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Edited by
Tom de Boer
Leiden University Medical Center, Leiden

Viviane van Kasteel
MC Haaglanden, Den Haag

Cathalijn Leenaars
University of Maastricht, Maastricht

Peter Meerlo
University of Groningen, Groningen

Els Møst
Philips Research, Eindhoven

Floor van Oosterhout
Slotervaart Hospital, Amsterdam

Johan Verbraecken
University of Antwerp, Antwerp
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PREFACE

Dear colleagues

The Netherlands Society for Sleep and Wake Research NSWO is celebrating this year its 25th anniversary. This special issue of our “yearbook 25” contains a summary of the history of our society and is a compilation of the highlights in sleep research and sleep medicine in the past 25 years.

Great names in Sleep research and Sleep medicine

Sleep research in the Netherlands has focused on the function of the circadian clock, the sleep homeostatic process and all disorders that develop when these processes are hampered. The early work of Rudi van den Hoofdakker on sleep deprivation and depression is a good example of how basic research resulted in clinical treatment. Also light therapy for Delayed and Advanced Sleep phase Disorders is the result of this extensive research and basic work on the circadian clock. This work is at present still continued by a large group of researchers that have spread out over the Netherlands and the rest of the world. It is therefore that we honour Van den Hoofdakker with a yearly lecture in his name.

Basic animal research was also performed in the early seventies by Piet Visser in cats. Lesions at several levels of the brainstem resulted in sleep with and without atonia, which contributed tremendously to the present day knowledge on sleep disorders during REM sleep and Non REM sleep. His lectures with sham-rage cats were quite remarkable if not to say spooky. Although at the time this may have been underestimated, his lectures are embedded in everyone’s memory and his research resulted in knowledge that is only recently understood in world of sleep medicine. It therefore that the NSWO honours Visser with a yearly poster price in his name.

Hilbert Kamphuisen was the first clinical neurophysiologist that focussed medical attention on the use of polysomnography for diagnosis and treatment of day-to-day sleep problems in the medical practice, starting with sleep apnea. He brought the knowledge of science to the clinic. From his work and that of others the modern sleep centres are a result. He also understood the importance of combining the knowledge of sleep research and sleep medicine. His drive and that of Guus Declerck resulted in the founding of our society on the 25th of November 1989, of which we celebrate today’s 25th anniversary.

In the honour of Kamphuisen we therefore decided to have a bi-annual award for the best PhD thesis in the field of sleep research and sleep medicine in the Netherlands which will be awarded this year for the first time.

Public awareness and sleep

The public awareness of NSWO activities has grown tremendously in the last years. The yearly polls on sleep related subjects have established an important and focussed attention in media land. Some newspapers quote spontaneously our yearly results and the PR committee of NSWO is consulted frequently about news concerning sleep and wake and its effect on mental and physical functioning.

Training for sleep specialist

The field of teaching in sleep medicine and the accreditation of sleep centres made a huge step forward in the past 25 years. From a single sleep monitoring tests per month in one or
two Dutch centres we have come to a multitude of focused sleep medicine departments where 12 or more sleep recordings are performed each day. An accreditation process which was earlier developed in the US and Germany is now fully under way also in the Netherlands. Multidisciplinary work in this respect is indispensable and has resulted already in approximately 10 accredited general sleep centres in the Netherlands. Although the title “somnologist” is not yet recognized in our country, but we are happy to announce that we already have at least 10 of these specialists in the Netherlands, after they passed the ambitious European Somnologist Exam, which took place this year for the third time. In addition, NSWO is partner in an Anglo-Belgian-Dutch organization to host in alternation an annual trainings meeting called the International Sleep Medicine Course (ISMС). This sleep medicine course focuses on the preparation for the yearly European Somnologist examination and the European examination for Sleep technician. The last ISМС course took place November 17-20 this year in the Netherlands. The May 2014 meeting on “Age and Sleep” in Amsterdam which was co-hosted by the pulmonologists specialized in Sleep (WAS) and neurologists in sleep (SWS-neurology) was a big success. Together with both societies we are planning to continue this effort of a yearly meeting on important topics in sleep research and sleep medicine.

Future role of NSWO

The NSWO is a society for sleep research and sleep medicine. Since the field of sleep medicine is expanding rapidly we have noticed that this is not reflected by the perception of most clinicians of our society. Sleep experts from many different specialties in medicine have founded their own society to promote their interests within their specific professional organizations. This is most prominent for pulmonology and neurology. Since Sleep Medicine is not yet a separate specialty we do not yet have a professional Sleep Medicine society. However, we assume that such a specialty will be established in the near future. It is therefore the wish, and we consider it as our duty, that the NSWO prepares the ground for such an organization within the framework of our society. We consider our society in this respect more as “lumper than splitter”! We will do our utmost to establish a Netherlands Society for Sleep medicine and Sleep research in which all different specialties concerned with sleep are welcome and feel at home. Together we can better reach our goals of higher standards in sleep research and sleep medicine then when we stay separate.

It is therefore my wish as present chairman of our society to be able to establish such a platform in the near future.

HLH

November 2014
EDITORIAL NOTE

The yearbook is a tradition where we are proud off. Before you lies the 25th edition of the proceedings of the Dutch Society for Sleep-Wake Research. To celebrate this milestone the first part of the book is dedicated to a historical overview, in images and writing, of our society. Two past presidents and the present president have written a personal view on the period in which they were active in the society. I would like to thank Ton Coenen, Gerard Kerkhof and Hans Hamburger for their contribution.

The scientific part of this edition kicks off with the summary of 3 PhD thesis. They are followed by comments and reflections on the thesis, written by senior researchers –experts in the field- who put the research in a broader perspective. I want to thank all contributors for their efforts.

This is followed by a list of 8 mini-papers and 47 abstracts. On behalf of the scientific committee I want to thank all NSWO members who contributed to this issue. I also want to thank my co-editors for their help with reviewing the mini-papers, ensuring that we achieve the highest quality possible.

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

This is my last yearbook as chief editor. I am resigning as chair and member of the scientific committee. My membership of the scientific committee started in 2004 and enabled me to get to know most aspects of sleep-wake research in the Netherlands. Chairing the committee was a new experience to me, but I learned a lot and I am glad that I took up the challenge. After 10 years, and some recent developments, particularly becoming the co-chair of the scientific committee of the European Sleep Research Society, I think it is time to hand over the task.

I wish you interesting reading!

Leiden, October 2014

Tom de Boer
Chair Scientific Committee
Chief Editor NSWO Proceedings
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Twenty-five years NSWO
On November 25 of the year 1989 24 sleep researchers gathered in the Academic Hospital in Utrecht. The meeting started at 13.15 and was closed at 14.30. In that time the ‘Nederlandse Vereniging voor Slaap-Waak Onderzoek’ (‘Dutch Society for Sleep-Wake Research’) (‘NSWO’) was founded. Hilbert Kamphuisen, who took the initiative for founding, was chosen as the first president, Rudi van den Hoofdakker as vice-president, Guus Declerck as secretary, Hans de Groen as treasurer, and Ton Coenen as chair of the scientific committee. Officially the society was founded at June 7, 1990 when Hilbert Kamphuisen with notary Verhees signed the founding act in Leiden. Hence, June 7 1990 is regarded as the official founding date of the Dutch Society for Sleep-Wake Research.

Figure 1: The cover of the foundation act, signed on June 7, 1990, of the Dutch Society for Sleep-Wake Research.
The formation of the Society did not come out of the blue. Before 1990 attempts to unite Dutch sleep researchers were already undertaken. An early publication in the ‘Nederlands Tijdschrift voor Geneeskunde’ (‘Dutch Journal of Medicine’) by the neurologist Hans de Groen, indicating the significance of ‘clinical sleep disorder centers’ in the USA, raised the interest for clinical sleep research and led to the formation of a ‘Project group CPAP-UPPP’, under the chair of Frans van der Meché. It cannot, however, be denied that mainly the group of professor Visser at the University of Amsterdam, planted sleep on the scientific agenda. Piet Visser (1919-2009), a physician and professor in psychophysiology, was the leader of a research group involved in fundamental and clinical sleep research. This was the first sleep research group in The Netherlands; reason that Visser is regarded as the grandfather of Dutch sleep research. On the sixth floor of the Jan Swammerdam Institute people worked and dreamed of sleep. Anand Kumar, a computer scientist and signal analyst of Piet’s group, endeavored in assembling researchers working in all areas of sleep. He organized in 1975 and 1976 a series of meetings for Dutch sleep specialists which should lead to the formation of a Workgroup Sleep and Dream. This resulted also in the organization of the first Dutch symposium entirely dedicated to sleep. Speakers at this meeting held in the sport center Papendal in October 1975, were, among others, Piet Visser, Rudi van den Hoofdakker, Heinz Prechtl and Ton Coenen. The work group, originally consisting of about 20 persons, gathered several times, but later dissolved. Nevertheless, despite the lack of a formal group structure, sharing of information between sleep researchers was achieved and informal contacts appeared strong. Looking back it cannot be denied that this workgroup was the forerunner of the later official Dutch society.

Figure 2: From left to right: Piet Visser with his wife Ata and (young) staff members Anand Kumar and Winni Hofman at a conference on sleep research in 1980. Prof. Visser was the first honorary member of the NSWO.
In the eighties Gerard Kerkhof and Ton Coenen made plans to reactivate the Kumar group, but they were overpowered by Hilbert Kamphuisen and Guus Declerck. All four travelled to the Ninth European Congress of Sleep Research in Jerusalem in 1988. Waiting on a taxi on airport Ben Goerion, Hilbert and Guus casually informed Gerard and Ton that plans to create a Dutch sleep society were already in an advanced stage. Relative newcomer in the field Hilbert Kamphuisen together with old hands Guus Declerck succeeded in doing so on November 25, 1989! With his promotional and charming talent Kamphuisen paved the way and pushed his plans through, as he used to do, and Guus did the formal things. The first official member meeting of the society was held in Utrecht on February 17, 1990. Rules and regulations of the society were discussed and a scientific committee installed. This committee, consisting of Domien Beersma, Gerard Kerkhof, Winni Hofman, Rob-Jan Schimsheimer, and chaired by Ton Coenen, launched two plans. The first was to organize two scientific meetings per year, one in the spring and one in the autumn, in rotating locations, and the second was to produce a yearbook in which research and scientific progress could be published.

Figure 3: The first board of the Dutch Society for Sleep-Wake Research. From left to right: Prof. Hilbert Kamphuisen (1931-2013), University of Leiden, founder and first president, Prof. Rudi van den Hoofdakker (1934-2012), University of Groningen, vice-president, Dr. Guus Declerck (1933), Kempenhaeghe Heeze, secretary, Dr. Hans de Groen (1943), University of Maastricht, treasurer, and Dr. Ton Coenen (1943), University of Nijmegen, chair of the scientific committee.

The first scientific meeting was held in December 12, 1990, at the Radboud University in Nijmegen. The content and topics of this gathering have disappeared in the oblivion of the past, but scarce minutes suggest that members presented their general research lines. It can be concluded that the scientific content was attractive since numerous meetings have followed. The first years of the Society were dedicated to provide a firm basis for existence, with opportunities for scientific discussions and an exchange of information. This goal was reached in the first years. The society had over 150 members with an average attendance of the meetings of more than 50. Next to the annual meetings, the yearbook of the society played an important role in the success of the Dutch sleep-wake society. The first volume of ‘Sleep-Wake Research in The Netherlands’ appeared already in 1990 and since that time the annual volume became a tradition. A tradition of which the society is proud of. Indeed, most national sleep organizations are jealous on this pearl of the Dutch society.
Publication of the yearbook was initially made possible by the sponsorship of the pharmaceutical company Lorex-Synthélabo, a subsidiary of the French company Sanofi-Synthélabo. Product managers of Lorex, Ineke van Boven and Francoise Isnard, were the driving forces behind sponsoring and were actively involved in an attractive appearance of the yearbook. At the introduction of the new sleeping medicine Stilnoct (zolpidem) in October 1993 in The Netherlands, Lorex-Synthélabo invited several members of the society for a visit to the research center of Synthélabo in Tours in France. This was integrated in a three day trip to Paris.

Figure 4: Twenty four volumes of ‘Sleep-Wake Research in The Netherlands’ have already been published. All volumes are in digital form available at www.nswo.nl/publicaties.

Figure 5: In 1993 Lorex-Synthélabo launched the hypnotic zolpidem (Stilnoct) in The Netherlands. To celebrate this, a biking tour for members of the Dutch Society for Sleep-Wake Research was organized in Paris. Among others are recognizable Ton Coenen, Hilbert Kamphuisen, Gerard Kerkhof en Hans de Groen.
A special scientific meeting took place at Janssen Cilag in Tilburg on November 16 and 17 1995 at the occasion of the first lustrum of the Society. At that meeting Hilbert Kamphuisen and Rudi van den Hoofdakker withdrew as board members and were succeeded by Ton Coenen and Gerard Kerkhof. The founder of the society, Hilbert Kamphuisen, emeritus professor in Clinical Neurophysiology at the University of Leiden, was appointed honorary member, as well as Rudi van den Hoofdakker, emeritus professor in Biological Psychiatry of the University of Groningen. Rudi van den Hoofdakker, famous in The Netherlands under his poet name Rutger Kopland, represented the Dutch society in an international scope. The lectures and poster presentations of the members in this two-days meeting showed the scientific improvements of the society in the first five years of its existence. Pharmacology of sleep, chronobiology, information processing in sleep and sleep disorders appeared to be strong topics in Dutch sleep research.

Since it was felt that the organizational basis of the society was steady and firm, and the scientific knowledge on a high level, the strive of the society became to act as a forum for relevant information for patients as well as for physicians, and, last but no least, for the general public. Consensus reports with guide lines were written on the fields of the ‘Non-pharmacological treatment of sleep disorders’ (chair Winni Hofman, 1996), of the ‘Obstructive sleep apnoea syndrome’ (chair Ton van Keimpema, 2001), and of the ‘Evaluation and measurement of vigilance’ (chair Gert-Jan Lammers, 2005). Guidelines for accreditation of sleep disorder clinics were discussed as well as for the use of CPAP treatment of OSAS patients. A start was made with the ‘Handboek slaap en slaapstoornissen’ (‘Handbook of sleep and sleep disorders’) under the editorship of Lex van Bemmel, Domien Beersma, Hans de Groen and Winni Hofman. The handbook came on the market in 2001 and is still in use.

In April 1998 the Sleep Service Line was installed in The Netherlands, implying that a telephone number became available for people with sleeping problems. The initiative was taken by the sleep society together with Lorex-Synthélabo, and supported by two patients associations, the Dutch Society for Narcolepsy and the Dutch Society of Sleep Apnoea Patients. The purpose of this line was to inform the general public about sleep hygiene and sleep disorders, and to advice people with sleeping problems. Information and advise were given by a computerized telephone. Over a period of one year, 10.000 people called the Sleep Service Line and according to structured interviews by the NIPO, an institute for market
research, about 27% of callers experienced improvements of their sleep. It is concluded that a minimal intervention by telephone using the sleep service line could be useful. The rise of internet and mass media outmoded the classic telephone line and offered alternatives for an adequate distribution of relevant sleep information.

Figure 7: This advertisement referred to the Sleep Service Line. With the installation of this telephone line, the Dutch sleep society showed that even simple instructions could be helpful for a better sleep.

Members of the society were active in the European Sleep Research Society (ESRS) founded in 1972. Every two years an ESRS congress was organized, but the congress in 1980, initially decided to be held in Birmingham, was a nightmare for Pierre Passouant, ESRS president at that time. At the last moment Birmingham announced not to be able to organize the congress. As an emergency measure, the ESRS contacted Piet Visser, who accepted the challenge. Visser and his group did a wonderful job. Anand Kumar introduced the now traditional ‘welcome meeting’ and ‘the young researchers grant’ at the ESRS conferences. Rudi van den Hoofdakker was a long time member of the Scientific Committee of the ESRS, while the Groningen group with Serge Daan and Domien Beersma played a leading role in the chronobiological part of the ESRS.
In November 1996 at the autumn meeting in Nijmegen, Guus Declerck, of Flemish origin, left the society as secretary and became an honorary member. In honor of Guus’ retirement a joint scientific meeting of the Belgian and Dutch sleep societies, BASS and NSWO, were organized at the Center of Sleep-Wake Disorders and Epilepsy Clinic Kempenhaeghe. Quality of lectures and quantity of attendants were high and since that time all spring meetings of the society are organized in collaboration with Kempenhaeghe. A second joint meeting with the Belgian Society, also attended by the Luxemburg colleagues, ‘Sleep at the third Millennium’, was held in Esch-sur-Alzette (Luxemburg) in 2000.
The first decade of the existence of the Dutch Society for Sleep-Wake Research was celebrated in November 2000 at the University of Nijmegen hosted by Ton Coenen. A wide variety of topics, presented by particularly young researchers was discussed extensively. During the business meeting some changes in the board were approved by the membership. The chair was transferred to Prof. Gerard Kerkhof, while Dr. Ingrid Verbeek succeeded Hans de Groen as treasurer. Furthermore the membership ratified the guidelines for the accreditation of Sleep-Wake Disorders Centers and those for the admission into the register of Clinical Sleep-Wake specialists. All these guidelines were implemented in the year 2001.

**Figure 10:** Shortly before the Nijmegen meeting in which the society chair was transferred from Ton Coenen to Gerard Kerkhof, members of the Dutch society flew to Istanbul to attend the 15th Congress of the European Sleep Research Society (ESRS). From left to right: Eus van Someren, Gerard Kerkhof, Ton Coenen and Ingrid Verbeek.

**Figure 11:** The third board of the society installed in November 2000. From left to right Prof. Gerard Kerkhof (1948), Prof. Hans Folgering (1943), Dr. Arie Knuistinighe Neven (1944), Dr. Ingrid Verbeek (1967), Dr. Lex van Bemmel (1949) and Dr. Marijke Gordijn.

In the ten years of its existence the Dutch Society for Sleep-Wake Research was transformed from a small number of sleep researchers scattered over The Netherlands, to a solid and viable society in which almost Dutch sleep researchers are cooperative members. The society could enter the second decade of its life with trust and in the security to extend the society further in membership size as well as in scientific respect and status.
CONSOLIDATION AND GROWTH
History NSWO 2000 – 2010

Gerard Kerkhof

Thanks to the Prefaces of the unsurpassed Yearbooks, started in 1990 on the initiative of Ton Coenen, my predecessor as chair, I have enough mnemonics to help me write this brief overview of the major events that occurred in the period 2000 – 2010, my term as chair of the NSWO. During the general membership meeting on November 10th 2000, mentioned by Ton Coenen in his overview of the 1990 – 2000 period, new board members were elected, i.e. Marijke Gordijn as secretary, Ingrid Verbeek as treasurer, Hans Folgering as member and Gerard Kerkhof as president.

From the perspective of and with the support of the board, I have witnessed, encouraged and occasionally initiated the following activities. But I don’t want to take off before thanking the board, in all its changing compositions, for our fraternal and truly heartening collaboration!

Figure 1: Ton Coenen (left) and Gerard Kerkhof, during the ESRS congress in Helsinki, 1992.

During the general membership meeting of November 10th 2000, the first step was taken on the long and winding road to the realization of the accreditation procedure for Sleep Disorders Centers as well as the certification of clinical sleep specialists. With the aims 1. to ensure the already existing quality of Dutch sleep disorder centers and specialists; as well as 2. to promote the quality of newcomers to the field, guidelines had been formulated, inspired by the example given by the association of clinical neurophysiologists and suggested by Al de Weerd. In hindsight, these guidelines proved the forerunners of European efforts to formulate standards for accreditation and education in the field of sleep medicine. The green light for this concerted European action was given during the first annual meeting of the presidents of 22 national sleep societies in April 2004, chaired by Irene Tobler, president of the European Sleep Research Society. Few suspected then that it would take almost a decade to coordinate all national objections, considerations, deliberations, etc. and to finalize the standards.
An excellent example of how energetic and successful a project similar to the aforementioned can be completed, was given by the OSAS Guidelines committee, chaired by Hans de Groen and Anton van Keimpema. In January 2001 this committee published the book entitled ‘Diagnostics and Treatment of the Obstructive Sleep Apnea Syndrome in Adults’. Subsequently, during the NSWO Spring meeting in March 2001 at the Kempenhaeghe Clinic, this book was formally presented as consensus report.

