specialist. It is located at the Carolus-location of the Jeroen Bosch hospital.
Patients will be assessed by standardized questionnaires after which they will be invited for PSG or apnea-link. Most patients will be investigated by clinical overnight-registration, but ambulatory registration is also possible. Disorders of sleep and parasomnias will be further treated if necessary by the team; the pulmonologist takes responsibility for the OSAS-treatment.
In 2009 a psychologist will take part in the center.

Researchers: drs. Th.P.J. Timmerhuis, neurologist; dr. T.M. Macken, pulmonologist;
dr. E. Teunissen, ear nose and throatspecialist

LEEUWARDEN: MCL CENTRE FOR SLEEP AND WAKE DISORDERS

Since 2000 the Medical Centre Leeuwarden (MCL) has had a fully equipped Centre for Sleep and Wake Disorders for diagnosis of insomnia, parasomnias and the several forms of sleep apnoea syndrome. The emphasis is on clinical oriented investigation. Most of the studies are out-patient studies. Hospital studies are mainly used for unsolved problems and for adjustment of patients to CPAP. The centre has a regional function for the province of Fryslân.

Researchers: drs. J. den Heijer, drs. H. Pasma, drs. R. Plaat, drs. H. Postma.

LEIDEN: UNIVERSITY MEDICAL CENTER

The Department of Public Health and Primary Care investigating sleep disorders and the prevalence of sleep apnoea in general practice. The Dutch standard for general practitioners 'Insomnia and Hypnotics' is being evaluated. Furthermore, aspects of sleep disturbances in patients with chronic fatigue syndrome are evaluated. Moreover, the department is involved in research projects concerning the treatment of patients with chronic use of benzodiazepines.

Researchers: dr. A.W. Graffelman, dr. A. Knuistingh Neven

LEIDEN UNIVERSITY MEDICAL CENTRE

The Department of Pulmonology is involved in the care for patients with sleep disordered breathing, mainly sleep apnea and obesity hypoventilation syndrome.
Sleep disordered breathing is a small part of the curriculum for medical students. Physicians in training for pulmonologist participate in clinical care for sleep apnea patients. The research activities concern sleep disordered breathing in patients with pulmonary hypertension and the role of disturbed sleep in endocrine dysfunction such as hypophyseal, hypothalamic tumors and paragangliomas. Collaboration is being intensified with the department of Endocrinology, Neurology and Vascular Medicine.

Researchers: dr. K.W. van Kralingen

LEIDEN: UNIVERSITY MEDICAL CENTER

Our research group in the Laboratory for Neurophysiology at the Department of Molecular Cell Biology is involved in fundamental research on sleep regulation with emphasis on the interaction between the circadian clock and sleep regulatory mechanisms. Research is mainly approached in rats and mice applying long-term recordings of the electroencephalogram and neuronal activity on the multi-unit and single-unit level together with behavioral techniques to record daily rest-activity patterns.

Researchers: dr. T. de Boer, drs. T. Houben, drs. H.-T. van der Leest, prof. dr. J. H. Meijer, dr. S. Michel, drs. F. F. T. O. van Oosterhout, drs. J. Rohling, dr. R Yasenkov.

http://www.lumc.nl/1050/research/Neurophysiology3_research.html

LEIDEN: UNIVERSITY MEDICAL CENTER

The department of Neurology and Clinical Neurophysiology hosts an outpatient clinic for patients suffering from narcolepsy and related disorders. Research topics include the role of sleep in metabolism and pathophysiological and clinical aspects of narcolepsy and cataplexy. The department also serves as European reference centre for the measurement of hypocretin-1. There is a close collaboration within the LUMC with the departments of Pulmonology, Endocrinology and Neurophysiology(basal sciences). On a national level there is a close collaboration with the sleep centres in the Radboud University Nijmegen Medical Centre and the Center for Sleep/Wake disorders in the Hague.

Researchers: dr. G.J. Lammers, dr. S. Overeem, prof. dr. J.G. van Dijk, drs. C.E.H.M. Donjacour, drs. R. Fronczek and drs. W.L.M. van der Zande.