![Figure 2: 'Handbook Sleep and Sleep Disorders' and 'Diagnostics and Treatment of the Obstructive Sleep Apnea Syndrome in Adults', both published in 2001, under the auspices of the NSWO.](image)

In 2001 NSWO experienced another joyful success. The scientific committee, chaired by Lex van Bemmel, succeeded in realizing the publication of the ‘Handboek Slaap en Slaapstoornissen’, including chapters on normal sleep, the interaction of sleep and wake functions, the many facets of disturbed sleep and the various methods of treating sleep disorders, all chapters written by members of the NSWO.

A major item on the NSWO agenda was, is, and will be the promotion of public awareness of the functions of sleep and sleep-wake rhythmicity and the impact of disturbances of these functions. One of the ways to achieve this was the writing of 7 brochures covering the main aspects of sleep and sleep disturbances, intended for use by general practitioners and other health care workers (the brochures are available through the NSWO website). This joint effort of NSWO members was coordinated by Marijke Gordijn and was presented on November 9th 2001, during a public symposium on Sleep-Wake Disturbances held in the Meervaart, Amsterdam. This symposium was attended by more than 150 participants and attracted much attention from the various media.
The contacts with our Belgian colleagues of the BASS have always been very pleasant, not in the least because of the very enjoyable venues that were selected for our regular meetings. As an example of this, I remember a very comfortable and ‘Burgundian’ conference center, a former priorate in Corsendonk, that was booked by our Belgian hosts to accommodate the third Benelux sleep meeting, on October 19th 2002. The variety and quality of the local beers was impressive, as well as the themes ‘melatonin in health and disease’ and ‘pediatric sleep’, of course.

In past and present the board of the NSWO relied heavily on the activities in its various committees, i.e. the permanent committees for Science, Education, and Communication, and, not in the least, the ad hoc ‘consensus’ committees, e.g. for Insomnia and its treatment and for Vigilance, its disturbances and relevant methodology.

- The Science committee focuses primarily on two core events within the NSWO, i.e. 1. the organization of the scientific program of the annual membership meetings, and 2. the preparations for the publication of the annual Yearbook. As mentioned earlier, the members of this committee also served as editorial board for the Handbooks of 2001 and, jointly with Belgian colleagues, 2013.

- From 2011 onwards, it is the main task of the Education committee to organize the International Sleep Medicine Course, a 4-day in-depth course alternating between Belgium, the Netherlands and the United Kingdom, and started in 2007 on the initiative of the former presidents of the BASS and NSWO, Dirk Pevernage and Gerard Kerkhof. The course covers the essential basic and clinical aspects of sleep disorders and is intended for university graduates who want to pursue a clinical career in sleep medicine. A final exam offers the opportunity to qualify for the theoretical part of the ESRS certificate as sleep specialist.
The Communication committee started in 2006 (March 25th) with the organization of the annual ‘National Sleep Day’, on the Saturday preceding the annual changeover to daylight saving time, in Spring. On that occasion a selection of sleep disorders centers and sleep research institutes open their doors, welcome the general public and provide information about their activities and expertise. Preceding this public event, the communication committee draws up a web-based poll about a specific aspect of sleep, recruits as many respondents as possible, analyzes the data and publishes the results in a press release.

Both the Insomnia and the Vigilance committees have successfully produced consensus reports, in 1996 and 2005 respectively, and made these reports available to the membership.

In 2004 the NSWO board took the initiative to strengthen its contacts with the three patients’ associations in the field of sleep disorders, respectively the Dutch Society for Narcolepsy (NvN), the Restless Legs Foundation (SRL), and the Apnea Society. In a joint meeting of a board delegation and representatives of these associations, the latter expressed the wish to establish a structural basis for these joint meetings. These intentions have not materialized and deserve to be revitalized.

On November 4th 2005, during a very successful NSWO meeting at the epilepsy center SEIN in Zwolle, the Piet Visser challenge trophy (“In pursuit of the highest”) for the best poster was awarded for the first time. This award reflects the importance the NSWO attaches to participation of junior colleagues in particular, realizing that they deserve an optimal starting position to take over the ‘sleep stick’ successfully.
Figure 5: The Piet Visser challenge trophy (“In pursuit of the highest”). Prof.dr. Piet Visser, honorary member of the NSWO, has played a pivotal role in the development of sleep research in the Netherlands as well as the founding of the society for sleep-wake research. As a clinician and scientist he was uniquely qualified to inspire and unite all those involved in the multidisciplinary science of sleep. In recognition and appreciation the NSWO has established ‘The Piet Visser challenge trophy’, an annual reward for the best poster, set as encouragement for young sleep researchers in The Netherlands. We are grateful for his pioneering work and will remember him as an enthusiastic inspirer of all scientists and clinicians devoted to the science of sleep (In memoriam Piet Visser, deceased: February 23rd 2009).

Following the meeting of the National Sleep Societies within the ESRS and the ESRS board, held in 2007, the NSWO was officially authorized as an Associate Society Member of the ESRS.

On March 30th 2007, already the 9th edition of the annual clinical symposium ‘Epilepsy and Sleep’ was held in the Kempenhaeghe Clinic, and included a session on sleep and its disorders, given by colleagues from Belgium and our country. The annual ‘Epilepsy and Sleep’ meetings have become memorable events, perfectly organized in a warm southern, nearly Belgian atmosphere, and a natural successor of the annual Benelux conferences. The last of the series of Benelux meetings, on the subject of ‘Sleep and Health’, was held on May 11-12th 2007, in Luxembourg, and organized by Michel Kruger. Mainly because of declining funds, this series could no longer be continued, unfortunately.

On March 26th 2010 I stepped down as president, with the following farewell message.

More and more, the topic of Sleep is drawing the attention of already established fields of expertise, e.g. disciplines such as molecular genetics, cognitive sciences, dentistry, pulmonology, neurology and other medical sciences. Specific, discipline-oriented scientific journals publish increasing numbers of articles that report on sleep research. This is an
encouraging development, as it reflects a growing broadening of the recognition that sleep has a major impact on many, indeed if not all, aspects of life.

In my opinion, there is reason for some concern, however. The study of Sleep, at all possible levels of analysis - from the dynamics of single cells, through the brain systems involved, the development and acquisition of human sleep behavior, its formal and computational modeling, to the pathological and therapeutic aspects of sleep disorders -, is of an intrinsically interdisciplinary nature. Major progress can only be made by integrating already existing fields of expertise into one interdisciplinary effort.

Lately, parallel to the recently increasing number of sleep-related papers in many different scientific journals, we witness the emergence of discipline-specific societies focusing on sleep. Examples are sleep medicine societies within the framework of disciplines like dentistry, neurology and pulmonology. Although I welcome the formation of such expert groups, there is a risk that the interdisciplinary nature of sleep research and sleep medicine is pushed into the background and does not get ample opportunity to develop itself into an interdisciplinary science.

The NSWO is in an excellent position to cross disciplinary borders and to offer an interdisciplinary, federative platform for all these discipline-specific sleep societies and their members. To this end, it should actively approach these disciplinary sleep groups and explore the possibility of a federal association. In concerted action it should define interdisciplinary themes and organize expert meetings and workshops, with the intention to stimulate the exchange of ideas, formulate research plans and grant proposals, draw up consensus reports for clinical applications, etc. In addition, the NSWO should actively involve the different disciplinary sleep groups in formulating programs for (inter-)national teaching courses. In this way the NSWO can stimulate the development of sleep research and sleep medicine into a truly interdisciplinary science of sleep.

Figure 6: “NSWO under steam”. From right to left: Arie Knuijtingh Neven (former secretary), Marijke Gordijn (secretary) and Gerard Kerkhof (president) during the ESRS congress in Iceland in 2002.
THE NSWO IN A NEW MILLENNIUM
History NSWO 2010 – Present

Hans L. Hamburger

My start in the board of the NSWO was in November 2005 as a member of the public relations (PR) committee. At the beginning of 2006 the first web poll was launched on sleep habits in children, organized by the PR committee of NSWO. The lively preparatory discussions using the new Skype programme, chaired by Marijke Gordijn, turned out to be quite intense and lengthy but with a well defined common goal and result. These results were published in a press release at the end of March at the change to our European summer time or daylight saving time.

From that year on NSWO enjoyed considerable media coverage, even including a small report on sleep and its diseases during the national eight o’clock NOS TV news. This was the beginning of a nationwide appreciation of NSWO as “the society” for questions concerning the field of sleep.

NSWO meetings
The scientific highlights of every NSWO year are the spring and autumn conferences. The NSWO autumn meeting in November is the day of the yearly business meeting with all members, followed by a whole day with science in the form of posters and oral presentations, also for non-members. This is the place to be for elections, prizes and an overview of science in sleep in the Netherlands. This day is also the moment for presentation of the NSWO yearbook by the chairman of our scientific committee. We are proud that Tom de Boer is chosen into the scientific committee or the ESRS, a vacancy for our society that will be difficult to fill in.

The yearly meetings were and are still held on invitation and hosted by one of the members at a university department, sleep medical centre, or an industry oriented location. Many memorable beautiful locations were visited, amongst others the meeting at places with great names in memory of famous Dutch researchers: the Kamerlingh Onnes building in Leiden, the Antoni van Leeuwenhoek hospital in Amsterdam, the Zernike campus of the Groningen University, and also the Science park of Philips in Eindhoven and the Janssen Pharmaceutica complex in Tilburg.

Memorable were also the executive board meetings at the head quarters of Philips Amsterdam on invitation by our secretary Roy Raymann.

International Sleep Medicine Course
In 2008 the first International Sleep Medicine Course (ISMC) meeting was held in the Netherlands. The organization committee started of with all the board members at a meeting in a tiny hotel room in Utrecht. Since rules for sponsoring of pharmaceutical companies were getting stricter, the room barely fitted us all. We had some soft drinks, but a box with sweets, as optional extra’s was not touched due to the exorbitant high prices. Finally the organizing
committee shrunk to 3 persons Gerard Kerkhof, Klaas van Kralingen and Hans Hamburger. Further meetings were held during lunchtime at the Slotervaart hospital in Amsterdam. The first International Sleep Medicine Course 2008 was a great success with attendees from not only The Netherlands and EU countries, but also from outside the EU. Although the Leeuwenhorst centre in Noordwijk hout was quite big, the social events kept the party together where life music entertained all.

In 2009 Roy Raymann and our chairman at that time Gerard Kerkhof, organized an afternoon session at the DOM-church in Utrecht to discuss concerns on the future of NSWO. Many of the lively discussions were focussed on how to combine pure research, clinical sleep research and the growing attention for sleep medicine. A specific conclusion or document could not be made from the too many divergent opinions. In this respect we were not alone. A huge discussion took place on the same subject during the meeting of the ESRS members in Lisbon in September 2010. There was even a proposal to rename the society from sleep research to sleep medicine society, since clinical attention for sleep had exploded by that time.

At the 2010 autumn meeting we were hosted by the sleep centre of the Antonius hospital in Nieuwegein. Undersigned, who served until that time as chairman PR, was elected as the new chairman of NSWO. After a decade of giving his valuable energy to the NSWO, Gerard Kerkhof resigned as president. The first pressing tasks were to organize a new web based nation wide survey for the next spring on Sleepy Driving in the Netherlands and the ISMC for the year 2011. Kristiaan van
der Heijden was asked to chair the PR committee and Al de Weerd was elected as chair of the educational committee to help organizing the 2011 ISMC. Both turned out to be excellent choices. The surveys resulted in growing attention from the media. Since then, every spring, local and national newspapers, radio and TV channels compete for exclusive reporting of our results.

The ISMC 2011 was a big success and was attended by more than 120 participants from many countries even so far as the US and Australia. The Ruwenberg castle in Sint Michielsgestel turned out to be an excellent location to host the 4-day training. There we introduced for the first time a double meeting schedule, for beginners and advanced specialists in the field of Sleep Medicine. The midweek party diner was attended by virtually all participants and faculty and was an eloquent success also due to the band Sun Prophets, urging all that were present to dance.
The success of the meeting was only possible due to participation of Monique Vlak as treasurer and the involvement of Nanneke Joustra, a professional congress organizer. Although the set back of the world economy has made it more difficult, we have embarked again on having the ISMC2014 at the same location: castle Ruwenberg in the south of the Netherlands.

**European perspective**

NWSO is the single representative of the Netherlands at the European Sleep Research Society (ESRS) and the Associated National Sleep Societies (ANSS), which meet yearly in the beginning of May. At these meetings the national sleep societies of more than 20 European countries, including Russia and Turkey are represented by their chairpersons. The task for the chairman is to give presentation providing information on number of members, different field of work of the members and accreditation of sleep clinics and courses on sleep medicine. These meetings are co-hosted by the ESRS board, and decide on common goals for all societies to embark on, as for instance the European campaign on prevention of sleepy driving, which culminated in a meeting with representatives of the European parliament and a presentation in Brussels in October 2013.

**The coming 25 years**

In 2011 our website was updated under the supervision of Pim Drinkenburg, it was a great success. So much so, that we were overwhelmed with applications for new functions, which will be integrated step-by-step by our webmasters. It took furthermore a large effort to update the actual list of paying members, in which the present secretary and treasurer succeeded.
In 2012 the NSWO board embarked on a discussion about the future of the NSWO. To this purpose we recently initiated a newsletter that appears twice per year. In the light of many emerging small clinical communities involved in one of the many sub specialization in sleep medicine it seemed appropriate for the NSWO to offer an umbrella function to all, to stimulate convergence instead of divergence of interest in our common field of Sleep Research and Sleep Medicine. Neurologists, pulmonologists, dental surgeons, Ear nose and throat (ENT) specialists, and many more have now their own specialized sleep community. It would be profitable for all to have a channel for communication and organizing joined meetings on fields of mutual interest. The representation of NSWO at the level of ESRS renders coordination and communication on the European level easier. Since 2012 NSWO has organized in cooperation with the sleep societies of neurologists (SWS), pulmonologists (WAS), dental surgeons and ENT specialists a yearly meetings in May/June on subjects of mutual interest. Dedicated symposia on sleep apnea, sleepiness and driving, and age and sleep were the result.

The NSWO board is certain that this has taken away the fear of cold feet of our members and the other societies, and that a new future together is possible.

Sleep medicine centres cannot live without basic researchers and basic research has often practical implications. Therefore basic researchers are part of the staff of medical sleep centres since several years.

The NSWO board has therefore embarked on the seemingly simple but in reality difficult task to bring all those in the field of sleep research and sleep medicine together under the umbrella of this well-established society that is happily celebrating its 25th anniversary.
SLEEP-WAKE
Research in The Netherlands

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PhD Theses
THE BROKEN CYCLE OF SLEEP – ENERGY BALANCE THROUGH CIRCADIAN ALIGNMENT

Hanne K.J. Gonnisen
Dept. of Human Biology, Maastricht University

The observation of a reduction in sleep duration in parallel to the increased prevalence of obesity over the past 50 years has drawn attention to sleep as a contributor to positive energy balance. This thesis addresses the role of inadequate sleep and mistimed sleep in the regulation of energy balance and body-weight control.

The effects of sleep fragmentation on appetite and related hormone concentrations were investigated. A single night of fragmented sleep resulted in reduced REM sleep without a change in total sleep duration. Insulin concentrations were increased while GLP-1 concentrations and fullness scores were decreased in the afternoon following fragmented sleep. These results may support an increased food intake and snacking, contributing to a positive energy balance. In addition, a positive energy balance due to overeating was explained by SWS and REM sleep emphasizing the importance of sleep architecture. To further elucidate the relation between sleep architecture and energy balance, the effects of sleep stages on energy expenditure were determined. Energy expenditure did not vary according to sleep stages overnight. During wake episodes after sleep onset energy expenditure was higher than during SWS and REM sleep. Changed sleep architecture can decrease quality of sleep, defined as the sum of SWS and REM sleep divided by total sleep time. Therefore, the relation between quality sleep and energy expenditure was assessed. A disadvantageous shift in energy balance was primarily expressed in subjects with a higher percentage of quality sleep.

Furthermore, the effects of circadian misalignment, resulting in mistimed sleep and meal consumption, on energy metabolism, appetite and related hormone concentrations were investigated. Acute circadian misalignment resulted in disturbance of the glucose-insulin metabolism and a shift in substrate oxidation towards carbohydrate oxidation. The secretion pattern of meal-related blood variables (glucose, insulin, ghrelin, leptin, and GLP-1) followed the new meal patterns, while the circadian clock remained the primary driver of cortisol secretion. The circadian phase at which sleep occurs also affected the distribution of sleep stages, more specifically REM sleep distribution over the night changed with a relatively shorter REM sleep duration during the second part of the night. To establish if the metabolic consequences of circadian misalignment were connected with the effects of circadian misalignment on sleep architecture, the relations between REM sleep, cortisol levels and HOMA-IR index were examined. Shorter REM sleep during the second part of the night was associated with elevated cortisol concentrations and a higher HOMA-IR index. These studies indicate that synchrony between circadian and metabolic processes is crucial in the regulation of energy balance.

Moreover, the effects of energy-balanced diets differing in protein and carbohydrate content on body composition, sleep architecture and appetite were investigated to elucidate the interaction between diet, sleep and body-weight control in energy balance. An energy-balanced high carbohydrate diet caused an acute decrease in SWS and in women long-term increases in body weight and fat mass, pointing at a diet-sleep interaction and a diet-body
composition interaction. These phenomena were not shown with a high protein diet. No interaction was observed between sleep and body composition in energy-balanced conditions, which deserves more attention in future studies. Additionally, future research might focus on the interaction between diet, circadian rhythm and body-weight control.

In conclusion, the studies described in this thesis highlight the importance of preservation of quality sleep and circadian alignment, including synchrony between central and peripheral circadian processes, related to a macronutrient-balanced diet in the regulation of energy balance and body-weight control.
More and more research indicates that an adequate amount of sleep is essential for optimal health and functioning throughout life. However, over the past 50 years the proportion of young adults with self-reported sleep durations of fewer than 7 hours per night has more than doubled. Modern life includes longer working days, an increased use of the computer and more television viewing; consequently the time spent in artificial light has increased. Moreover, an increasing number of people perform shift work, which requires them to work at night and to sleep during daytime. These reversed sleep patterns cause misalignment of circadian rhythm that often leads to sleep disturbance. Sleep disturbance can refer to either shorter sleep durations or poor sleep quality with or without the presence of sleep disorder. Sleep disturbance has been associated with unfavorable health effects such as weight gain. The observation of a reduction in sleep duration in parallel to the increased prevalence of obesity over the past 50 years has drawn attention to sleep as a contributor to positive energy balance. The thesis of Hanne Gonnissen addresses the role of inadequate sleep and mistimed sleep in the regulation of energy balance and body-weight control. Hanne and colleagues investigated the effects of sleep fragmentation on both sides of the energy balance equation. In chapter 2 and 3 it was shown, in coherence with previous studies that sleep fragmentation may alter appetite control via changes in concentrations of appetite-related hormones (1, 2). The observed alterations may create a vulnerable condition in which food intake is increased in excess. Also, it was confirmed that sleep stages such as REM and SWS play an important role in overeating. Chapter 4 and 5 give insight in the effects of sleep stages on energy expenditure and consequently energy balance (3-5). Hanne and colleagues were among the first to investigate sleep fragmentation and energy expenditure in metabolic chambers. Previously, it was assumed that energy expenditure would be decreased after sleep fragmentation. However, it seems that when investigating this matter in the short-term energy expenditure does not change or is even increased. Whether this is similar in the long-term remains to be investigated. In addition to Hanne’s original work, she conducted an extensive literature research that resulted in chapter 6, which reviews all current knowledge about the interplay between sleep and energy balance (6). Furthermore, in chapters 7, 8 and 9 the effects of circadian misalignment, resulting in mistimed sleep and meal consumption, on energy balance were investigated. These well-conducted studies showed a disadvantageous effect on energy metabolism and appetite-related hormones after acute circadian misalignment (7-9). The work of Hanne points out how important synchrony between circadian and metabolic processes is for the regulation of energy balance and which consequences shift work may have eventually. The final chapter looked into sleep-diet interactions from a different perspective. The long-term effects of different macronutrients on sleep architecture and body-weight control were studied. Hanne and colleagues showed that not only sleep affects energy balance, but that our diet can also affect our sleep quality. The thesis of Hanne Gonnissen has
highlighted the importance of preservation of quality sleep and circadian alignment for the regulation of energy balance and body-weight control. Future research should continue to build on Hanne’s findings and focus on the interaction between diet, circadian rhythm and body-weight control. Also, it may be worth investigating associations between physical activity and sleep, as these seem to reinforce each other.