MAASTRICHT: EXPERTISE CENTRE FOR SLEEP DISTURBANCES IN INDIVIDUALS WITH INTELLECTUAL DISABILITY, MAASTRICHT UNIVERSITY (GOUVERNEUR KREMERS CENTRE)

This expertise centre is an initiative of the Gouverneur Kremers Centre (Maastricht University) in collaboration with the department of Special Education (Radboud University Nijmegen), the department of Sleep-Wake Disorders and Chronobiology (Gelderse Vallei Hospital), the Koraal Groep and ‘s Heeren Loo Zuid-Veluwe. Research is focused on sleep problems in individuals with intellectual disabilities (ID) and individuals with syndromes (for example Angelman syndrome, Prader-Willi syndrome, Cri du Chat syndrome and Jacobsen syndrome). Research topics are, amongst others, prevalence of sleep problems in specific syndromes, behavioural treatment of sleep problems and melatonin treatment of circadian rhythm disorders. Also clinical data of the Sleep clinics for individuals with intellectual disability are evaluated. Methods of research include materials such as (sleep) questionnaires, sleep diaries, actigraphy, ambulatory polysomnography, measurement of melatonin levels in saliva and designs such as double-blind placebo controlled trials and single case studies.

Researchers: W. Braam, M.D., Ph. Collin, M.D., prof. dr. L.M.G. Curfs, dr. R. Didden, A.P.H.M. Maas, M.A., and dr. M.G. Smits.

MAASTRICHT: SLEEP CLINICS FOR INDIVIDUALS WITH INTELLECTUAL DISABILITY, MAASTRICHT UNIVERSITY (GOUVERNEUR KREMERS CENTRE)

On the initiative of the Gouverneur Kremers Centre (Maastricht University) two outpatient sleep clinics are functioning at this moment. One is located at the Koraal Groep and the other at 's Heeren Loo Zuid-Veluwe (Wekerom). Each clinic is specialized in diagnosis and treatment of sleep problems in children and adults with intellectual disability. Treatment is based on results obtained from sleep questionnaires, sleep diaries, measurement of melatonin levels in saliva and if considered necessary ambulatory polysomnography and actigraphy. Treatment is multidisciplinary: medical treatment (for example melatonin treatment for circadian rhythm disorders) and/or behavioral treatment (for example gradual distancing for co-sleeping). Treatment is performed in the patient's home setting, if possible. All clinical data are stored in the database of the Gouverneur Kremers Centre which guarantees scientific evaluation.

Staff members: W. Braam, M.D. (physician for individuals with intellectual disabilities), Ph. Collin, M.D. (child and adolescent psychiatrist), A.P.H.M. Maas, M.A. (orthopedagoge/behavior specialist), dr. M.G. Smits (neurologist/sleep specialist), dr. R. Didden (health care psychologist) and prof. dr. L.M.G. Curfs (professor of learning disabilities).
www.slaapstoornissen.nl (button: Verstandelijk Gehandicapten)
(0318) 59 35 65 (Monday, Wednesday or Thursday between 8:00 and 12:00)

MAASTRICHT: MAASTRICHT UNIVERSITY

The Department of Respiratory Medicine studies, in collaboration with the Sarcoidosis Management Center, the Department of Neurology, the Nutrition and Toxicology Research Institute Maastricht (NUTRIM) and the Department of Pulmonary Medicine University of Antwerp (Belgium), the association between disturbed sleep and sarcoidosis. Patient care is also focussed on hypoventilation, sleep apnea and indications for non-invasive ventilation.

Researchers: Dr. C. van der Grinten, Dr. N. Cobben, Prof. Dr. M. Drent, Prof. Dr. J. Verbraecken and Prof. Dr. E. Wouters.

MAASTRICHT: MAASTRICHT UNIVERSITY, Faculty of Psychology and Neuroscience

The section Neuropsychology and Psychopharmacology of the faculty of Psychology and Neuroscience is involved in research on the effects of drugs and nutritional manipulations on sleep quality and daytime functioning, with a special focus on car driving. One of our research programs projects aims to assess the effects of insomnia and chronic use of hypnotics on driving performance in insomniacs. Another line of research assesses next day residual effects of newly developed hypnotics on cognition and driving of healthy volunteers, using various computerised psychomotor, cognitive and attention tasks and a standardized highway driving test on a public road in normal traffic. Another project investigates the involvement of the brain serotonin (5HT) system in sleep and sleep related cognitive and emotional decline by means of dietary brain manipulation methods.