REFERENCES


CIRCADIAN RHYTHM DETERIORATION IN EARLY ALZHEIMER DISEASE AND THE PREVENTIVE EFFECTS OF LIGHT

Els I.S. Møst
Netherlands Institute of Neuroscience, Amsterdam, the Netherlands
VU medical center, Amsterdam, the Netherlands

Alzheimer’s disease (AD), though first and foremost associated with memory complaints, has multiple behavioral symptoms. Many of these behavioral symptoms are linked to the circadian system, such as rest-activity disturbances and mood disturbances, which become more severe as the disease progresses. Circadian rhythms are controlled by suprachiasmatic nucleus (SCN), which has an internal endogenous rhythm on average slightly longer than 24 hours. In elderly, and especially in demented elderly, the circadian rhythms fragment. This is mainly due to the diminished pacemaker function of the SCN. It is reasonable to hypothesize that the SCN pacemaker function in demented elderly could be restored when applying increased light levels, reactivating the SCN. Such a light intervention should start as early as possible in the disease process for the maximum effect.

Chapter 2 describes the background and methods of a double-blind, placebo-controlled, Randomized Clinical Trial (RCT). The aim was to evaluate the effects of bright light on community dwelling elderly people with memory complaints related to the earliest stage of probable AD or at an increased risk of developing it. After a baseline measurement (T0), all participants received either a placebo (±200 lux) or an active (±10 000 lux) light box. They were then followed up for a maximum of four half yearly visits (T1, T2, T3 and T4). For comparison, one assessment was obtained in a reference group consisting of healthy elderly people. The primary purpose of this study was to investigate the effects of long-term daily bright light exposure on depressive symptoms. Secondary outcome measures were the effects on sleep-wake rhythm disturbances, cognitive deficits and caregiver burden. Furthermore, it was investigated whether the effects on mood and sleep were indeed mediated through the circadian pacemaker.

In chapter 3, we aimed to determine the effect of long-term daily bright light exposure on mood and hypothalamic pituitary adrenal (HPA) axis function in elderly people with memory complaints, using the protocol described in chapter 2. The primary outcome measure was subjective mood rating; secondary outcome measure was the diurnal profile of cortisol. At T0, the RCT participants showed more depressive symptoms than the reference group, but the average cortisol levels across the day did not differ significantly between the reference group and the RCT participants. Over time, daily bright light exposure improved mood in the active group as compared to the placebo condition. While evening cortisol increased over the years in the placebo condition, its levels did not change in the bright light condition. Long-term bright light treatment positively affects depressive symptoms and evening cortisol levels in community-dwelling elderly people with early or moderate probable AD or with an elevated risk of developing it.

When applying light therapy there are practical implementation issues to be considered, which are probably crucial for compliance and acceptance. Chapter 4 describes a systematic evaluation of the appreciation of bright light therapy. Overall, participants as well as caregivers indicated that the application of light therapy represented only a marginal burden in daily life and had only few adverse effects. Importantly, light therapy should be introduced as
an everyday lighting option that addresses not only biological effectiveness, but also takes into account the appearance of the luminaire and the visual ambience. Also, managing participant expectations may prevent disappointments: both patient and caregiver should be informed that any improvements are likely to be small and gradual.

In chapter 5, we studied the reliability of subjective sleep reports in early and moderate stage AD by investigating whether they differ from a healthy non-demented reference group with respect to the discrepancy of subjective and objective sleep estimates. As compared to the reference group, AD patients complained less of insomnia, while in fact their objective sleep estimates indicated more disturbed sleep, with a longer sleep onset latency and a lower sleep efficiency. Regression analyses revealed only very few predicative subjective sleep questionnaire parameters which could significantly predict their objective counterpart. The overall predictive value of sleep questionnaires is limited, especially in early and moderate stage AD. An objective sleep measurement may be essential to prevent sleep problems from going undetected.

In chapter 6, we aimed to investigate the skin temperature rhythm in AD and its association with daytime sleepiness and nocturnal sleep. Recent work has suggested that even small changes within the thermo-neutral zone may contribute to daytime sleepiness and nocturnal sleep depth. AD patients had a significantly higher daytime proximal skin temperature as compared to the reference group. Both in AD patients and in the reference group, an elevated daytime proximal skin temperature was associated with more daytime sleepiness. The findings suggest a deficient down-regulation of daytime proximal skin blood flow, which might contribute to daytime sleepiness and consequently to cognitive dysfunction in AD.

In spite of confirming our primary hypothesis – that long term light therapy can ameliorate depressive symptoms – we could not confirm that light therapy could halt cognitive deterioration or ease caregiver burden. A small, but favorable, effect of light was found on sleep, but not for the sleep-wake rhythm. The last hypothesis, that the effects of light were mediated by the circadian system, could only be partially confirmed; there was a positive effect on cortisol levels, but it could not be confirmed that this was the underlying cause of the effects in mood.

The output signals of the circadian system were shown to be in different states of disintegration in the very early stages of AD. There were clear differences between healthy elderly and AD patients in temperature rhythms, but not in their sleep-wake rhythm or cortisol rhythms. This variability can be explained by the degradation of the SCN on the one hand and by compensating measures further down in the circadian system on the other hand. Compensating measures can include peripheral clocks gaining a more prominent role when the SCN cannot fulfil its central pacemaker function anymore. Depending on the different compensating mechanisms involved, circadian behavior- and physiological rhythms could degrade in various manners.

Light therapy implementation should take into account that in the neurodegenerative process there is a balance between a circadian system functioning well enough to render an additional synchronizing agent unnecessary and a system too degenerated to be reactivated. Furthermore, it might be that the timing of light therapy is only optimal for a certain period of time and that this period is different for different pathways. Following this hypothesis, the timing and duration that light therapy might actually work could be different for e.g. sleep and mood. In this case, the preventive effect of light therapy would actually be most effective if it
were started before dementia onset, even though the behavioral effects will not be noticeable. When started during or after dementia onset, the effect might be noticeable, but is possibly less effective in the longer run. Although a functional circadian system would only benefit marginally from the added input, an early start would ensure capturing the optimal time-point of implementing the therapy, reducing the risk of developing any circadian disturbances later on. This would, however, indicate that patients could spend a considerable period of time receiving light therapy without any significant changes in their physiology and behavior. In addition, as it is unclear when the circadian system starts to unravel and at what speed, one would have to continue the therapy for the rest of one’s life for maximal benefit.
Commentary on the dissertation by Els Møst

CIRCADIAN RHYTHM DETERIORATION IN EARLY ALZHEIMER DISEASE AND THE PREVENTIVE EFFECTS OF LIGHT

Marijke C.M. Gordijn

Chrono@Work B.V., Groningen, The Netherlands

Dr. Els Møst received her PhD with the defence of her thesis entitled “Circadian rhythm deterioration in early Alzheimer Disease and the preventive effects of light” in Amsterdam (VU) on December 3rd, 2013. The work was performed at the Netherlands Institute for Neuroscience and the VU University Medical Center in Amsterdam under supervision of her promotors Prof. dr. E.J. W. van Someren and Prof dr. Ph. Scheltens. The work was financially supported by grants from ZonMw, Hersenstichting, NOW and Philips Lighting B.V.

Circadian rhythms are endogenously generated by a master pacemaker, located in the hypothalamus of the brain. The light-dark cycle is the primary synchronizing signal of the circadian timing system. Depending on the timing of exposure to light, phase shifts of the circadian system are induced, showing up either as delays (shifts to a later time point) or as advances (shifts to an earlier time point). In addition to these phase shifting effects, light has several other non-image forming effects, such as (in humans) increasing alertness, increasing cortisol early in the morning, and inducing a therapeutic effect on depressive symptoms. Light is therefore considered a therapeutic agent, not only for the treatment of circadian rhythm sleep disorders but also to treat depressive symptoms.

Aging, and especially pathological aging, is accompanied by an increase in sleep problems and depressive complaints. Already in the early 90’s, Van Someren and colleagues showed that the amplitude of daily rest-activity rhythms is clearly attenuated in Alzheimer and concluded that a malfunctioning of the circadian pacemaker may be the underlying cause (Van Someren et al 1996). Light was thought to be effective by stimulating the circadian pacemaker and this was shown in aging rats; light increased the amplitude of disturbed circadian patterns of rest and activity (Witting et al 1993). The idea that light may be a therapeutic agent to treat aging related sleep disturbances and probably even other Alzheimer complaints was raised. In 2000, data were published supporting the idea that the disturbances in circadian rhythmicity in Alzheimer are due to neurological changes in the Nucleus Suprachiasmaticus (SCN), the biological clock in the brain, and that the stimulating effect light has on the rest-activity rhythms may be explained by an activation of the remaining SCN cells (Liu et al 2000). A challenging idea is that enhancing neuronal functioning in the SCN by light and the resulting improvement in rest-activity cycles and sleep may prevent the cognitive decline in Alzheimer patients. In 2008, data of a longitudinal study covering 3.5 years of a placebo controlled study with experimentally enhanced light levels in nursery homes, showed that indeed increased light levels may attenuate the cognitive decline in Alzheimer patients (Riemersma et al 2008). The effect was not very large, but similar to the effect that may be achieved in Alzheimer patients treated with drugs. The fact that the effects are small raised the question whether the neurological detriment of the brains of Alzheimer patients in nursery homes may be too large already to allow for
considerable improvement. Wouldn’t it be better to treat elderly with light already prior to this stage of Alzheimer disease? A study was set up to test whether starting the light treatment in the home situation of people with early onset memory complaints and Alzheimer disease may have a larger effect on the cognitive decline and may delay the necessity for hospitalization. The project of Els Møst was born. Els investigated the therapeutic effects of light as well as the effects of light treatment on several circadian outputs. The intricate relationship between these aspects and the role they may play when considering light therapy for improving life quality in early Alzheimer patients are thoughtfully discussed. Considering the difficulty of performing “field studies” in people suffering from memory complaints, Els did a great job in testing the results of light treatment, as well as testing the reliability of recording methods in this specific group of people.

The main goal of the study was to test the therapeutic effects of light in elderly people with memory complaints, probably at risk of developing Alzheimer Disease. Although the authors could not confirm that light therapy prevented or attenuated the cognitive decline – no difference was observed between the group that was actively treated and a placebo control group – a small effect on sleep quality and an effect on the development of depressive symptoms was observed. The control group showed an increase in depressive symptoms over time, while the group receiving light therapy did not show an increase in depression. In addition, the observed increase in evening cortisol levels, developing over time in the control group, was not observed in the group that received light therapy. These data support earlier findings from Lieverse et al (2011). These authors showed that 3 weeks of light therapy in elderly suffering from Major Depressive Disorder is effective, and they also found a decrease in elevated evening cortisol levels. The current study shows that light treatment is even able to reduce the risk of developing depressive mood and elevated cortisol levels in the evening. In other words, light is a therapeutic agent preventing psychiatric problems in the elderly and in that sense clearly improving quality of life.

In her thesis, Els combines a fundamental discussion on the possible mechanism of the action of light with clear applied questions like the appreciation of the light therapy. Her final conclusion is that light therapy might even be needed before any complaints arise, to be able to activate neurons prior to any degenerative process. Together with the fact that in that case the only beneficial effect to be expected is not to become ill, light therapy should indeed be appreciated and should not interfere at all with everyday life. Actually it should be part of a healthy lifestyle in the same way as we learn to eat better, move more and sleep longer. In that context it may not have come as a surprise that after finishing her studies, Els started to work at the company that became famous for inventing the light bulb, and that now focus on “improving people’s lives through innovations on healthcare, lifestyle, and lighting”.


The present thesis focuses on interactions between the regulation of body temperature and the regulation of sleep and vigilance in humans. Skin blood flow, and consequently its temperature, changes with many factors that have shown to affect vigilance, including environmental light, anxiety or stress and one’s posture. Even under thermoneutral conditions, skin temperature is not fixed, but fluctuates. Previous studies have shown that experimentally induced changes in skin temperature affect sleep and alertness. The induction of a somewhat higher skin temperature, yet within the thermoneutral range, resulted in increased sleepiness; slower responses on sustained attention tasks; faster sleep onset; and deeper sleep. However, so far it has not been studied whether naturally occurring fluctuations in skin temperature within the thermoneutral zone are similarly associated with vigilance. The present thesis aimed to evaluate whether naturally occurring fluctuations in skin temperature are related to fluctuations in vigilance, and whether such association is still present after sleep deprivation. Furthermore, the thesis addressed brain mechanisms that could be involved in the link between fluctuations in vigilance and skin temperature. Finally, the thesis addressed whether the link can be utilized by adding skin temperature assessment to devices that aim to unobtrusively assess the sleep-wake state from wrist movements, and thus improve the performance of these devices.

In the second chapter, we examined whether fluctuations in skin temperature are associated with those in vigilance level, under conditions similar to everyday-life situations requiring sustained attention. Eight healthy participants participated in a two-day protocol during which vigilance and skin temperature were assessed 4 times per day in a silent dimly-lit, temperature-controlled room. Out of the three measured locations, distal, proximal and intermediate, especially the spontaneous fluctuations in proximal temperature were negatively associated with fluctuations in response speed, and positively with lapse rate on the vigilance task. We therefore concluded that a higher proximal skin temperature was associated with decreased vigilance.

Since the previous study was limited to the study of temperature and vigilance under well-rested conditions, in the third chapter, we set out to obtain a detailed view on the effect of sleep deprivation on the profile of human skin temperature gradients over the body, as well as on their association with sustained attention. Eight healthy young adults participated in a repeated-measures constant routine design, in which skin temperatures were assessed continuously from 14 locations while performance was assessed using a reaction time task, including eyes-open video monitoring, performed five times a day for two days, following a normal sleep or sleep deprivation night. Mixed-effect regression models were used to evaluate the effect of sleep deprivation on skin temperature gradients of the upper (ear-mastoid), middle (hand-arm) and lower body (foot-leg), and on the association between fluctuations in performance and temperature gradients. Sleep deprivation induced a marked dissociation of thermoregulatory skin temperature gradients, indicative of attenuated heat loss from the hands co-occurring with enhanced heat loss from the feet. Sleep deprivation moreover attenuated the
association between fluctuations in performance and temperature gradients; the association was best preserved for the upper body gradient. Therefore, we concluded that sleep deprivation disrupts coordination of fluctuations in skin temperature gradients. The dissociation of middle and lower body temperature gradients may therefore be pursued as a possible marker for sleep debt, and the upper body gradient as possible aid in vigilance assessment when sleep debt is unknown. Importantly, our findings suggest that sleep deprivation affects the coordination between skin blood flow fluctuations and the baroreceptor-mediated cardiovascular regulation that prevents venous pooling of blood in the lower limbs when there is the orthostatic challenge of an upright posture. The finding is important because it suggests limited generalizability of lab studies on the effects of sleep deprivation on human physiology when participants are only studied in a supine position.

Following up on the studies that assessed the association of skin temperature with behavioural indicators of vigilance, we set out to study the association of skin temperature with neurophysiological indicators of vigilance. The fourth chapter described how fluctuations of skin temperature are associated with changes in the electroencephalographic power spectrum and event related potentials, recorded during a sustained attention task both under well-rested and sleep-deprived conditions. Simultaneous measurement of activity in the central nervous system (CNS), the autonomous nervous system (ANS), and behavior allowed us to determine whether the association between skin temperature and vigilance is not only visible in performance, but in cerebral activity as well. Correlating event related potentials elicited by stimuli in a reaction task to temperature measured at the ear, we have shown that a higher skin temperature is associated with a longer latency of the P300 evoked potential, which has previously been shown to indicate decreased vigilance. A practical consequence of this finding is that the sensitivity of ERP studies might increase if skin temperature would be co-registered and included in the statistical analysis as a nuisance variable. Furthermore, after sleep deprivation, fluctuations in the skin temperature gradient measured from the earlobe and mastoid were associated with fluctuations in parieto-occipital high beta band (20-40 Hz) power of the pre-stimulus background EEG, which has previously been interpreted as compensatory efforts in order to maintain vigilance.

To investigate brain structures involved in the link between skin temperature and vigilance, the fifth chapter focused on the relationship between skin temperature and sleep onset in subjects with hypothalamic damage. The hypothalamus is crucially involved in the circadian timing of the sleep-wake rhythm, and also accommodates the most important thermoregulatory neuronal network. We have shown before that adults with pituitary insufficiency and history of chiasm compression due to a tumor with suprasellar extension fall asleep later and sleep shorter than those without such history, and presume hypothalamic involvement. To further evaluate the hypothesized hypothalamic involvement in the association between vigilance and thermoregulation, we investigated whether hypothalamic impairment also affects skin temperature and its association with sleep onset. In a case-control study in fifty patients with pituitary insufficiency, thirty-three of which had a history of chiasm compression, ambulatory distal and proximal skin temperatures were assessed continuously for 24 hours. Sleep parameters were assessed by questionnaires. Group differences in mean skin temperature, calculated over the wake and sleep periods separately, and group differences in the strength of association between pre-sleep skin temperature and sleep onset latency were compared. Results showed that patients with a history of chiasm compression had a lower proximal skin temperature during the day (34.1 ± .7 vs. 34.6 ± .7 °C, p = .045). Additionally, the typical association between sleep onset latency and pre-sleep distal-to-proximal skin temperature gradient was absent in these patients (r = -.01, p = .96),
while it was unimpaired in those without chiasm compression ($r = -.61$, $p = .02$). Thus, patients with a history of chiasm compression show impaired skin temperature regulation in association with disturbed sleep.

The sixth chapter focused on the practical application of the knowledge acquired on the association between skin temperature, sleep and vigilance. Due to its low invasiveness and costs, actigraphy is widely used as an alternative to polysomnography (PSG) to measure sleep wake rhythms in human subjects. However, although actigraphy and PSG correspond relatively well during sleep, actigraphy has problems detecting wake during immobility. Since skin temperature is closely correlated to vigilance and sleep under so many conditions and in so many populations, we considered the possibility that it could increase the accuracy of sleep/wake classification. Under normal daily routine conditions, 52 subjects either without sleep disorder or diagnosed with sleep disorders such as OSAS, insomnia, and PLMS, were monitored using ambulatory EEG, an actigraph and skin temperature sensors. The congruency of actigraphic sleep estimates with PSG-defined sleep was calculated before and after the use of wrist temperature to reclassify actigraphic sleep estimates. Results showed that skin temperature was lower during epochs that actigraphy falsely classified as sleep than during epochs that actigraphy correctly classified as sleep. Also, skin temperature was higher during epochs that actigraphy falsely classified as wake than during epochs that actigraphy correctly classified as wake. However, using temperature as additional information in the actigraphy scoring algorithm did not significantly alter the percentage of misclassified epochs. We propose that the sluggish response of the sensor and/or skin to changes in skin perfusion may have interfered with the possibility to exploit the systematic skin temperature differences. Infrared temperature sensing or even perfusion sensing may be required to improve actigraphic sleep estimates.

Taken together, the findings in this thesis demonstrate that naturally occurring fluctuations in skin temperature are related to fluctuations in vigilance. We have shown that higher proximal skin temperature is associated with lower alertness under well-rested conditions (chapter 2). Furthermore, this correlation is still present after a vigilance-challenging occurrence such as an entire night of sleep deprivation (chapter 3). As a first step towards elucidating the brain mechanisms involved in the coupling of infraslow fluctuations in skin temperature and alertness, the present work showed that they also coincide with fluctuations in the latency of an event related potential, the P300 (chapter 4). As a second step towards understanding brain mechanisms involved in the coupling we showed that it is compromised in patients with hypothalamic damage (chapter 5). Finally, the correlation between naturally occurring skin temperature fluctuations and vigilance was used in an attempt to improve movement-based sleep-wake assessment (chapter 6). The findings presented in this thesis may also have relevance for the field of environmental ergonomics. Because the skin is rather poikilotherm, its manipulation by means of environmental temperature in combination with clothing could make the difference between being alert and being sleepy. This contention is indeed supported by the skin temperature manipulation studies.
Commentary on the dissertation by Nico Romeijn

SKIN TEMPERATURE AND VIGILANCE: FROM ASSOCIATION TO APPLICATION

Roy Raymann
Cupertino, USA

The relationship between temperature and vigilance has been a topic of extensive studies either in the field of ergonomics or in the field of chronobiology. Ergonomics mainly focuses on the interaction of environmental temperature and vigilance, whereas chronobiology mainly focuses on the 24h changes in core body temperature and it’s relation to vigilance. It seems a logical step to study the relation between skin temperature and vigilance, since the temperature of the skin is affected by both the environmental temperature and the body temperature. This step has been taken by Nico Romeijn and his scientific contributions to the field of sleep, vigilance and thermoregulations are summarized in his thesis entitled “Skin temperature and vigilance: from association to application”.

The thesis starts with the general idea that skin temperature is a very likely candidate to serve as a sleep-permissive or wake-promoting signal to the brain, where a cooler skin signals increased vigilance and a warmer skin favors sleep. Earlier work of the Van Someren group at the Netherlands Institute for Neuroscience provided strong support for this idea. In a series of studies it was shown that mildly warmed skin resulted in more optimal nocturnal sleep and decreased vigilance at daytime. Nico Romeijn extends the support for the role of skin temperature as a sleep-permissive or vigilance-promoting factor to the more daily practice, by looking at the naturally occurring fluctuations in skin temperature, rather than manipulating the skin temperature.

The results of the first 3 studies reported on in the thesis show a relation between daytime vigilance and skin temperature. In Chapter 2, higher chest temperatures are related to poorer performance on a behavioral vigilance task. In Chapter 3 it was shown that sleep deprivation (known to affect vigilance) resulted in a change of the gradients of skin temperatures measured on 14 different locations on the body; the temperature gradients were indicative of more heat loss from the feet and less heat loss from the hands when sleep deprived as compared to well rested. Moreover, the association between behaviorally measured vigilance and skin temperature gradients was weaker after sleep deprivation. In Chapter 4, it was shown that a decrease in the gradient between the skin temperature measured at the mastoid and the earlobe was related to a reduced vigilance, measured using a central nervous system marker (i.e. ERP derived P300 latency).

Taken together all the evidence presented in the aforementioned chapters, it is clear that the relation between thermoregulation and vigilance is apparent in day to day life (and not only during the night or when changing temperatures in an experimental protocol) and that gradients of skin temperatures are affected by sleep deprivation or by naturally changes in vigilance in a different way. The latter might be of interest as a new way to assess sleep deprivation and/or vigilance.
The results of the studies reported in Chapter 5 and 6 clearly show that the measurement of skin temperature gradients has potential to be implemented in more clinical settings. Chapter 5 shows that patients with a history of chiasm compression had lower skin temperatures during the day and did not show the commonly observed skin temperature gradient during the pre-sleep period. Chapter 7 explores the use of wrist temperature as a measure to fine tune the sleep-wake classification of actiwatches. It was shown that the wrist temperatures that were measured during a polysomnographically derived sleep epoch that was incorrectly classified as being wake by actigraphy were relatively higher than the ones that were correctly classified as sleep. Next to that it was also shown that the wrist temperatures that were measured during a polysomnographically derived wake epoch that was incorrectly classified as being sleep by actigraphy were relatively lower than the ones that were correctly classified as wake. These results were implemented in an adapted actigraphy scoring algorithm, but unfortunately this algorithm did not lead to a significant drop in misclassified epochs.

One of the questions that remain to be answered is what location and/or what gradient of skin temperature measurement is correlated optimally to sleep and vigilance processes. In this thesis, different locations and gradients pop up as being best predictors. A next step should be a systematic approach in mapping full body changes in skin temperature at a high resolution and a high sampling frequency.

The work presented in this thesis is extensive and clearly shows that our skin temperature represent information on our behavioral state. The reason why skin temperature is less well studied and has been hardly used as a marker should be partly searched in the fact that (the measurement of) skin temperature is affected by a lot of different factors, such as activity, perspiration, body position, environmental temperatures, weather conditions, inflammation and so one. Cleaning and correct interpretation of this kind of data, especially when acquired in a less controlled setting, is a work of skill and required a lot of time and expertise. Nico Romeijn succeeded in mastering the big amount of data and compressing it into comprehensible results, a task that has not been easy for sure.

Although you shouldn’t judge a book by its cover, it is allowed to do so this time. Nico Romeijn shows to be multi-talented in telling a story: The cover tells the story of cold and warm, peaks and troughs, a journey through unknown territories.
SLEEP-WAKE
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EFFECTS OF ACTIVATION AND INHIBITION OF 5-HT\textsubscript{7} RECEPTORS IN RATS: CARDIOVASCULAR AND SLEEP-WAKE ANALYSIS

A. Ahnaou and WHIM. Drinkenburg

Dept. of neurosciences, Janssen Research & Development, a Division of Janssen Pharmaceutica NV.
Turnhoutseweg 30, B-2340 Beerse, Belgium

INTRODUCTION
Serotonin (5-hydroxytryptamine, 5-HT) is involved in a large variety of behavioural and psychological processes, considering the extensive 5-HT projections in the brain and the large number of the 5-HT receptor subtypes. Of the 14 known serotonergic receptors, the 5-HT\textsubscript{7} receptor, which is the most recently identified member of the 5-HT receptor family, has been implicated in a variety of (patho) physiological processes of the central nervous system (CNS). This 5-HT\textsubscript{7} receptor belongs to the G protein-coupled receptor superfamily, which couples positively to adenylate cyclase (AC) through activating the G protein regulator signalling subunit (G\textsubscript{q}), resulting in an increase in cAMP. The 5-HT\textsubscript{7} receptors are expressed in both the CNS and in peripheral tissues. In the CNS, they are abundantly expressed in the thalamus, the hypothalamus, the hippocampus, cerebral cortex (both on pyramidal and GABAergic neurons), amygdala, and dorsal raphe\textsuperscript{1}. Distribution studies and the use of genetic tools have increased our knowledge on the functional role of the 5-HT\textsubscript{7} receptor. The distribution of 5-HT\textsubscript{7} binding sites in the limbic system, the thalamocortical regions and suprachiasmatic nucleus suggests a possible role in the pathophysiology of affective disorders\textsuperscript{1} and in the mechanisms underlying sleep and circadian rhythms\textsuperscript{2}. Increasingly available selective pharmacological compounds targeting the 5-HT\textsubscript{7} receptor are very useful to further elucidate the CNS function in which 5-HT\textsubscript{7} receptor is implicated. Here, we have evaluated the effects of selective activation (BASF agonist, EP-00998923; 2000) or inhibition (SB269970 and DR4004) of 5-HT\textsubscript{7} receptors on telemetry hemodynamic variables in freely moving rats and sleep-wake organization in rats chronically implanted with EEG/EMG electrodes.

METHODS

Animals
Male, adult Wistar SPF rats weighing 250–300 g at the time of surgery were used in this study. Animals were maintained in individually ventilated cages under controlled environmental conditions throughout the study: 22 ± 2 °C ambient temperature, relative humidity 60%, standard 12:12 light cycle regime (lights-on 12:00 and illumination intensity: \( \sim 100 \text{ lx} \)). All experimental protocols were carried out in strict accordance with the European Communities Council Directive of 24th November 1986 (86/609/EEC).

Telemetric testing
Mean arterial blood pressure (BP), heart rate (HR), body temperature (BT) and locomotor activity (LMA) were recorded by means of telemetry (DSI, USA). Under isoflurane anaesthesia, the biopotential probes were implanted in the peritoneal cavity and the catheter was inserted in the descending aorta at the level of iliac bifurcation. Following recovery and adaptation to the monitoring conditions for minimally 2 weeks, telemetric hemodynamic data were sampled in 10 seconds epochs and averaged over 10 minutes. All 5-HT\textsubscript{7} compounds were intraperitoneally administered 1.5 h after light onset while the recordings started half
hour before pharmacological treatments (only BASF 5-HT7 agonist is presented here for the first 4 hrs).

**Sleep/EEG monitoring**
Electrodes for recording frontal and parietal cortical EEG (AP ± 2 mm, L ± 2 mm; AP – 6 mm, L ±3 mm respectively from bregma), EMG (nuchal muscle) and EOG (ocular movements) were implanted under isoflurane anaesthesia. Following recovery and adaptation to the monitoring conditions, online polygraphic recordings started for 16 hours following intraperitoneal administration of saline or a single dose of the 5-HT7 receptors agonist and antagonists.

An off-line automated scoring analysis of the sleep-wake stages in control and treated groups was executed per 2-second epoch for 60-minutes periods over 16 hours recording sessions. The six sleep stages were classified as being indicative of active wake, passive wake, light sleep, deep sleep, intermediate stage or rapid eye movement (REM) sleep. Different variables were calculated and only the time-course profile of different vigilance states and the REM sleep onset latencies (defined as the time between the beginning of the recordings and the appearance of the first sleep period lasting at least 30 s) are presented here.

**Data analysis**
Telemetric data were presented in consecutive 10 minutes intervals during first 4 hours after administration. Vigilance states were presented in consecutive hours during the 16 hours of the recording session. All data are presented as mean value ± S.E.M Statistical significance was evaluated by using a Wilcoxon Mann Whitney Signed Rank test for paired samples. A value of \( p<0.05 \) was considered to be significant.

**RESULTS**
No consistent changes were observed in BT, BP, HR and LMA following the administration of both 5-HT7 antagonists (SB269970 and DR4004) at different doses tested (data not shown). Conversely, when administered at the higher dose of 30 mg/kg, the 5-HT7 agonist (BASF) induced significant decrease in BT for 60 min over the first 4 hours of the registration period (see figure 1, upper panel) followed by an increase of BP lasting up to 100 minutes after a slight onset delay (see figure 1, bottom panel).

![Figure 1](image_url)

*Figure 1:* Effects of intraperitoneal administration of the 5-HT7 agonist BASF (1, 10 and 30 mg/kg) or saline on BP (upper panel) and BT (bottom panel) during each 10 min of the first 4 hour following the administration. Data are expressed as mean +/- SEM, n=8 for each condition. \( p<0.05 \) is indicated by horizontal lines underneath the curves (light grey colour for the low dose, dark grey for the middle dose and black for the higher dose).
Both antagonists significantly reduced the time spent in rapid eye movement sleep (REMS) and increased REM sleep latency. The REM sleep inhibition could last for at least 2 hours in case of SB269970 at 30 mg/kg, while it could reach up to 8 hours following DR4004 administration at 10 mg/kg.

The BASF agonist at 30 mg/kg produced a biphasic effect on sleep-wake distribution: reduced significantly REM sleep at the expense of wakefulness during the first 2 hours after administration followed by a decrease in wakefulness in favour of REM sleep for the following 3 hours.

**Figure 2:** Effects of intraperitoneal administration of the selective 5-HT7 agonist BASF (30 mg/kg) and antagonist SB269970 (30 mg/kg) and DR4004 (10 mg/kg) on sleep-wake architecture during 30 min of the 16 consecutive hours. Data are expressed as mean ± SEM, n=8 for each condition. P<0.05 is indicated by horizontal lines underneath the curves. The inset bar graph indicates the REM onset latency (ROL). P<0.05 is indicated by horizontal lines underneath the curve (light grey colour for BASF, dark grey for SB269970 and black for DR4004).

**DISCUSSION**

Pharmacological and genetic tools targeting the 5-HT7 receptor in preclinical animal models have implicated this receptor in the control of circadian rhythms and thermoregulation. The availability of specific 5-HT7 agonist (BASF agonist) and antagonists (SB269970 and DR4004) has provided a springboard for further investigation into its role.

In the present study, specific activation of 5-HT7 receptors caused hypothermia in freely conscious rats thus supporting a role of this receptor in the regulation of body temperature. Earlier evidence based on 5-carboxamidotryptamine (5-CT)-induced hypothermia in guinea pigs suggested a role for the 5-HT7 receptor in thermoregulation processes. We and others have demonstrated that 5HT7 receptor blockade attenuated the 5-CT-induced hypothermia.3,4 The use of 5-HT7 receptor knock-out mouse strains, confirmed the hypothesis that 5-HT and
5-CT, which both exhibit agonistic activity at 5-HT\textsubscript{7} receptors failed to induce hypothermia in knockout mice\textsuperscript{5}. The specific 5-HT\textsubscript{7} receptor antagonists had no major effects on BP, whereas the 5-HT\textsubscript{7} receptor agonist at the highest dose raised blood pressure without any effect on motor behaviour. There is evidence suggesting that 5-HT\textsubscript{7} receptors participate in the central modulation of the cardiovascular system. In line with the present findings, the antagonism of 5-HT\textsubscript{7} receptors produced no consistent changes in baseline mean blood pressure in naïve rats without any previous cardiovascular reflex activation. However, the selective 5-HT\textsubscript{7} receptor antagonist SB-269970 induced a consistent reduction in the bradycardia and hypotensive response in both awake and anesthetized rats previously submitted to cardiopulmonary reflex activation\textsuperscript{6,7}. Together, these observations suggest that central 5-HT\textsubscript{7} containing pathways in the brainstem areas may be important in buffering the autonomic imbalance and contribute to normalize arterial blood pressure in situations of challenge-induced 5-HT release and activation of cardiovascular reflexes.

Lastly, it has been tried by using non-specific 5-HT\textsubscript{7}-ligands to determine a possible role of 5-HT\textsubscript{7} in the cardiovascular system: A hypotensive effect was suggested after 5-CT, a partial agonist\textsuperscript{8,9}, while tachycardia was observed after agonistic activity. Both antagonists were effective to reduce time spent in REM sleep and increased the latency of REM sleep onset.

Earlier reports implicate an important role of 5-HT\textsubscript{7} receptors in the regulation of REM sleep\textsuperscript{10}. Systemic and oral administration of specific 5HT-7 antagonists (SB-269970 and SB-656104) in rats and of JNJ-18038683 in human has been shown to reduce total amount of REM sleep, whereas the other vigilance states were not significantly modified\textsuperscript{4,11}. The present data are in agreement with the REM suppression effects of 5-HT\textsubscript{7} blockade, albeit that the magnitude of effects being more pronounced with the potent dose used for DR4004. Unlike the effects of the 5-HT\textsubscript{7} receptor blockade on REM sleep, the 5-HT\textsubscript{7} receptor agonist BASF also suppressed REM sleep time in the first 2 hours post-administration at the expense of wakefulness. Monti et al. infused the selective 5-HT\textsubscript{7} agonist LP-44 into the dorsal raphe and found a similar reduction of REM sleep in favour of waking in the rat\textsuperscript{12}. In the dorsal raphe, the 5-HT\textsubscript{7} receptors are localized on GABAergic-containing neurons, which activation inhibits GABAergic interneurons, leading to decreased GABA release. Therefore, it is likely that reduced GABAergic inhibitory tone on 5HT neurons in essential brainstem structures might increase cortical excitability and suppressed REM sleep occurrence.

The 5-HT\textsubscript{7} receptor is involved in biological processes of circadian rhythms; thermoregulation and sleep. Disturbance in these mechanisms are considered to be an important contributing factor in mood disorders such as depression. Indirect evidence associates 5-HT\textsubscript{7} receptor activity to depression as chronic treatment with fluoxetine down regulated 5-HT\textsubscript{7} receptors in the rat hypothalamus\textsuperscript{13}. In addition, functional studies using 5-HT7 receptor-selective antagonists appeared to alter REM sleep parameters in the same way as certain antidepressants and in a pattern opposite from that seen in patients with clinical depression. Moreover, knockout mice showed a reduced REM sleep time and exhibited antidepressant-like behavior in two frequently used animal models of depression, namely the forced swim test (FST) and tail suspension test (TST)\textsuperscript{14}. Altogether, our observations are in line with recent reports supporting the role of 5-HT\textsubscript{7} receptor in the mechanism underlying thermoregulation and REM sleep. Based on these sleep-wake results, the activation of the 5-HT\textsubscript{7} receptor suggests a stimulant-like property while its inhibition showed antidepressant-like activity.
REFERENCES


IMPAIRED SLEEP-WAKE STABILITY IN MICE LACKING GHRELIN NEUROPEPTIDE

A. Ahnaou and WHIM. Drinkenburg

Dept. of neurosciences, Janssen Research & Development, a Division of Janssen
Pharmaceutica NV. Turnhoutseweg 30, B-2340 Beerse, Belgium

A reciprocal interaction exists between sleep and endocrine activity, while diverse hormones (steroid or neuropeptide) contribute to sleep regulation. Ghrelin, a 28-amino-acid peptide, primarily produced in the stomach and to a lesser extent in the brain, is a recently discovered endogenous ligand of the growth hormone secretagogue (GHS) receptor. Ghrelin is hypothesized to play a pivotal role in energy balance, stimulating food intake and body weight. In rodents, systemic and central ghrelin administration induced body weight gain and adiposity by increasing food intake, which was reduced following co-administration with the ghrelin receptor antagonists\(^1,2,3\). Ghrelin exerts various other endocrine effects, such as stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, to increase secretion of adenocorticotropic hormone (ACTH) and cortisol in humans\(^4\), and corticotropin-releasing hormones (CRH) in rats\(^5\). Ghrelin also appears to be involved in regulatory processes of sleep, e.g. it promotes deep slow wave sleep and nocturnal hormone release of GH, cortisol and prolactin in human\(^6,7\), as well as NREM sleep in mice\(^8\). These endogenous functions of ghrelin, linking metabolic control with higher brain functions, could be targets for novel therapeutic strategies beyond approved medications in psychiatric disorders where these regulatory processes are disrupted, e.g. major depression and stress. In the present telemetric study, we determined whether a lack of ghrelin neuropeptide compromises the sleep-wake architecture in ghrelin (-/-) and wild-type (WT) mice, which were chronically instrumented with a telemetric transducer and electrodes for continuous recording of vigilance states, body temperature (BT) and locomotor activity (LMA).