Researchers: Dr. A. Vermeeren (a.vermeeren@psychology.unimaas.nl), Drs. T. Leufkens, Dr. R. Markus, Prof. Dr. W. Riedel

NIEUWEGEIN/UTRECHT: CENTRE FOR SLEEP AND WAKE DISORDERS St. ANTONIUS HOSPITAL

www.slaapstoornissen.nl
The Nieuwegein/Utrecht Centre for Sleep and Wake disorders of the St Antonius Hospital is a multidisciplinary sleep centre in which two neurologists, two pulmonologists, an ear nose throat specialist, a psychiatrist, an oral and maxillofacial surgeon, a special dentist and a behavioural therapist all work closely together for the benefit of about 1500 sleep and wake disordered patients each year.
Research focuses on restless legs syndrome (associated with polyneuropathies; associated with spinal anesthesia; ferritin; somato-sensory evoked potentials; contractresearch drug studies), on sleep quality in chronic sarcoidosis patients, on light to moderate sleep apnea syndrome (multilevel hyoidothyreoidopexy surgery; palatal implants; new intra-oral device) and on insomnia (behavioural therapy; contractresearch drug studies).

Researchers: dr OJM Vogels, dr LL Teunissen, V Duurkens; H van der Zeijden; dr MP Copper; S Roelfs; FW Huisman; HP Volkers; L Bronts

NIJMEGEN: RADBOUD UNIVERSITY NIJMEGEN

At the Department of Biological Psychology of the Radboud University Nijmegen, the neurophysiology and neuropsychology of sleep, including REM sleep, is the central topic. Using the concept of 'sensory gating', information processing during the various sleep-wake states is investigated. This is partly done in co-operation with Johnson and Johnson, Pharmaceutical Research and Development, in Beerse, Belgium. Also effects of various psychoactive drugs on sleep-wake states are determined. Research is mainly approached in rats, using EEG and ERP recordings and behavioral techniques. The cognitive capacities of the brain in several states of vigilance and alertness are studied both in rats and humans. Neuronal activities underlying components in the human ERP and effects of vigilance and attention on these components are studied.

Researchers: prof. dr. A. Coenen (contact: a.coenen@nici.ru.nl), dr. W. Drinkenburg, dr. P. Eling, dr. E. van Luijtelaar

NIJMEGEN: NISPA

Nijmegen Institute of Scientist-Practitioners in Addiction is a knowledge centre for addiction and addiction care. NISPA is a part of the Academic Centre for Social Sciences at the Radboud University Nijmegen and consists of 4 addiction care institutions in the southern ans eastern part of the Netherlands. Participating institutions are: Novadic-Kentron, TACTUS, Iris-zorg and the GGZ Noord en Midden-Limburg. One of the NISPA research groups aims to study quality and quantity of sleep during detoxification of drugs and alcohol in an inpatient population. The main issues are sleep quality (subjective and observed) and

sleep problems in detoxified patients in addiction care and the the use of non-farmalogical treatment in this population.

Researchers: Cor A.J. De Jong, M.D., Ph.D., Associate professor of Clinical Psychology, prof. dr. A. Coenen (contact: a.coenen@nici.ru.nl), Dr. C, Klaassen, psychiatrist GGZ Noord- en Midden-Limburg, Drs. Ellis H. B. Magnée, PhD student and researcher in addiction care in the GGZ Noord- en Midden-Limburg,.

NIJMEGEN: UNIVERSITY MEDICAL CENTRE NIJMEGEN

The Department of Pulmonary Diseases 'Dekkerswald' of the University Medical Centre Nijmegen (UMC) is specialised in sleep disordered breathing in patients with chronic obstructive pulmonary disease, chest wall deformations, respiratory muscle failure, problems with control of breathing, chronic heart failure and obstructive sleep apnoea syndrome. Research and patient care are performed on administration of nocturnal oxygen, respiratory muscle training, respiratory stimulants, NIPPV and CPAP treatment, OSAS and diastolic heart failure.