METHODS

Animals and surgery

14 mice (7 male homozygous ghrelin (-/-) mice generated from a mixed 129SvEvBrd background and 7 (WT) littermates) weighing 25-30 g at the time of surgery were used. Animals were individually maintained in ventilated cages under controlled environmental conditions throughout the study: 22 °C ± 2 °C ambient temperature, relative humidity 60%, standard 12:12 light cycle (illumination intensity: ~ 100 lx). All experimental protocols were carried out in strict accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Under deep gaseous anaesthesia (\(O_2\) 0.6 l/min + \(NO_2\) 1.5 l/min + Isoflurane 1.5%), mice were surgically implanted with the telemetry transmitter TA10ETA-F20 (Data Science International, USA), containing biopotential electrodes for monitoring the electroencephalographic activity at the following atlas coordinates (AP -2.3 mm, L ± 1.4 mm from bregma). After surgery the animal were subcutaneously given 0.3 ml analgesic (Carprofen, Rimadyl, 50mg/ml, Pfizer Ltd, UK diluted 1:10) and local analgesic was applied on the wounds (Lidocaine spray Xylocaine, 1 % solution, Astra Pharmaceuticals Ltd, UK). Animals were then individually placed in their home cage and kept warm in a heating box, set at 26 °C ± 2 °C, to avoid hypothermia. The temperature was progressively decreased over the recovery days to reach room temperature.
Telemetric recordings and determination of vigilance states

After 2-3 weeks of recovery and adaptation to the recording conditions, spontaneous sleep-wake cycle and circadian rhythms of BT and LMA were recorded in 12 light: 12 dark. BT and LMA were sampled every 10-sec and averaged into 1-hr bins. The EEG signals were digitized at a sampling rate of 200 Hz, imported offline into Neuroscore software (Neuroscore, DSI) and digitally filtered (high frequency band 50 Hz and low frequency band at 0.5 Hz). The vigilance states were analysed in consecutive 4-s epochs (Neuroscore software, Data Sciences International) as wakefulness, non-rapid eye movement (NREM) sleep or rapid-eye movement (REM) sleep, on the basis of EEG/EMG and LMA signals and according to the standard criteria. Wakefulness is characterized by low-amplitude EEG signal with mixed frequencies, together with high and variable EMG activity. NREM sleep is characterized by high EEG amplitude dominated by delta (1-4 Hz) and low EMG activity. REM sleep is characterized by regular EEG theta oscillations (5-9 Hz) and low amplitude EMG activity. The following sleep variables were calculated for the 12h light and dark period: number of episodes and mean duration of episodes for each vigilance state, and total time spent awake and asleep.

Data analysis
The different sleep variables under spontaneous conditions were expressed as the mean ± SEM. The Wilcoxon Mann-Whitney test was used to compare changes in sleep parameters between groups. A value of \( p<0.05 \) was considered to be significant.

RESULTS
A clear-cut circadian pattern of waking, NREMS and REMS sleep with lowest sleep levels occurring during the active dark phase and highest levels during the inactive light phase was present for both genotypes. However, quantitative differences between strains were detected in sleep-wake parameters. Ghrelin (-/-) mice exhibited less NREM sleep (299 min) and more waking (355 min) particularly during the dark phase, compared to age-matched WT controls (349 min NREM and 310 min wake) (Figure 1). The reduced NREM sleep time resulted from shorter NREM sleep periods (-46%, \( p<0.05 \)), in spite of an increased number of NREM sleep periods (+54%, \( p<0.05 \)). The increased waking resulted from more waking periods (+54%, \( p<0.05 \)), while the mean duration of waking periods was shorter (-27%, \( p<0.05 \)). A slight increase in REM sleep was found during the light phase in ghrelin (-/-) mice. The increased waking observed in ghrelin (-/-) mice was not associated with consistent changes in locomotor activity and body temperature (Table 1).
Overall, a clear fragmentation of the sleep-wake cycle was found in ghrelin (-/-) mice, as shown by the increase in the number of periods of all vigilance states. This could indicate an impairment of sleep stability.
Figure 1: The time spent in wake, NREM sleep, REM sleep, Total sleep, number of period of different vigilance states and mean period duration across the 12 h light-dark phases in WT (grey bars) and ghrelin (-/-) (dark bars) mice. Data are expressed as mean +/- SEM. * P<0.05 between groups.

Table 1: Mean of locomotor activity and body temperature recorded by telemetry system during the 12-hrs light-dark phases. LMA (arbitrary unit) and BT (°) were sampled every 10-sec and averaged into 12-hrs bins. Data are presented as mean +/- SEM.

<table>
<thead>
<tr>
<th></th>
<th>Light phase</th>
<th>Dark phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT</td>
<td>Ghrelin (-/-)</td>
</tr>
<tr>
<td>LMA</td>
<td>2.8 ± 0.1</td>
<td>2.9 ± 0.03</td>
</tr>
<tr>
<td>BT</td>
<td>36.0 ± 0.03</td>
<td>36.0 ± 0.03</td>
</tr>
</tbody>
</table>

DISCUSSION

Waking, NREM sleep and REM sleep, BT and LMA expressed a clear diurnal rhythm in ghrelin (-/-) mice and their WT control littermates. Large amounts of waking occurred during the dark active phase, whereas sleep dominated the light inactive period, as expected in rodents. Thus, circadian rhythmicity appeared to be preserved in this mutant.

The present study demonstrated deterioration of sleep architecture in ghrelin (-/-) mice compared to their WT control littermates. Ghrelin KO mice had more fragmented sleep-wake architecture and spent more time in wakefulness and less in NREM sleep.

A role of ghrelin in sleep regulation has been suggested previously. In human, ghrelin promotes slow-wave sleep and the nocturnal release of GH, and high levels of this hormone were observed during sleep curtailment in human subjects. In rodents, central administration of ghrelin suppressed NREM sleep and enhanced waking. If ghrelin
promotes and maintains sleep, then it should be decreased in ghrelin (-/-) mice. Indeed, our findings indicate that ghrelin (-/-) mice had less NREM sleep, more waking and a more fragmented sleep; they had higher numbers of NREM sleep periods with shorter mean duration.

The present results are in agreement with previous reports, in which ghrelin (-/-) mice had significantly less NREM sleep and more fragmented sleep\textsuperscript{12}, and WT mice had enhanced NREM sleep after systemic ghrelin\textsuperscript{7}. These observations strongly suggest that adaptive mechanisms are not fully operating in the ghrelin (-/-) mouse strain. The lack of ghrelin peptide had an impact on sleep-wake architecture and maintenance in this mutant, which supports the role of ghrelin in sleep regulation.

Our studies demonstrate that ghrelin (-/-) mice, compared to their WT counterparts, showed no locomotor hyperactivity during the passive light or active dark phase.

Ghrelin has long been implicated in the regulation of feeding and weight gain. Both peripheral and central administration of ghrelin strongly stimulate food intake in rodents\textsuperscript{1,2,10}. The increased waking observed in ghrelin (-/-) mice was not associated with altered motor activity or food intake. Thus, the lack of ghrelin neuropeptide did not result in hyperlocomotor behaviour or lean phenotype in this mutant.

The central ghrelin signalling, which targets key hypothalamic and mesolimbic circuits of appetite and reward, is closely integrated in circuits regulating mood and stress. Preclinical studies reported increased ghrelin levels by acute and chronic stress in rats\textsuperscript{13,14}. Central administration of ghrelin stimulated secretion of corticosterone and CRH\textsuperscript{3,5}, as well as increased anxiety- and depression-like behavior in rats\textsuperscript{15}. Clinical studies showed that ghrelin stimulates the HPA axis by secretion of ACTH and cortisol in humans\textsuperscript{4}, while serum ghrelin levels were higher in depressive patients and were normalized by antidepressant and electroconvulsive therapies\textsuperscript{16,17,18}. Changes in the activity of the HPA axis are known to contribute to the alterations of sleep in mood disorders; e.g. disinhibition of REM sleep, reduced NREM sleep and impaired sleep maintenance and continuity. It is possible that the characteristic changes in sleep-wake architecture in ghrelin (-/-) mice, such as reduced NREM sleep and impaired sleep maintenance and continuity, could result from an over-activation of the HPA axis. Assessments of corticosterone levels in this mutant as well as evaluation of specific ghrelin receptor agonist/antagonist on the HPA activity in rats are warranted to test this hypothesis.

Collectively, the lack of ghrelin compromises the stability of sleep-wake cycles in ghrelin (-/-) mice, which supports a role of ghrelin in sleep processes.

REFERENCES


CORRELATIONS BETWEEN OVERNIGHT BREATHING RATE VARIATION AND SUBJECTIVE SLEEP QUALITY SCORES

Maaike S. Goelema\textsuperscript{a,b}, Xi Long\textsuperscript{a,c} and Reinder Haakma\textsuperscript{a}

\textsuperscript{a} Philips Group Innovation, Research, High Tech Campus, 5656 AE Eindhoven, The Netherlands
\textsuperscript{b} Department of Industrial Design, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands
\textsuperscript{c} Department of Electrical Engineering, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands

INTRODUCTION

The relationship between objective sleep parameters, derived from polysomnography (PSG), and subjective sleep quality, obtained from questionnaires, has been researched thoroughly in the past. However, inconsistent results were found, the study outcomes differ to which extend above-mentioned variables are correlated and only a few objective parameters were related to the subjective sleep experience. The most profound association was between wake time and subjective sleep quality ($r = -.59$).\textsuperscript{1–3} New methods to analyze PSG data was proposed by Krystal and Edinger\textsuperscript{4}. They suggested to analyze PSG data more at a measure of nature/depth of sleep, such as indices for the frequency content of electroencephalogram (EEG) signals obtained during non-rapid-eye-movement (NREM) sleep, or to look at particular patterns in the NREM sleep and their sequence between NREM sleep patterns, instead of only taking the sleep stage classification. Yet, correlations between other objective measures, such as respiratory parameters, and subjective sleep quality have not been analyzed. We expect that a stable sleep, seen in, for example, a low breathing rate variation overnight, is indicative for a good sleep quality rating. In this preliminary work, we investigated whether respiratory parameters are related to subjective sleep quality the next morning.

METHODS

Data from the SIESTA project was used\textsuperscript{5}. The SIESTA project was carried out in seven countries of Europe with as main objective to gather a normative database of healthy and sleep-disturbed patients. In short, at the beginning of the study, participants did an entrance examination, which consisted of a physical examination and medical screening. For two weeks participants wore a wrist actigraphic device that records activity counts and went for two consecutive nights (night 7 and night 8) to a sleep laboratory during which PSG recordings were acquired. Additional questionnaires, like neurocognitive tests, were obtained and are described elsewhere.

Our analyses were based on data of 165 healthy participants, aged from 20 to 95 yrs (mean ± SD: 51.8 ± 19.4 yrs; 77 men). A participant was considered healthy when neither having a sleep disorder and nor a mental or physical disorder.

The Sleep and Awakening questionnaire (SSA)\textsuperscript{6} was assessed to determine the subjective sleep quality each morning for the past night. The SSA consists of 27 questions, divided in four parts: sleep quality, awakening quality, somatic complaints and estimates about their
sleeping times of last night. A total score can be calculated when taking the first three parts, or a sub score of each part separately can be calculated. The total score range is between 20 and 80. Higher scores indicate worse sleep quality.

For PSG recordings, 16 channels of bio-signals were measured, such as EEG, electromyogram (EMG), electrooculogram (EOG), electrocardiogram (ECG), oxygen saturation and respiratory effort. For objective measurements two respiratory parameters extracted from the overnight respiratory effort signals were considered: mean breathing rate (BR) and mean standard deviation of breathing rates (SDBR).

Spearman rank correlations were conducted to analyze the association between the SSA scores and the two respiratory parameters BR and SDBR. For the respiratory parameters, analyses were performed based on the mean of the whole night, calculated by taking the mean BR and mean SDBR for each sleep stage separately and followed by calculating the mean of those separate means for different sleep stages. This was done so that the final mean variable was not influenced by the differences in the percentages of the sleep stages, serving to purely look at the physiological measures without including information of sleep stages. Furthermore, supplementary analyses were executed to investigate gender and age effects in the abovementioned association. For age analysis, participants were divided in three groups: young: 20 – 39 yrs (n = 52), middle aged: 40 – 69 yrs (n = 69), elderly: ≥ 70 yrs (n = 44).

RESULTS AND DISCUSSION

Positive correlations were found between the mean SDBR and the total SSA score [night 7: r = .179, p = .024; night 8: r = .213, p = .007, Figure 1(a)]. This means that a higher variation of breathing rate is associated with worse sleep experience. However, the correlation coefficient was not high, implicating that the association is weak.

A gender effect was observed in both nights, as significant correlations were found between mean SDBR and total score on SSA for females [night 7: r = .263, p = .014; night 8: r = .300, p = .005, Figure 1(b)]. Therefore, a higher mean variation of the breathing rate is associated with worse sleep quality in women. An explanation for this is not clear and needs to be further investigated.

Additionally, moderate correlations were found between the mean BR and the mean SDBR and the total score of the SSA of night 7 in the elderly group (BR: r = .400, p = .008 and SDBR: r = .399, p = .008, Figure 2). No significant correlations were observed for the other age groups. This suggests that, especially for elderly persons, a higher breathing rate variation is associated with worse sleep experience. However, these results are not present in the second night (night 8), meaning that these findings might be due to the first-night effect present in this data set.

This is a preliminary study and future research with more in-depth analyses of the PSG data is needed to better understand the relationship between objective sleep measurements and subjective sleep quality. Moreover, multiple nights are necessary to assess the night-to-night variability within this relationship.
CONCLUSIONS

Breathing rate and its variation were found to be correlated with subjective sleep quality rating. The association between the breathing rate variation and the SSA score was more profound for women and seen to a greater extent for the first night in the elderly group. However, these correlations were not as high as we expected. If future research can find a strong relationship between other objective parameters and sleep quality ratings, this would mean a great improvement in the credibility of sleep monitoring devices. Moreover, predictions can be made the next morning about how someone has slept. Additionally, a complete PSG recording would not always be necessary as the insight in other objective sleep parameters improves.

REFERENCES

CHRONOTYPE, SLEEP QUALITY AND DEPRESSIVE SYMPTOMS: A CROSS-SECTIONAL STUDY AMONG DUTCH STUDENTS

Katinka M. John and Julia F. van den Berg

a Leiden University, department of Clinical Psychology, Leiden, The Netherlands
b Parnassia Psychiatric Institute, The Hague, The Netherlands

INTRODUCTION

In 2010, a Dutch health survey has shown that 27% of the population aged 12 years or older reported having had depressive symptoms at some point in their life. This illustrates that depressive symptoms are very common. Several studies have investigated the relation between depressive symptoms and chronotype. Chronotype indicates the human preference in timing of sleep and waking, caused by the periodicity of their biological clock. Morning types have a periodicity of less than 24 hours, and prefer to go to bed early and wake up early, whereas evening types have a periodicity of more than 24 hours and prefer a later bed time and wake-up time. Studies of students and healthy subjects aged 18 to 99 have shown a relation between chronotype and depressive symptoms, with evening types reporting more depressive symptoms. So far, the underlying mechanism of this association is unknown. Depressive symptoms are also associated with poor sleep quality; sleep problems are frequently reported by patients with depression. Sleep problems often precede depression, or relapse of an earlier depression. Besides the fact that evening types report more depressive symptoms, they also report a poorer sleep quality in comparison with morning types. This may be due to a discrepancy between the desired sleep time and the actual, socially determined sleep time in evening types, also known as “social jetlag”.

As it is unclear whether there is a direct relation between a later chronotype and depressive symptoms, or this relation is mediated by sleep quality, Kitamura et al. have investigated the relation between chronotype and depressive symptoms when adjusting for sleep quality. They found an association between an extreme preference for the evening and more depressive symptoms; an extreme preference for the morning was associated with fewer depressive symptoms. These analyses were adjusted for various sleep parameters, including subjective sleep quality. Therefore, in their study, the association between chronotype and depressive symptoms was not fully explained by mediation by sleep quality.

To investigate whether the same results will be found in a population of Dutch students, the objective of this study is to examine the relation between chronotype and depressive symptoms when adjusting for sleep quality.

METHODS

Subjects
Participants were students, mostly recruited at Leiden University. There were no exclusion criteria except sufficient command of the Dutch language.
Instruments
Depressive symptoms were assessed with a Dutch version of the 16-item Quick Inventory of Depressive Symptomatology self-report (QIDS-SR16). This questionnaire contains 16 questions about the 9 DSM-IV domains of depression. The total score ranges from 0 to 27. Chronotype was assessed with a Dutch version of the Morningness-Eveningness Questionnaire (MEQ). The MEQ is a 19-item questionnaire developed to estimate chronotype based on self-report. The total score ranges from 16 to 86 points; higher scores indicate an earlier chronotype. Sleep quality was assessed with a Dutch version of the Pittsburgh Sleep Quality Index (PSQI). This self-report questionnaire contains 19 questions and measures sleep quality and sleep disturbance during the previous month. The total score ranges from 0 to 21, with higher scores indicating poorer sleep quality.

Procedure
The questionnaires were administered as an online survey. On the first page the study and its purpose were explained and participants were asked to give informed consent.

Statistical analysis
Three linear regression analyses were performed, to examine the associations between chronotype and depressive symptoms, between sleep quality and depressive symptoms, and between chronotype and sleep quality. Finally, a linear regression analysis was performed with chronotype and sleep quality as independent variables and depressive symptoms as a dependent variable. All analyses were adjusted for age and gender. IBM SPSS Statistics version 22 was used for all statistical analyses.

RESULTS AND DISCUSSION
Initially, 165 persons responded to the survey. Of these, 11 had not completed the questionnaire and were excluded, which resulted in a study population of 154 subjects. Of these 154 subjects, 119 were female (77.3%) and 35 male (22.7%). Age ranged from 18 to 50 years (M = 20.5 years, SD = 4.0). The majority (92.9%) were university students. The mean total scores on the MEQ, PSQI and QIDS-SR16 were 46.0 (SD = 9.4), 5.2 (SD = 2.5) and 5.1 (SD = 4.3), respectively.

Linear regression analysis demonstrated a negative association between chronotype and depressive symptoms, adjusted for age and gender: \( \beta = -0.10, t(153) = -2.70, p = .008 \) (Table 1). This means that a later chronotype was associated with more depressive symptoms. Linear regression analysis also showed that poorer sleep quality was associated with more depressive symptoms, \( \beta = 0.98, t(153) = 8.79, p < .001 \) (Table 1). The last linear regression analysis showed that a later chronotype was associated with a poorer sleep quality, \( \beta = -0.085, t(153) = -3.95, p < .001 \).

Finally, multiple regression analysis showed that chronotype and depressive symptoms were no longer significantly associated, \( \beta = -0.018, t(153) = -0.56, p = .574 \) when the analysis was additionally adjusted for sleep quality (Table 2). This could very well be an indication of a mediating role for sleep quality, in which a later chronotype causes a poorer sleep quality and a poorer sleep quality leads to more depressive symptoms. Thus the hypothesis, that the relation between chronotype and depressive symptoms exists independently of sleep quality, was not confirmed.
Table 1. Associations between chronotype and depressive symptoms, and between sleep quality and depressive symptoms* (N = 154).

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronotype (MEQ)</td>
<td>-0.10</td>
<td>-2.70</td>
<td>.008</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>2.64</td>
<td>3.24</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.055</td>
<td>0.65</td>
<td>.515</td>
</tr>
<tr>
<td>Sleep quality (PSQI)</td>
<td>0.98</td>
<td>8.79</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.37</td>
<td>2.07</td>
<td>.040</td>
</tr>
<tr>
<td>Age</td>
<td>-0.067</td>
<td>-0.95</td>
<td>.345</td>
</tr>
</tbody>
</table>

*Linear regression analyses, adjusted for age and gender
MEQ = Morningness-Eveningness Questionnaire; PSQI = Pittsburgh Sleep Quality Index

Table 2. Association between chronotype and depressive symptoms, adjusted for sleep quality* (N = 154).

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$t$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronotype (MEQ)</td>
<td>-0.018</td>
<td>-0.56</td>
<td>.574</td>
</tr>
<tr>
<td>Sleep quality (PSQI)</td>
<td>0.96</td>
<td>8.18</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>1.49</td>
<td>2.14</td>
<td>.034</td>
</tr>
<tr>
<td>Age</td>
<td>-0.058</td>
<td>-0.81</td>
<td>.420</td>
</tr>
</tbody>
</table>

*Linear regression analysis, adjusted for age and gender
MEQ = Morningness-Eveningness Questionnaire; PSQI = Pittsburgh Sleep Quality Index

The results of the present study support previous studies. The association between a later chronotype and depressive symptoms was also reported by Chelminski et al. and Hidalgo et al. Chelminski et al. investigated the relation in a group of students suffering from a mild depression. This depression was ascertained with three different questionnaires about depressive symptoms. They showed that a later chronotype was associated with higher scores on the depression scales. Hidalgo et al. investigated the relation in a group of 200 Portuguese volunteers aged 18 to 99 years. They also found an association between a later chronotype and more depressive symptoms. These results suggest that a late chronotype is a risk factor for depression.