Researchers: dr. Y. Heydra, drs. J van Haren-Willems, drs. H van Helvoort

NIJMEGEN: RADBOUD UNIVERSITY NIJMEGEN MEDICAL CENTRE

At the Department of Neurology, sleep disturbances in neurodegenerative disorders are evaluated, with an emphasis on extrapyramidal syndromes. Within this line, REM Sleep Behavior Disorder receives special attention, both in clinical care and basis research. This research is performed in close collaboration with the Centre for Sleep Medicine 'Kempenhaeghe'. Research on narcolepsy, especially the pathophysiology of cataplexy is performed in close collaboration with the group of the Neurology department of the Leiden University Medical Center.

Researchers: dr. S. Overeem, prof.dr. B.R. Bloem, prof.dr. M. Zwarts

OSS: SCHERING PLOUGH RESEARCH INSTITUTE (SPRI)

The effects of newly developed as well as established psychotropic drugs are studied on rat sleep and waking behavior in the research facilities in Schotland at Newhouse. Special emphasis is given to the study of drug effects on electroencephalographic parameters during waking and sleeping. In phase I clinical trials sleep and electroencephalographic changes during sleep are often taken along as a sensitive biomarker for the CNS effects of drugs in first human exposure studies. Occasionally sleep is studied in depressed patients for the study of putative antidepressant compounds, as it is well-known that antidepressants can reverse the typical sleep disturbances of depression. Apart from the use of sleep as a biomarker for the CNS effects of psychotropic drugs, SPRI is currently developing novel pharmacotherapeutic interventions for insomnia.

Researchers: dr. G. Ruigt, dr. B. Slaap, dr. F. Ruwe, dr. L. Stet, dr. G. van Osta, dr. N. Ward, dr. N. Ivgy-May

ROTTERDAM: ERASMUS MC

At the Department of Epidemiology and Biostatistics, insomnia and its determinants are studied in more than 1,000 elderly inhabitants of Ommoord, a suburb of Rotterdam, representative of a normal population aged 55 and over. Actigraphy, sleep diaries and questionnaires are used to assess sleep patterns and the presence of insomnia. This research is carried out within the Rotterdam Study, an ongoing population-based cohort study. Its overall aim is to investigate the incidence of, and risk factors for, chronic disabling diseases.

Researchers: dr. H. Tiemeier, drs. J.F. van den Berg, dr. A. Knuistingh Neven (LUMC), dr. J.H.M. Tulen, prof.dr. A. Hofman

At the Department of Psychiatry, ambulatory recording methods (based on accelerometer sensors) are used to study daily functioning in relation to psychomotor disturbances, clinical symptoms and efficacy of treatment in depression, ADHD, and Tourette's syndrome. In addition, we use wrist-actigraphy to quantify disturbances in sleep-wake pattern and behavioral recovery in post-operative delirium; as such, 24-hr motor activity parameters are quantified and explored for their usefulness to contribute to an improvement of prognosis of delirium by early treatment, and relevance for the development and evaluation of treatment strategies.

Researchers: dr. J.H.M. Tulen, drs. R.J. Osse, drs. M. Vegt, prof. dr. M.W. Hengeveld, Prof. dr. A.J.J.C. Bogers

RIJSWIJK BIOMEDICAL PRIMATE RESEARCH CENTRE

Sleep-Wake Research at the Department of Diagnosis and Therapy of TNO is focussed on applied fundamental research on sleep and alertness management. Research is performed with non-human primates applied with telemetric transmitters for electroencephalogram and electromyogram. Besides effects on various sleep-wake states of the sleep architecture, behavioral techniques like activity, motor functions and cognition are theme of the expertise to measure effects of hypnotics, alertness enhancers or effects of sleep deprivation. Recently the research of the relation between neurodegeneration or stress on the sleep pattern has started in human-like models for stress and for Parkinson's disease.

Researchers: Ingrid Philippens, Raymond Vanwersch

SOESTERBERG: TNO HUMAN FACTORS

Since 1988, TNO Human Factors-Aerospace Medicine Group (until 2002 known as Netherlands Aeromedical Institute) has extensively used objective and subjective methods in large studies on sleep, sleepiness, fatigue, and performance in commercial and military aircrew and operators engaged in safety-sensitive jobs. Our expertise is centered on the evaluation of sleep, alertness, and performance under operational conditions (e.g. aircrew, professional drivers, sea transport, railroad, military crew) and in clinical trials on hypnotics, stimulants, and side-effects of drugs. The results of the studies incorporated in our Sleep and Alertness Management Program have provided reliable and practical assessment tools for investigating humans in real life settings. Our research and consultations are commissioned by the Ministries of Transport and Defense, Joint Aviation Authority (Europe), International

Civil Aviation Authority (ICAO), NATO, airlines and patient organizations. In collaboration with our international partners (German Centre of Aviation Medicine, Karolinska Instutet, Université René Descartes, Qinetiq Centre for Human Sciences, NASA), a database has been established, which enables interpretation of results in terms of practical relevance for impact on daily life, performance of operator tasks, etc.