The results of the present study do not support the hypothesis that the relation between chronotype and depressive symptoms is independent of sleep quality, and are therefore inconsistent with the results of Kitamura et al. There are some differences between the studies that may explain the different outcomes. For instance, Kitamura et al. investigated different sleep parameters simultaneously, including sleep debt, sleep duration, sleep quality and sleep timing. Subjective sleep quality was assessed by three items from the PSQI. Instead, in the present study global sleep quality, assessed with the total PSQI score, was investigated. Perhaps the current measurement of sleep quality is more comprehensive than the measurement of Kitamura et al., leading to different results. In addition, the study population of the current study consisted mainly of students, whereas 45.5% of the population of Kitamura et al. were shiftworkers. This may have led to different results. Finally, depressive symptoms were assessed with different questionnaires, and Kitamura et al. used a dichotomous outcome.

This study has several limitations, which must be considered when interpreting the data. First, this is a cross-sectional study; therefore it is not possible to indicate a cause and effect in the relations. Second, the population consisted mainly of university students, which does not allow generalisation of the data to other groups. Finally, all variables were measured with self-report questionnaires. A key strength of the present study was the quality of the
questionnaires that were used. For future studies of the relation between chronotype, sleep quality and depressive symptoms, it is recommended to investigate a larger and more heterogeneous study population. Finally, it would be interesting to investigate the relation in a longitudinal study, which makes it possible to investigate causal relations.

CONCLUSIONS

In summary, the results of the present study show an association between a later chronotype and more depressive symptoms. Poor sleep quality was associated with more depressive symptoms as well. A later chronotype was associated with poorer sleep quality. The association between chronotype and depressive symptoms was strongly attenuated when adjusting for sleep quality, which indicates that a mediating role of sleep quality in this association is highly likely.

ACKNOWLEDGEMENTS

This research project was performed as part of the third year’s curriculum of Psychology at Leiden University. The authors would like to thank Sophia Buts, Emma Groot Wassink, Leonard de Ruijter, Karine van Schie and Rik Stoeverlaar for their contributions to the project.

REFERENCES

SENSITIVITY OF PSYCHOMETRIC TESTS MEASURING DRIVING RELATED SKILLS TO THE EFFECTS OF ONE NIGHT OF SLEEP DEPRIVATION

S. Jongen, E.F.P.M. Vuurman, J. Perrier, J.G. Ramaekers, A. Vermeeren

Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, the Netherlands

INTRODUCTION

Medicinal and illicit drugs can have detrimental side effects, such as sedation and reduced alertness, which can cause driving impairment possibly leading to traffic accidents. Performance testing should be applied to provide meaningful precautions for users and prescribers regarding the impact of particular drugs on driving, either as part of the drug registration process or for already marketed drugs. Relatively simple driving related tests may be used to screen a drug’s impairing potential, as these tests often provide the earliest evidence of impairment. The advantage of simple laboratory tests is that these tests are generally easy to administer, are cost-effective, and have a relative short duration. However, no consensus has been reached about which specific initial screening tools are best to be used, as the link between test outcomes and clinical relevance (which means that the impairment is indirectly linked to an increased crash risk) are often unclear. Therefore, it is needed to establish a link between tests and clinical relevance in order to compare results over separate studies. To provide this information, a requisite of a test is to be sufficiently sensitive to detect relevant levels of impairment. One way to establish relevant performance impairment of a test is to assess its sensitivity to clinically relevant levels in drowsiness induced by one night of sleep deprivation. After alcohol, sleepiness is the most frequent cause of motor vehicle accidents. Being sleep deprived while driving is a serious problem and is a direct or contributing cause of road related accidents.

The main objective of present study is to determine the ability of nine psychometric tests to detect clinically relevant impairing effects of drowsiness as induced by one night of sleep deprivation. More specifically, the sensitivity of these psychometric tests were assessed during and after a single night of sleep deprivation at 1:00 am, 5:00 am, and 11:00 am and compared with performance after a normal night of sleep. A secondary objective is to determine and compare the magnitude of the sedative effects on these tests during and after a night of sleep deprivation.

METHODS

Twenty-four healthy volunteers (12 males, 12 females) aged between 23-45 years were recruited through advertisements at Maastricht University. The mean (± SD) age of the participants was 26.9 (± 3.4) years. The study was conducted in accordance with the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Seoul (2008). All participants indicated their informed consent in writing. The study was conducted according to a 2-period cross-over design to compare performance after prolonged wakefulness (i.e. one night of sleep deprivation) with performance after a  
normal night of sleep. The psychometric tests were conducted on 4 occasions: once after normal sleep (at 11:00 am) and three times during a single night of sleep deprivation (at 1:00 am, 5:00 am, and 11:00 am). Both conditions were separated by an interval of at least one week, and the order was balanced over participants.

The following laboratory tests were administered: the Psychomotor Vigilance Test, the Digit Symbol Substitution Test, the Divided Attention Test, the Determination Test, a test of Useful Field of View, the Concept Shifting Test, the Attention Network Test, a Postural Balance Test, and the Critical Tracking Test. To reduce order effects between the tests, the test battery was divided into two parts. Half of the participants started with part one followed by part two; the other half with part two followed by part one.

Change scores from baseline (i.e. performance after a night of normal sleep) for each of the dependent variables were transformed to z-scores. These were calculated across the pooled changes in the single night of sleep deprivation on three occasions (i.e. at 1:00 am, 5:00 am, and 11:00 am), relative to performance on a separate day at 11:00 am after one night of normal sleep. This allows for easy comparison across each of the various performance tests (figure 1).

To determine the magnitude of the simple effects at various times during the night of sleep deprivation, Dunlap et al.’s effect size (ES) statistics (i.e. $t(2(1-r)/n)^{1/2}$) were calculated. ES between 0 and 0.19 are considered small, between 0.20–0.69 are considered moderate and 0.70 or higher are considered large.

**RESULTS AND DISCUSSION**
The effect sizes indicated that tasks and parameters differ in sensitivity to the effects of one night of sleep deprivation (Table 1). At 11:00 am after a night of sleep deprivation, largest effect sizes were found in the DAT on primary task performance and false alarms in secondary task performance (ES = 1.26 and 0.86, respectively), inverse reaction time, mean reaction time and lapses in the PVT (ES = 1.13, 0.98, and 1.23, respectively), overall reaction time in the ANT (ES = 1.13) and total detection time in the UFOV (ES = 0.70). At 5:00 am during the night of sleep deprivation, all these tests showed smaller effect sizes (0.60 ≤ ES ≤ 0.88). At 5:00 am, effect sizes were moderate (0.56 ≤ ES ≤ 0.62) on the test parameters of the CST and PBT, but smaller (0.00 ≤ ES ≤ 0.41) at 11:00 am after a night of sleep deprivation. At 1:00 am during the night of sleep deprivation, two test parameters showed moderate effect sizes (both ES = 0.28): correct responses in the DSST and median reaction time in the DT. These parameters showed moderate effects (0.60 and 0.43, respectively) at 5:00 am and 11:00 am (0.45 and 0.39, respectively) during and after a night of sleep deprivation. Smallest effect sizes were found on lambda in the CTT: 0.11 and 0.29 at 5:00 am and 11:00 am during and after a night of sleep deprivation, respectively.

CONCLUSIONS

From the psychometric tests used in this study, the PVT, DAT, and UFOV test seem most promising for initial evaluation of impairment induced by sedative drugs based on sensitivity, short duration and minimal influence of circadian effects. The effects of one night of sleep deprivation on these tests assessing driving related skills are similar to or larger than clinically relevant levels of alcohol. Such decreases in arousal are socially and clinically relevant, as an increased crash risk has been indicated at night or in the early morning hours. The suggested initial screening tools can be used as a first step to provide meaningful precautions for users and prescribers about the impact of drugs on driving.
Table 1. Dunlap’s effect sizes\(^9\) of performance parameters between 1:00 am, 5:00 am, and 11:00 am during and after a night of sleep deprivation and at 11:00 am after a normal night of sleep

<table>
<thead>
<tr>
<th>Test</th>
<th>1:00 am (16h awake)</th>
<th>5:00 am (20h awake)</th>
<th>11:00 am (26h awake)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor Vigilance Test</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1/Reaction Time</td>
<td>-0.15</td>
<td>0.60*</td>
<td>1.13**</td>
</tr>
<tr>
<td>Mean Reaction Time (ms)</td>
<td>0.21*</td>
<td>0.62*</td>
<td>0.98**</td>
</tr>
<tr>
<td>Lapses</td>
<td>0.22*</td>
<td>0.78**</td>
<td>1.23**</td>
</tr>
<tr>
<td>Critical Tracking Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Lambda (rad/s)</td>
<td>-0.16</td>
<td>0.11</td>
<td>0.29</td>
</tr>
<tr>
<td>Divided Attention Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z-RT + z-lg10(cl)</td>
<td>-0.22</td>
<td>0.62*</td>
<td>1.26**</td>
</tr>
<tr>
<td>z-AE + z-lg10(mi)</td>
<td>0.01</td>
<td>0.32*</td>
<td>0.67*</td>
</tr>
<tr>
<td>False Alarms</td>
<td>0.19</td>
<td>0.88**</td>
<td>0.86</td>
</tr>
<tr>
<td>Attention Network Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Reaction Time (ms)</td>
<td>0.00</td>
<td>0.63*</td>
<td>1.13**</td>
</tr>
<tr>
<td>Alerting Effect (ms)</td>
<td>0.06</td>
<td>0.16</td>
<td>0.51*</td>
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medium effect size; \(^*\) large effect size

REFERENCES
A SURVEY OF SLEEP DISORDERS AMONG DUTCH VISUALLY IMPAIRED PERSONS

Karin J. van Rijn, Maurits V. Joosse and Gerard A. Kerkhof

Centre for Sleep and Wake Disorders, Medical Center Haaglanden, The Hague, The Netherlands; Ophthalmology, Medical Center Haaglanden, The Hague, The Netherlands

INTRODUCTION

The majority of visually impaired persons (VIP’s) suffer from excessive daytime fatigue, sleepiness and dysphoria. Both VIP’s and therapists consider these complaints to be caused by compensatory effort needed to fulfill daytime activities in case of blindness or diminished sight. Alternatively, insomnia and disturbed circadian control of sleep may play a pivotal role in the causation of this syndrome. Sleeping problems among the totally blind are well known and documented. Several studies show that over 50% of the blind have severe problems with the quality of their sleep and fatigue during the day. Research in New Zealand suggests a 26% prevalence of Circadian Rhythm Sleep Disorder (CRSD) among VIP’s. In 2005 the prevalence of blindness in the Netherlands is estimated to be 0.4% (75,881 people) and of visual impairment 1% (225,525 people). The number of people with visual impairment suggests the possibility of a widespread sleeping problem. The presence of sleeping problems will be compared with results from a sample of the Dutch population.

METHODS

Respondents (VIP’s as well as their partners) were recruited through a national fair for VIP’s. At the fair an online questionnaire was launched that was made available on a secluded website. Respondent were also invited through publications in media that were targeted at VIP’s. The questionnaire included validated questions about sleepiness and sleeping disorders, and additional questions about visual disability, personal status and sleep habits. The presence of a sleep disorder was measured with the 32-item Holland Sleep Disorders Questionnaire (HSDQ). The HSDQ generates one global sleep disorder score and differentiates between the 6 main categories of sleep disorders as defined in the ICSD-2, i.e. insomnia, parasomnia, CRSD, hypersomnia, restless legs syndrome, and sleep-related breathing disorder. In this research we focus on the incidence of a General Sleep Disorder (GSD) and two specific sleep disorders: insomnia and CRSD. Sleepiness was measured using the 8-item Epworth Sleepiness Scale (ESS), and a set of 15 additional questions about demographics, ophthalmic disease quality of sleep and daytime fatigue. Daytime rhythm was measured with the questions: ‘do you have a regular daily rhythm e.g. regular mealtimes, working hours and/or bedtimes’ (range 1-5) and ‘do you have daily activities outdoors’ (range 0-7). Subjects were asked to select the category that best described their current percentage of vision (visual acuity). Response choices included: “no visual impairment, sighted,” “over 30% vision,” (11.7%) “15-30% vision,” (18.6%) “5-15% vision,” (18.6%) “1-5% vision,” (24.8%) or “blind.” (26.3%). Individuals identifying themselves as sighted (n=16) were described as a separate category. Respondents were also asked to select the category that best described their ophthalmic disease. Based on the answers...
(n=270) an anatomical classification due to the specific location of the visual impairment was made, leading to the following 5 categories: blindness because of absent bulbus (15.2%), visual impairment due to optic nerve disease (15.2%), to retinal disease (56.3%), to other neuro-ophthalmologic disease (3.7%) and to unknown causes (9.6%). In further analyses the categorization visual acuity and location was used to determine whether these factors influence the presence of a sleeping disorder. Adults between the ages of 18 to 85 years were eligible. A total of 289 data records were completed by 273 visually impaired individuals (159 females age 52.48 ± 16.57 years, 114 males; mean age 52.11 ± 15.40 years) and 16 fully-sighted individuals (8 females, 8 males; mean age 48.19 ± 14.84 years). There was no statistically significant difference for age or gender between the fully-sighted and visually impaired groups.

Missing values on the HSDQ were replaced by the average score on the specific item. Continuous variables (HSDQ, ESS) were presented as mean ± standard deviation. Categorical variables (location, vision) were expressed as percentages and their 95% confidence intervals. The presence of a General Sleep Disorder (GSD) and the incidence of Insomnia or CRSD was assessed. Next the incidence of a GSD was compared across the groups vision and location using chi-square test with Bonferroni correction or Fisher’s exact test, as appropriate. Additional questions about sleep and daily activities were compared between groups using analyses of variance (ANOVA), and the Mann–Whitney U-test. Correlations were evaluated using the Pearson test. Logistic regression (method enter) was used to test the association between the presence of a sleep disorder as dependent factor and age, gender, visual acuity, location, daily activity and daily rhythm as predictors. Statistical procedures were performed using the Statistical Package for Social Sciences, (SPSS version 21.0: SPSS Inc., Chicago, IL, USA). For all tests values of p<.05 were considered to be significant.

RESULTS AND DISCUSSION

A majority of the visually impaired respondents (54%) has a general sleep disorder (GSD). Gender and age did not have a statistically significant effect on GSD. In table 1 the presence of a general sleep disorder is presented per category of vision.

| Table 1: Prevalence of General Sleep Disorder by category of visual acuity |
|-----------------------------|------------------|
| Vision                      | Percentage       |
| Blind (n=71)                | 50.7 a           |
| 1-5 % (n=67)                | 46.3 a           |
| 5-15 % (n=51)               | 49.0 a           |
| 15-30 % (n=51)              | 58.8 a, b        |
| Over 30% (n=32)             | 78.1 b           |
| Fully sighted partners (n=13)| 46.2             |

Each subscribt letter denotes a subset of visus categories whose column proportions do not differ significantly from each other at the .05 level.

For every category of visual acuity the incidence of a GSD is significantly higher than for the general Dutch population (32.1%). The respondents with 15-30% vision and with 30% vision have a significant higher incidence of a GSD as compared to the categories with less vision. When considering insomnia and CRSD more closely, the incidence of both sleeping disorders is almost twice as high as the prevalence in the Dutch population, (Figure 1).
Of the 31 respondents meeting the CRSD criteria, 24 (77%) were diagnosed with insomnia as well. In the next table information about the sleep related questions, for each category vision is presented.

| Table 3: Mean score on sleep related questions compared for vision. |
|-----------------------------------|-----------------|-----------------|-----------------|------------------|
| Sleep related questions           | Blind           | 1-5%            | 5-15%           | 15-30%           | More than 30%    |
| How many hours of night sleep do you usually get? (n=272, range 4-9)*  | 6.24            | 6.96            | 6.69            | 6.65             | 6.97             |
| Do you consider your night sleep to be enough? (n=270, range 1-3)*       | 1.46            | 1.56            | 1.51            | 1.43             | 1.50             |
| How do you consider the quality of your night sleep? (n=271, range 1-5)*  | 2.99            | 3.22            | 3.22            | 3.18             | 3.10             |
| Do you experience fatigue or sleepiness during the day? (n=273, range 1-5)* | 2.96            | 3.19            | 3.22            | 3.16             | 3.19             |
| I am a … sleeper (n=274, range 1-5)*                                     | 2.88            | 3.26            | 2.90            | 3.00             | 3.03             |
| Do you have a regular daily rhythm? (e.g. regular mealtimes, working hours and/or bedtimes (n=273, range 1-5)* | 3.89            | 3.96            | 3.78            | 3.73             | 3.56             |
| Do you have daily activities outdoors? (n=271, range 0-7)                 | 4.56            | 4.59            | 4.12            | 4.55             | 4.19             |
| Sumscore Epworth Sleepiness Scale (n=248, range 0-23)*                    | 7.64            | 4.59            | 4.09            | 4.50             | 3.56             |

With regard to the vision categories there are no significant differences. However, there is a trend for hours of sleep (p<.06) and the sumscore on the ESS (p<.09). The additional questions in Table 3 marked with an asterisk (*) differ significantly between the groups with and without a GSD. We tested the predictive value of a model for developing a GSD. Variables entered in the logistic regression as predictors were age, gender, visual acuity, location of ophthalmic disease, daily activities and daily rhythm. A (self-reported) irregular daily rhythm is the strongest independent predictor for developing a GSD. The more irregular the rhythm, the higher the odds to develop a GSD. (OR 6.91, p<.05). Nagelkerke Rsquare .09. Vision contributes to a GSD as well, the higher the remaining percentage of vision, the more likely to develop a GSD (OR 5.31, p <.05). There seems to be a relation between a higher
percentage of vision, and a more irregular daily rhythm. A possible explanation for this unexpected result might have to do with the fact that respondents with Macular Degeneration (an age related ophthalmic disease) are overrepresented in these categories. Similar results as for daily rhythm were found for daily activity. The lower the number of days with daily activity within a week, the higher the likelihood to develop a GSD (OR 4.54, p<.05).

Although a large number of VIP’s filled out the questionnaire, and good sleepers were invited to participate, it is possible that respondents with sleeping problems are overrepresented. This sample is not representative for ophthalmic disease. We advise a broader investigation, with visual acuity and ophthalmic disease diagnosed by an ophthalmologist instead of self report. Reactions from VIP’s on the results from this research however, suggest a widespread sleeping problem.

CONCLUSIONS

VIP’s have a higher risk for a sleep disorder, in particular insomnia and Circadian Rhythm Sleep Disorder than the general Dutch population. An irregular daily rhythm is the strongest predictor for developing a GSD, followed by the degree of visual acuity and a lack of daily activities on the third place. Thus, the reported daytime fatigue seems more likely to be caused by a sleeping disorder than by the strain caused by the visual impairment. Deregulation of the sleep-wake cycle might play a crucial role. Although a person can be blind, unconscious perception of light by retinal ganglion cells, might still be possible. If synchronization by light is missing, ‘Zeitgebers’ like regular mealtimes and sport times, can synchronize the circadian rhythm. For therapy we suggest to strengthen alternative ‘Zeitgebers’ more often.