Researchers: Hein Daanen, Ineke Klöpping, Roy Raymann, Ries Simons, Pierre Valk, Susan Vrijkotte & Ellen Wilschut.

THE HAGUE: 'ParnassiaBavo Group' PSYCHO MEDICAL CENTRE

PsyQ
Department of Affective Disorders
Section Medical Chronobiology

The aim of this centre is to evaluate the subjective and objective aspects of sleep, mental status and circadian rhythms in the research program 'chronobiology and psychiatry'. The links between chronobiological disturbances and psychiatric disorders are examined in a clinical setting. Emphasis is laid on the treatment with psychoeducation, chronotherapy and bright light therapy in depression, sleep disturbances, chronic fatigue syndrome, dementia, post-partum depression and schizophrenia. Moreover the role of melatonin in the human reproductive system is studied. Other topics of interests and research is focussed on the premenstrual syndrome, perinatal depression, atypical depression and social rhytms. The role of light therapy on the reproductive cycle is studied as well as polymorphisms in cortisol receptors (functioning of HPA axis) in seasonal affective disorders and bipolar disorders.

Researchers: Dr. P.M.J. Haffmans, Drs. L. den Hoed, Dr. M. Blom, Drs. A. Spijker, Drs. V. Koppelaar, Drs. P.Leydens, Drs. M. v.d. Zon, Prof Dr E Hoencamp.

THE HAGUE: CENTER FOR SLEEP/WAKE DISORDERS

The Center for Sleep/Wake Disorders, a department of the Medical Center Haaglanden, location Westeinde, a large regional hospital in The Hague, is a general sleep center for the study, diagnosis and treatment of sleep/wake disorders. Situated within the framework of a general hospital, the center is characterized by a broad, multidisciplinary approach as evidenced by the close cooperation between neurologists and psychologists, physicists, IT-specialists, ENT-specialists, and others. In its diagnostic activities, the center focuses on the application of sophisticated ambulatory recording techniques (e.g. multi-channel 24h recordings, long-term actigraphy) and extensive in-depth psychological assessment. The center offers all available state-of-the-art treatment facilities, which are continuously updated on the basis of careful monitoring of treatment outcome measures.
Both applied and fundamental research of the center focuses on the following main themes: chronic insomnia, parasomnia, circadian rhythm disorders and automatic sleep analysis. Most research is carried out in close cooperation with both the University of Amsterdam and the University of Leiden.

Clinicians/researchers: drs Marieke de Gier, drs. Viviane van Kasteel, dr.ir. Bob Kemp, prof.dr. Gerard Kerkhof, drs. Caroline Kluft, dr. Roselyne Rijsman, dr. RobJan Schimsheimer, drs. Marthe Sernee, Drs. Monique Geuke en Drs. Anna Brouwer

UTRECHT: UTRECHT UNIVERSITY

The research of the Department of Clinical Psychology focuses on nightmares; in particular on the assessment, associated features, and cognitive-behavioral treatment of nightmares. This applies to both posttraumatic and idiopathic nightmares. Questionnaires measuring other sleep disorders are evaluated as well.

Researchers: dr. V.I. Spoormaker, drs. J. Lancee, prof. dr. J. van den Bout

ZWOLLE, SLEEPCENTER SEIN ZWOLLE (SSZ)

The Sleepcenter is closely connected to the SEIN Epilepsycenter in Zwolle. Diagnostic and therapeutic facilities are available for all kinds of sleepdisorders. Special fields of interest are sleep in children and teenagers, restless legs syndrome and the interrelation between sleep and epilepsy. Contractresearch is done on a regular basis.

Researchers: Dr.Al de Weerd, Dr.Hanna van Hemert-van der Poel, Drs. Mireille Bourez-Swart, neurologists; Drs. Monique Thijssen, Drs. Wendy Pot, psychologists; technician (vacancy).