REFERENCES

DIFFERENTIAL ULTRADIAN ORGANIZATION OF VIGILANCE STATES IN THE LIGHT AND THE DARK PHASE

Magdalena K. Smyk\textsuperscript{a,b}, Gilles van Luijtelaar\textsuperscript{b}, Wilhelmus H. Drinkenburg\textsuperscript{c}

\textsuperscript{a} Dep. of Neurophysiology and Chronobiology, Chair of Animal Physiology, Institute of Zoology, Jagiellonian University in Krakow, Gronostajowa 9, 30-387 Krakow, Poland

\textsuperscript{b} Donders Centre for Cognition, Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Montessorilaan3, 6525 HR Nijmegen, the Netherlands

\textsuperscript{c} Dep. of Neuroscience, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse, Belgium

INTRODUCTION

According to the two process model of sleep regulation the occurrence of vigilance states is controlled by two mechanisms: homeostatic and circadian\textsuperscript{1}. The distribution of particular states across 24 h is non-uniform and behavior-dependent (diurnal/nocturnal). In nocturnal rodents, motor activity, feeding and grooming predominate during the dark phase, while the light phase is occupied mainly by sleep\textsuperscript{2}. Not only is the amount of sleep-wake states different, but also their consolidation and bouts duration are phase-related\textsuperscript{3}. Besides circadian periodicity, the occurrence of vigilance states is characterized by ultradian frequencies. During sleep in humans, non-REM and REM sleep alternates with a period length of 90 min\textsuperscript{4}. In rodents, vigilance states occur in a 4 – 7 h cycles\textsuperscript{5}. The presence of ultradian periodicities are the most pronounced when circadian influences are eliminated (e.g. after the lesion of the master circadian pacemaker)\textsuperscript{5}. The ultradian period of sleep-wake states across 24 h was found to be unstable with ultradian rhythms being more pronounced during the light than during the dark phase\textsuperscript{6}. Therefore, the main goal of the present study was to investigate internal organization with respect to dominant periodicities of vigilance states in the light and the dark phase in rats entrained to 12:12 light-dark cycle.

METHODS

20 h EEG/EMG recordings of 12 adult (8 months of age) male Sprague Dawley rats (Harlan, the Netherlands) were analyzed in order to investigate internal organization of 5 vigilance states: active and passive wakefulness, light and deep slow-wave sleep, REM sleep. Spectral analysis (single spectrum Fast Fourier Transforms, FFT) was performed on 10 h data recorded in both phases of the 12:12 light-dark cycle in standard laboratory conditions. Recordings started from 3\textsuperscript{rd} h of the light phase and were continued till 10\textsuperscript{th} h of the dark phase inclusive. Vigilance states were scored based on 2 sec epochs of EEG/EMG signal by means of an algorithm written in LabView (National Instruments Corp., USA). Active wakefulness was scored based on low voltage, fast EEG and high EMG activity; passive wakefulness based on low voltage fast EEG and high to moderate EMG activity. EEG of light slow-wave sleep consisted of high voltage slow waves interrupted by low voltage fast activity, EMG was reduced. Deep slow-wave sleep was characterized by slow waves of high amplitude and...
markedly reduced EMG. REM was scored based on low voltage, fast EEG activity with a dominant regular theta rhythm, while EMG activity was absent. Five time series of 30 sec bins were created by adding the number of 2 sec epochs of each vigilance state and then all these epochs were subjected to FFT. Spectral density estimates were computed and the periodogram values were smoothed by Hamming procedure (width of the data window: 5). All analyses were performed in Statistica (StatSoft Inc., USA).

RESULTS AND DISCUSSION

In general, phase-related differences in spectral density estimates were seen for all sleep-wake states. Differences included either higher spectral density for all periods in one of the phases or phase-related effects were restricted to some frequencies only. The highest spectral densities for all periods were observed for active wakefulness in the dark phase; therefore this period has the most pronounced ultradian rhythms. This time series was characterized by a wide peak for a range of periodicities between 42 and 100 min with the highest spectral density for the period of 65 min in the dark phase. In the light phase, all spectral densities were lower; peaks were also much less prominent and were shifter towards longer periods (75 and 300 min, the latter being the dominant period). Similar phase-related differences were observed for light and deep slow-wave sleep, albeit with higher values for deep slow-wave sleep. A wide and pronounced peak was seen for a range of periods between 46 and 120 min (the highest spectral density for a period of 65 min) for light slow-wave sleep in the dark phase, while in the light phase all estimates in this range were lower, including the peaks that shifted towards shorter periodicities (37 and 60 min respectively). However, starting from period of 120 min, spectral density was slightly higher in the light than in the dark phase. Time series of deep slow-wave sleep was characterized by two dominant peaks in the range of 43 to 85 min (the highest spectral density value for a period of 66 min) and 100 to 200 min (highest spectral density value for a period of 150 min) in the dark phase. In the light phase 3 peaks were observed for periods of: 35, 75 and 300 min, value of the last being higher than corresponding value from the dark phase. Opposite to active wakefulness and light slow-wave sleep, passive wakefulness was the state, in which higher spectral density was seen for all periods in the light phase. Dominant frequencies in the occurrence of passive wakefulness were: 33, 60 and 300 min. In the dark phase, all estimates had not only lower values; the peaks were shifted towards shorter (12 min) and longer periods (150 min) respectively. Time series of REM sleep were characterized by many peaks of high spectral density in a range of short periodicities in both phases. When longer periods were considered, 3 peaks were observed: 46, 66 and 300 min in the dark and 40, 60 and 100 min in the light phase respectively. Starting from a period of 150 min, spectral density estimates were higher for the dark phase. All data presented in figure 1.

It can be concluded that clear differences in internal organization with respect to dominant periodicities were found for all vigilance states. Spectral density of two states: active and passive wakefulness differed across all periods. However, the character of differences was opposite. Higher spectral density estimates were obtained for active wakefulness in the dark phase, while these of passive wakefulness were higher in the light phase. Remaining sleep-wake states differed
Figure 1. Mean and SEM (n = 12) of spectral density estimates for active wakefulness (A), passive wakefulness (B), light slow-wave sleep (C), deep slow-wave sleep (D) and REM sleep (E) in the light and the dark phase of 12:12 light-dark cycle.

either in a range of short or long periodicities exclusively. Both slow-wave sleep states had higher spectral density in a range of short periodicities in the dark phase; REM sleep had higher spectral density in a range of longer periods in the light phase.

The phase-related differences in dominant peaks seem to confirm previous reports about variability of the ultradian period across 24 h. However, the present data do not fully support the finding that ultradian rhythms are more pronounced during the light phase since higher spectral density was found for light and deep slow wave sleep states for periods between 50 and 100 min in the dark instead of the light phase. This finding was not restricted exclusively
to short periodicities but in case of active wakefulness and REM sleep covers also periods in a range from 2 to 5 h.

CONCLUSIONS

Active wakefulness and deep slow wave sleep showed the strongest ultradian organization: for active wakefulness during the dark phase, for deep slow wave sleep in the light phase but only for a restricted range of periods. All vigilance states show clear phase related differences in temporal organization. Interestingly, whether this is more pronounced in the dark or in the light phase is highly dependent on the vigilance state itself and the phase. In all, the temporal organization of sleep is also controlled by various ultradian rhythms and this is phase dependent.

ACKNOWLEDGEMENTS

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REFERENCES

FATIGUE DURING DEADLY FORCE DECISION-MAKING: MEASURING SKIN CONDUCTANCE RESPONSE DURING SIMULATIONS

Michael A. Winser\(^a\), John M. Hinson\(^b\), Stephen M. James\(^a\), Bryan Vila\(^a\), Paul Whitney\(^b\), Hans P. A. Van Dongen\(^a\)

\(^a\) Sleep and Performance Research Center, Washington State University, Spokane, WA, USA  
\(^b\) Department of Psychology, Washington State University, Pullman, WA, USA

INTRODUCTION

Sleep deprivation impairs performance on computer-based tasks of risky decision-making administered in the laboratory.\(^1,3\) It is unclear how such performance impairment may translate to more complex operational settings such as law enforcement officers’ deadly force decision-making (DFDM). We set out to measure DFDM in a high-fidelity simulator developed for training law enforcement officers. Skin conductance level (SCL), a measure of sympathetic arousal, increases in anticipation of risky decision outcomes and may be used as a measure of affective processes guiding risky decisions.\(^4\) However, anticipatory SCL measurement is sensitive to movement and speech,\(^5\) making its use potentially problematic in DFDM simulations, as these require use of an inert handgun and verbal interaction with characters on-screen. In this pilot study we evaluated anticipatory SCL signals during DFDM simulations with an inert handgun and with an alternate response device (a wireless mouse) as well as with and without verbal interaction.

METHODS

Seven civilian volunteers completed DFDM scenarios in a high-fidelity simulator (PRISim Suite, Advanced Interactive Systems, Seattle, WA). The simulator consisted of a sound-proof room (8.5m by 5.5m) with pre-recorded scenarios projected onto a screen (3.0m by 5.5m) at one end of the room. Subjects stood in the center of the room facing the screen, simulating the first-person perspective of a law enforcement officer responding to situations involving domestic disturbances, vehicle stops, or suspicious persons. Scenarios lasted between 15 seconds and 2 minutes, each leading up to a decision point where deadly force may or may not be appropriate.

During each of four 15-minute sessions, subjects experienced 4 scenarios randomly chosen from a full set of 16 scenarios. Within each session there was always one scenario where deadly force would not be appropriate. Two minutes of rest separated each scenario, and 30 minutes of rest in another room separated each session.

Every session was assigned one of four conditions (explained below), with each subject experiencing all four conditions in randomized order. Before each session, subjects were instructed to use force only when appropriate for the simulated situation presented, in ways that would minimize threats to bystanders or themselves and neutralize the threat from assailants. They were told to indicate a decision to use force using their dominant hand to pull the trigger on either a modified, inert Glock handgun, which fired an infrared laser at the screen, or a trigger-style wireless computer mouse held at their side (Gun or Mouse...
conditions). Furthermore, they were told to either actively, verbally interact with the characters on screen or passively observe the scenarios (Active or Passive conditions). During each session, two 8 mm Ag-AgCl electrodes filled with electrolyte gel were attached, using adhesive tape collars, to the palmar surface of the first and second medial phalanges of the non-dominant hand. This hand rested on a table adjusted to just below the subject’s elbow. SCL data was recorded from the electrodes at 20 Hz using PsychLab Acquire software via a SC5 skin conductance monitor (Contact Precision Instruments, Cambridge, MA, USA). Baseline SCL was calculated as the beginning SCL value for each simulation scenario. Peak SCL was calculated as the highest value before the decision point for each scenario. Area under the curve (AUC) of SCL from baseline to peak was used to quantify anticipatory SCL responses within scenarios. SCL AUC data were analyzed with repeated-measures analysis of variance (ANOVA) with factors Device (Gun or Mouse) and Interactivity (Active or Passive) and their interaction.

RESULTS AND DISCUSSION

Figure 1 illustrates the SCL data (measured in microsiemens, µS) acquired during the study with an example of one subject’s data over four scenarios in one session. As can be seen in the figure, within scenarios, SCL steadily increased from baseline to a peak just before the deadly force decision point. Indeed, across the whole dataset, there were significant increases from SCL baselines to SCL peaks ($F_{1,6}=33.8, P=0.002$).

![Figure 1](image-url)

**Figure 1.** Example of SCL data (in microsiemens) observed during a DFDM simulation session when a subject was using a trigger-style wireless computer mouse while actively interacting with characters on the screen. (In this example, the first scenario was one in which deadly force was not appropriate.) Black curve: observed SCL. White areas: DFDM scenarios (from scenario start to scenario end). Gray areas: rest breaks before DFDM scenarios.
Figure 2 shows the SCL AUC results of the study (measured in microsiemens times seconds, $\mu$S·s). There was a significant effect of Device, with the Mouse condition showing greater SCL AUC than the Gun condition ($F_{1,6}=6.4, P=0.045$). There was also a significant effect of Interactivity, with the Active condition actively showing greater SCL AUC than the Passive condition ($F_{1,6}=9.8, P=0.020$). There was no significant interaction of Device by Interactivity ($F_{1,6}=2.9, P=0.14$).

![Figure 2](image.png)

**Figure 2.** Mean ($\pm$ standard error) of SCL area under the curve (in microsiemens times seconds) as a function of response device used (inert hand gun versus trigger-style wireless computer mouse) and level of interaction with the characters on the screen (active interaction versus passive observation).

Lower SCL when using the inert handgun and when passively observing may have been the result of reduced engagement with the simulation scenarios. The subjects in this study were civilians, who were generally unfamiliar with the use of handguns. This unfamiliarity may have been distracting and/or may have reduced simulator immersion, which can reduce anticipatory SCL.\textsuperscript{7,8} Passive observation may have similarly reduced simulator immersion and reduced anticipatory SCL. Indeed, self-reports from law enforcement and military personnel in previous DFDM simulator studies have suggested that passive viewing is less engaging.

**CONCLUSIONS**

Our results indicate that SCL can be measured during DFDM in high-fidelity simulations with civilians as research subjects. Use of a trigger-style wireless mouse rather than an inert handgun and actively interacting with the simulation scenarios produced the most robust SCL responses.

These findings inform future studies of simulated DFDM during sleep deprivation, which will allow examination of affective processes underlying sleep loss-induced deficits in risky decision-making in the real world.

**ACKNOWLEDGMENTS**

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REFERENCES


Abstracts
THE COGNITIVE AND FUNCTIONAL STATUS OF STROKE PATIENTS ARE NEGATIVELY AFFECTED BY OBSTRUCTIVE SLEEP APNOEA

Justine Aaronson\textsuperscript{a,b}; Winni Hofman\textsuperscript{b}; Coen van Bennekom\textsuperscript{a}; Erny Groet\textsuperscript{a}; Wytske Kylstra\textsuperscript{a}; Tijs van Bezeij\textsuperscript{a}; Joost van den Aardweg\textsuperscript{c}; Ben Schmand\textsuperscript{b}

\textsuperscript{a}Heliomare Research & Development and Heliomare Rehabilitation Centre, Wijk aan Zee, The Netherlands; 
\textsuperscript{b}Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands 
\textsuperscript{c}Department of Pulmonary Medicine, Medical Centre Alkmaar, The Netherlands

Introduction: Obstructive sleep apnoea (OSA) is a common sleep disorder in stroke patients and is associated with decreased functional outcome and an increased risk of post stroke mortality. The effect of OSA on cognitive functioning following stroke has not yet been investigated. Therefore, the primary objective of this study was to compare stroke patients with and without OSA on cognitive and functional status upon admission to our rehabilitation centre.

Methods: A total of 170 patients underwent sleep examination for diagnosis of OSA. We performed a cognitive and neurological assessment, and rated their activities of daily living (ADL). We also administered questionnaires on fatigue, sleepiness and mood.

Results: Seventy patients were diagnosed with OSA. Stroke patients with OSA were older and had a higher BMI than non-OSA stroke patients. No difference in stroke type or classification was objectified. As regards to cognitive functioning, OSA patients performed worse on tasks of attention, vigilance, visuoperception, psychomotor speed and intelligence than patients without OSA. For memory, executive functioning and language no difference was seen. As for functional status, OSA patients had a worse overall neurological status and showed more ADL problems than non-OSA patients. There was no difference in the reported levels of fatigue, sleepiness and depressive symptoms.

Conclusions: Stroke patients with OSA show decreased cognitive functioning, have a worse overall neurological status and encounter more difficulties in ADL as compared to stroke patients without OSA. Thus, we conclude that OSA negatively affects the cognitive and functional status of stroke patients.

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MEDICAL TECHNOLOGY ASSESSMENT OF POLYSOMNOGRAPHY, TYPE 2: FULL PSG AT HOME; NIGHT-TO-NIGHT VARIABILITY: APNEA-HYPOPNEA INDEX & PERIODIC LIMB MOVEMENT INDEX


Sleep-Wakecenter SEIN, Dr. Denekampweg 20, 8025 BV Zwolle, The Netherlands.

Polysomnography (PSG) in a clinical setting (CPSG, type 1) is time consuming and expensive. Type 2, i.e. full PSG at home, is thought to be a good alternative, but has never been evaluated in terms of regular Medical Technology Assessment (MTA). In some countries this lack of MTA precludes reimbursement for PSG type 2. This communication is part of a series of posters which add up to MTA of PSG, type 2, and deals with night-to-night sleep variability. This study is designed to investigate the differences between the first and the second night, during two full PSG’s type 2, on AHI and PLMI.

Retrospective study of 339 patients (49,1% male, mean age = 45 ± 17 years) who underwent full PSG type 2 for two consecutive days. The number of patients who were diagnosed with Sleep Related Breathing Disorder (SRBD) (n=52), and those who were diagnosed with Sleep Related Movement Disorder (SRMD) (n=43), were compared with the total group of patients on the parameters AHI and PLMI.

The AHI in the total group of patients for the first night was 6.5±11.5 units/hour and for the second night 6.3±11.4 units/hour (p=0.62). The mean AHI values of the SRBD patients were considerably higher (24.1±21.1 vs. 22.5±22.1; p=0.21). For neither group was there a significant difference between the nights. Analysis of correlations in the total group (r=0.81, p<0.01) and the patient group (r=0.79, p<0.01) showed high values between the two PSG type 2 nights. Fourteen patients (26.9%) in the SRBD group showed a difference of more than 10 respiratory events per hour in AHI between the two nights. Eleven patients (21.2%) in the SRBD group would have been misdiagnosed in terms of OSAS severity, if the AHI of only one of the two nights had been used instead of both. Seven patients (13.5%) in the SRBD group would not have received treatment if the AHI of only one night had been used.

The PLMI in the total group of patients for the first night was 9.5±20.8 units/hour and the second night 10.7±22.9 units/hour (p=0.14). The mean PLMI values of the SRMD patients were considerably higher (34.9±39.2 vs. 38.1±45.0; p=0.26). Neither group displayed a difference between the two nights. Analysis of correlations in the total group (r=0.79, p<0.01) and the patient group (r=0.77, p<0.01) showed high values between the two PSG type 2 nights. Five patients (11.4%) in the SRMD group would have been misdiagnosed in terms of PLMD severity if the PLMI of only one of the nights had been used instead of both. As goes for the three patients (6.8%) in the SRMD group. They would not have received proper treatment if the AHI of only one night had been considered.

We conclude that one measurement could be valid in cases of no or mild disturbances regarding a breathing or a movement disorder during sleep. It turns out that a second PSG type 2 night shows only slight differences of the indexes. But, as we do not know on beforehand what the severity will be, we still need two consecutive PSG type 2 recordings. The change of a misdiagnosis is 13.5% in the SRBD group and 6.8% in the SRMD group. Therefore we again recommend to implement two consecutive PSG type 2 nights for these types of disorders.

Presented at the World Association of Sleep Medicine: 5th World Congress on Sleep Medicine, 5, 138. www.wasmcongress.com/abstracts
DIFFERENTIAL EFFECTS OF THETA/BETA AND SMR NEUROFEEDBACK IN ADHD ON SLEEP ONSET LATENCY.

Martijn Arns, PhD 1,2,3 Ilse Feddema 3 & J. Leon Kenemans 1

1 Dept. of Experimental Psychology, Utrecht University, Utrecht, The Netherlands
2 Department of Cognitive Neuroscience, Donders Institute for Brain Cognition and Behaviour, Radboud UMC, Nijmegen
3 Research Institute Brainclinics, Nijmegen, The Netherlands

Recent studies suggest a role for sleep and sleep problems in the etiology of ADHD and a recent model about the working mechanism of sensori-motor rhythm (SMR) neurofeedback, proposed that this intervention normalizes sleep and thus improves ADHD symptoms such as inattention and hyperactivity/impulsivity. In this study we compared adult ADHD patients (N=20) to a control group (N=28) and investigated if differences existed in sleep parameters such as Sleep Onset Latency (SOL), Sleep Duration (DUR) and overall reported sleep problems (PSQI) and if there is an association between sleep-parameters and ADHD symptoms. Secondly, in 38 ADHD patients we investigated the effects of SMR and Theta/Beta (TBR) neurofeedback on ADHD symptoms and sleep parameters and if these sleep parameters may mediate treatment outcome to SMR and TBR neurofeedback. In this study we found a clear continuous relationship between self-reported sleep problems (PSQI) and inattention in adults with- and without-ADHD. TBR neurofeedback resulted in a small reduction of SOL, this change in SOL did not correlate with the change in ADHD symptoms and the reduction in SOL only happened in the last half of treatment, suggesting this is an effect of symptom improvement not specifically related to TBR neurofeedback. SMR neurofeedback specifically reduced the SOL and PSQI score, and the change in SOL and change in PSQI correlated strongly with the change in inattention, and the reduction in SOL was achieved in the first half of treatment, suggesting the reduction in SOL mediated treatment response to SMR neurofeedback. Clinically, TBR and SMR neurofeedback had similar effects on symptom reduction in ADHD (inattention and hyperactivity/impulsivity). These results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD.

Abstract from a manuscript submitted to Frontiers in Human Neuroscience.
EVALUATION OF POSITION DEPENDENCY IN NON-APNEIC SNORERS

Linda B. Benoist\textsuperscript{a}, Sharon Morong\textsuperscript{a}, J. Peter van Maanen\textsuperscript{a}, Antonius A. Hilgevoord\textsuperscript{b}, Nico de Vries\textsuperscript{a}.

\textsuperscript{a} Department of Otolaryngology/Head Neck Surgery, Jan Tooropstraat 164, St. Lucas Andreas hospital, 1061 AE Amsterdam, the Netherlands

\textsuperscript{b} Department of Clinical Neurophysiology, St. Lucas Andreas Hospital, Amsterdam, the Netherlands

Introduction
The aims of this study are to determine the prevalence of position dependency in non-apneic snorers, as defined by the American Academy of Sleep Medicine (AASM) guidelines, and to investigate the influence of various factors such as BMI, neck circumference, age, gender, and sleep efficiency on sleeping position.

Methods
A cohort of consecutive patients was screened for complaints of excessive snoring or symptoms suspicious for sleep disordered breathing. Overnight polysomnographic data were collected and non-apneic snorers who met all the inclusion criteria were selected for statistical analysis. To assess position-dependent snoring, the snore index (total snores/h) was used. Supine-dependent patients were defined as having a supine snore index higher than their total non-supine snore index.

Results
76 patients were eligible for statistical analysis. Prevalence of position dependency in non-apneic snorers was 65.8\% (p < 0.008). A stepwise regression showed that only BMI had a significant effect (p < 0.003) on the supine snore index.

Conclusion
This is the first study that uses the AASM guidelines to accurately define non-apneic snorers (AHI < 5) and provides scientific evidence that the majority of non-apneic snorers are supine dependent. Furthermore, these results show that non-apneic snorers with a higher BMI snore more frequently in supine position. The use of sleep position therapy therefore, has the potential to play a significant role in improving snoring and its associated physical and psychosocial health outcomes in this population.

MEDICAL TECHNOLOGY ASSESSMENT OF POLYSOMNOGRAPHY, TYPE 2: FULL PSG AT HOME; HOW OFTEN DO TECHNICAL FAILURES OCCUR?


Sleep-Wakecenter SEIN, Dr. Denekampweg 20, 8025 BV Zwolle, The Netherlands.

Polysomnography (PSG) in a clinical setting (PSG, type 1) is time consuming and expensive. Type 2, i.e. full PSG at home, is thought to be a good alternative, but has never been evaluated in terms of regular Medical Technology Assessment (MTA). In some countries this lack of MTA precludes reimbursement for PSG type 2. This communication is part of a series of posters, which add up to MTA of PSG type 2 and deals with technical failures when recording full PSG at home. This study evaluates the failures and artifacts within PSG type 2. A retrospective study of 366 patients (age: 45.0 ± 16.7, male: 49,1%) who underwent full PSG type 2 for two consecutive days. The patients returned to the clinic for a check-up after 24 hours. The following signals were evaluated: EEG (including eye movements and chin EMG), EMG<sub>m.tibiialis</sub> nasal pressure, inductive belts<sub>torax</sub> and <sub>abdomen</sub> and oxygen saturation. A measurement fault was the result of a limited recording time or caused by a technical interruption. During successful PSG type 2 a fault was defined by an artifact which lasted more than 50% of the measurement duration.

Of all recordings 93,2% were without measurement faults. On the first night 3,8% of the recordings had a measurement fault, of which 57,1% were the result of a technical interruption and 42,9% were caused by a limited recording time. On the second night 3,0% of the recordings had a measurement fault, of which 72,7% were the result of a technical interruption and 27,3% were caused by a limited recording time. None of the patients had a measurement fault in both nights. Therefore in all cases a diagnosis could be made.

Artifacts in successful PSG type 2

Of the oxygen saturation measurements 20,1% were disrupted, of which 13,1% consisted of a total measurement fault and 7,0% of partial faults. Of all the nasal pressure faults (which occurred during 13,6% of the recordings) 4,6% were total faults and 9,0% were partial. The inductive belts<sub>torax</sub> and <sub>abdomen</sub> signal were disrupted for 2,3% of the measurements, the EMG<sub>m.tibiialis</sub> for 1,9% and the EEG for 1,8%. As stated above despite the objectified measurement faults a diagnose could always be made.

The results show that the amount of faults do not hinder the PSG measurements critically. The most prevalent measurement faults were for the saturation and nasal pressure signal. These are the two measurements which patients have to connect themselves before going to sleep at home. The occurrence of these faults was diminished by giving the patients even more instructions while they were at the clinic for their 24 hour check-up. The effect of giving more instruction was sufficient, since none of the patients had measurement faults during both nights. Therefore, we conclude the reliability of two consecutive PSG type 2 for a proper diagnosis is not influenced by measurement faults.

Polysomnography (PSG) in a clinical setting (PSG, type 1) is time consuming and expensive. Type 2, i.e. full PSG at home, is thought to be a good alternative, but has never been evaluated in terms of regular Medical Technology Assessment (MTA). In some countries this lack of MTA precludes reimbursement for PSG type 2. Our presentation is a sample of a series of posters that suggest an alternate MTA of PSG type 2, involving the detection of daytime naps during two consecutive PSG’s at home. If this method proves to be successful, such PSG recordings may prove to be a viable alternative for MSLT.

Retrospective study of 465 patients (52% male, 48% female, mean age = 43.6, SD 16.9) who underwent full PSG type 2 for two consecutive days (total of 930 PSG’s type 2). In these continuous 24 hour observations we focused on daytime naps, the quality of these naps, and the recognition of the naps by the patients themselves, as shown in their logbooks. Furthermore the result of the two PSG’s type 2 were compared to a 7 day continuous actigraphy if which included the 2 days of the PSG registration.

The results indicate that during two consecutive 24 hour PSG type 2 (N=930) 35% of these recordings contained daytime naps. Of all the patients who presented with recordable naps during the first 24 hour recording (n=167) 64% had one, 14% had two and 2% had three naps. During the second 24 hour observation (n=162) 58% recorded one, 15% had two, 4 % had three and 1% recorded as many as four naps. One-third of all the naps were not recognized as such by the patients (Table). The naps were most often observed between 3 p.m. and bedtime in two 24 hour observations. During those daytime naps 60 % contained only NREM stage 1+2, 27% also SWS, 2% REM and 2% REM and SWS. Sixty-four percent of the patients with daytime naps as recorded in the PSG’s type 2 were habitual when assessed over a one week actigraphy.

Twenty-four hour PSG’s type 2 provides reliable insight into the amount and quality of sleep during daytime. One-third of all naps were not recognized by the patients themselves. In comparison with the more global assessment through actigraphy, the PSG appears to have good sensitivity and therefore give a more comprehensive insight into the sleep parameter.

Table: Not recognized naps per time-interval.

<table>
<thead>
<tr>
<th></th>
<th>07.00-12.00</th>
<th>12.00-15.00</th>
<th>15.00-19.00</th>
<th>19.00-bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSG night 1</td>
<td>4%</td>
<td>29%</td>
<td>30%</td>
<td>36%</td>
</tr>
<tr>
<td>PSG night 2</td>
<td>1%</td>
<td>25%</td>
<td>36%</td>
<td>38%</td>
</tr>
</tbody>
</table>

INSOMNIA TREATMENT AND COGNITIVE FUNCTIONING IN ADOLESCENTS

E.J. de Bruin\textsuperscript{a}, J.F. Dewald-Kaufmann\textsuperscript{b}, F.J. Oort\textsuperscript{a}, S.M. Bögels\textsuperscript{a}, A.M. Meijer\textsuperscript{a}

\textsuperscript{a}Research Institute of Child Development and Education, University of Amsterdam
\textsuperscript{b}Department of Pediatric Endocrinology, Dr. von Hauner Children’s Hospital, Ludwig Maximilian University, Munich, Germany

Introduction: Despite the high prevalence of insomnia in adolescents and the relation with cognitive functioning, the effects of improved sleep on adolescents’ cognitive functioning has hardly been studied. This study examined the effects of internet-based Cognitive Behavior Therapy for Insomnia (CBTI) on adolescents’ sleep and cognitive functioning.

Methods: A treatment group (n = 18) and a waiting list group (n = 14) were assessed at baseline and post treatment. Sleep was measured at home with actigraphy, as well as sleep logs and questionnaires through an internet website. Cognitive functioning was assessed at the child laboratory of the University of Amsterdam for 32 adolescents (13-19 years, M = 15.9, SD = 1.6) with DSM-IV-TR primary insomnia. Participants received 6 weekly CBTI sessions through an internet website with preprogrammed modules, guided by a trained sleep therapist with personalized feedback and a chat session.

Results: More improvement occurred in symptoms of chronic sleep reduction and insomnia, as well as in sleep onset latency, wake after sleep onset, and total sleep time from sleep logs, and sleep efficiency from sleep logs and actigraphy in the treatment group than in the waiting list group. Also on cognitive functioning more improvement was found in the treatment group compared to waitlist for visuospatial processing, selective attention and phonological working memory, and a trend of more improvement for response inhibition and set shifting, letter fluency and sustained attention, but not for declarative memory, visuospatial working memory, category fluency and general cognitive speed.

Conclusions: These results indicate that CBTI can have positive effects on insomnia and some cognitive functions in adolescents, with a notable difference of improvement for phonological working memory but not for visual working memory.

Presented at the International Pediatric Sleep Association (IPSA) Congress, 5-7 December 2012, Manchester, UK.
PSYCHOMETRIC PROPERTIES AND CLINICAL RELEVANCE OF
THE ADOLESCENT SLEEP HYGIENE SCALE IN DUTCH
ADOLESCENTS

E.J. de Bruin, R.K.A. van Kampen, T. van Kooten, A.M. Meijer,
Research Institute of Child Development and Education, University of Amsterdam

Introduction: This study investigated reliability, validity and clinical relevance of the Adolescent Sleep Hygiene Scale (ASHS) in Dutch adolescents.

Methods: The Dutch translation of the ASHS was administered to 186 normal sleeping adolescents and 112 adolescents with insomnia. Their sleep variables were measured using sleep logs and questionnaires. From the insomnia group, scores were also obtained after six weeks of cognitive behavioral therapy for insomnia (CBT-I) (n = 58) or waiting list (n = 22).

Results: The full scale of the ASHS had acceptable internal consistency. The results showed moderate to strong correlations of the ASHS (domains) with sleep quality, sleep duration and chronic sleep reduction. Furthermore the Dutch ASHS was able to discriminate between normal sleepers and adolescents with insomnia, and scores of adolescents with insomnia improved after treatment.

Conclusions: These findings confirm the importance of sleep hygiene in adolescent sleep, and contribute to the validity of the ASHS and its applicability in research and clinical practice.

Efficacy of Internet and Group-Administered Cognitive Behavioral Therapy for Insomnia in Adolescents: A Pilot Study

E.J. de Bruin, F.J. Oort, S.M. Bögels, A.M. Meijer

Research Institute of Child Development and Education University of Amsterdam

Introduction: Research indicates that adolescents are at risk for insomnia, but are reluctant to seek help. Treatment of insomnia has been extensively examined in adults, but studies with adolescents are sparse. The purpose of this pilot study was to assess feasibility and efficacy of cognitive behavioral therapy for insomnia (CBT–i) for adolescents in both group and Internet settings.

Methods: Twenty-six adolescents received 6 weekly sessions of CBT–i in a group or individual Internet setting. Their sleep was measured with actigraphy, sleep logs, and questionnaires at baseline, posttreatment, and a 2-month follow up.

Results: For both treatments, results show a significant improvement, with medium to large effect sizes (ESs) of sleep onset latency, wake after sleep onset, and sleep efficiency. There was also a small ES increase of total sleep time in sleep log measures, but not in actigraphy measures. On questionnaires measuring symptoms of insomnia and chronic sleep reduction, significant improvements occurred either at posttreatment or at follow up. No differences were found between the groups.

Conclusions: This study indicates CBT–i, either in group or in Internet formats, is an effective treatment for insomnia in adolescents. Further studies in a randomized controlled design are warranted.

The definition of what sleep is depends on the method that is applied to record sleep. Behavioral and (electro)-physiological measures of sleep clearly overlap in mammals and birds, but it is often unclear how these two relate in other vertebrates and invertebrates. Homeostatic regulation of sleep, where the amount of sleep depends on the amount of previous waking, can be observed in physiology and behavior in all animals this was tested in. In mammals and birds, sleep is generally subdivided into two states, non-rapid eye movement (NREM) sleep and REM sleep. In mammals the combination of behavioral sleep and the changes in the slow-wave range of the NREM sleep electroencephalogram (EEG) can explain and predict the occurrence and depth of sleep in great detail. For REM sleep this is far less clear. Finally, the discovery that slow-waves in the NREM sleep EEG are influenced locally on the cortex depending on prior waking behavior is an interesting new development that asks for an adaptation of the concept of homeostatic regulation of sleep. Incorporating local sleep into models of sleep regulation is needed to obtain a comprehensive picture.
Ca$_V$2.1 CALCIUM CHANNELS AS EFFECTORS OF ADENOSINE’S SOMNOGENIC ACTION

Tom Deboer

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, The Netherlands, Tom.de_Boer@lumc.nl

Adenosine modulates sleep via A$_1$ and A$_2A$ adenosine receptors. As the A$_1$ receptor influences Cav2.1 calcium channel functioning via G-protein inhibition, there is a possible role for the Cav2.1 channel in sleep regulation. We therefore investigated sleep and sleep regulation in transgenic Cacna1a R192Q mutant mice that express mutant Cav2.1 channels, which are less susceptible to G-protein inhibition. We hypothesized that Cacna1a R192Q mice may show reduced susceptibility to adenosine, which could result in a sleep phenotype.

To investigate this, we subjected R192Q mutant and wild-type control mice to a 6-h sleep deprivation. In two further experiments mice were treated with caffeine (15mg/kg, a non-specific adenosine receptor antagonist, which induces waking), and cyclopentyladenosine (CPA, 1mg/kg, an A$_1$ receptor agonist which induces a sleep like state) i.p injections.

Compared to wildtype, Cacna1a R192Q mice were more awake with longer waking episodes and less non-rapid eye movement sleep in the dark period, but similar amounts of rapid eye movement sleep. After treatment with caffeine, R192Q mice initiated sleep 0.5 h earlier than wild-type. After CPA treatment, R192Q mice woke up 4.3 h earlier than wild-type.

Together, these results indicate that Cacna1a R192Q mice are less susceptible to adenosinergic signaling. This may explain the reduced amount of NREM sleep under baseline conditions. We here show that sleep, and responses to caffeine and CPA, are modified in the R192Q mutant, consistent with decreased susceptibility to adenosinergic inhibition. The data suggest that the Cav2.1 channel is an effector of adenosine’s somnogenic action.

Deboer, T; van Diepen, HC; Ferrari, MD; Van den Maagdenberg AMJM, Meijer JH (2013), Sleep 36: 127-136.

Presented at the Purines meeting in Bonn, July 2014.
CIRCADIAN AND HOMEOSTATIC SLEEP REGULATION:
MEASURING CLOCK-HOMEOSTAT INTERACTIONS

Tom Deboer

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands, Tom.de_Boer@lumc.nl.

Sleep is regulated by homeostatic and circadian processes [1]. In mammals, homeostatic sleep pressure is reflected by electroencephalogram (EEG) slow-wave activity (SWA, EEG power density between ~1 and 4 Hz) in undisturbed non-rapid eye movement (NREM) sleep. In all mammalian species investigated until now, not only the amount of sleep, but also SWA in NREM sleep increases after sleep deprivation. In several species a dose-response relationship between waking duration and subsequent SWA has been established and in humans taking an afternoon nap a predictable decrease in the nocturnal NREM sleep SWA was observed. Mathematical models predicting this phenomenon have been successfully applied in humans, rats, and mice [2,3].

The circadian process is controlled by an endogenous pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus [4]. This pacemaker is thought to provide the sleep homeostat with a circadian framework. The circadian clock has a molecular basis for generating electrical activity rhythms in the SCN. This electrical neuronal activity can be recorded in vivo in freely moving animals [5]. Kept in constant conditions, this activity is high during the subjective day, the part of the animal’s rhythm that normally falls in the light period, and low during the subjective night.

Whether homeostatic and circadian regulation of sleep work independently or interact closely has been subject of many discussions. Homeostatic responses in sleep persist after circadian rhythmicity has been abolished by SCN lesioning [6,7] and the circadian process can be manipulated by light in the morning without changing SWA [8]. It has, therefore, long been assumed that the timing of sleep is regulated independent from the need for sleep. However, more recent data indicate that there may be a continuous interaction between sleep homeostasis and the circadian clock [9,10].

To get as close as possible to both processes, we set out to record both signals simultaneously in vivo in rats. All experiments were performed under the approval of the Animal Experiment Committee of the Leiden University Medical Center according to the Dutch law on animal experiments. The animals were equipped with electrodes recording EEG and EMG, to determine vigilance states and SWA in NREM sleep, together with electrodes recording SCN neuronal activity. Before the experiments, the animals were kept in constant darkness for at least a week, to exclude direct influences of light on behaviour, and all signals were recorded simultaneously on the same computer. In addition, drinking behaviour was recorded to obtain an estimate of rest-activity behaviour.

From baseline recordings it became clear that SCN neuronal activity changed under influence of vigilance state changes. Activity was increased during waking and REM sleep and decreased during NREM sleep. In addition, there was a clear negative correlation between EEG SWA and SCN neuronal activity. Suppression of SWA by slow-wave deprivation resulted in increased SCN neuronal activity, whereas REM sleep deprivation resulted in decreased activity. Total sleep deprivation caused the predicted increase in SWA during subsequent NREM sleep, and simultaneously a long-term suppression of SCN neuronal activity. The latter lasted as long as the increase in SWA needed to recover [11,12].
Neuronal activity in the SCN clearly depended on the vigilance state of the animals, and deeper NREM sleep was accompanied by lower SCN neuronal activity. The data suggest an interaction between sleep homeostatic mechanisms and the circadian clock in which the clock receives continuous information about the status of the homeostatic process. Our present work is concentrating on possible consequences of this interaction on the circadian system, particularly when homeostatic sleep pressure is increased due to sleep loss. Sleep deprivation seems to diminish this functioning, as it was shown that the circadian clock phase shifting response to light is attenuated in sleep deprived animals [13,14]. With our techniques we are trying to resolve the neurophysiological mechanism behind this phenomenon and to investigate whether this can be reversed by pharmacological means.


*Presented at Measuring Behavior in Wageningen, August 2014.*
INTERACTION OF SLEEP HOMEOSTASIS AND CIRCADIAN RHYTHMS

Tom Deboer

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherland, Tom.de_Boer@lumc.nl.

In mammals, homeostatic sleep pressure is reflected by electroencephalogram slow-wave activity (SWA, electroencephalogram power density < 5 Hz) in non-rapid eye movement sleep. The timing of sleep is controlled by the circadian pacemaker, located in the suprachiasmatic nucleus (SCN). The circadian pacemaker generates electrical activity rhythms in the SCN which is high during the subjective day and low during the subjective night.

Whether homeostatic and circadian regulation of sleep function independently has been subject of discussion since the two were brought together in the two process model. It was shown that the timing of sleep is regulated independent from the homeostatic sleep need. However, other data indicated that there may be a continuous interaction between sleep homeostasis and the circadian clock.

To gain more insight, we recorded the electroencephalogram and SCN neuronal activity simultaneously in vivo in rats and showed that SCN neuronal activity is influenced by vigilance state changes. In addition, suppressing SWA by slow-wave deprivation, resulted in increased SCN activity, whereas total sleep deprivation resulted in increased SWA, and simultaneously a suppression of SCN neuronal activity. Recent fMRI studies show a similar negative relationship in humans.

The data suggest a continuous interaction between sleep homeostasis and the circadian clock. Our present work is concentrating on the consequences of increased homeostatic sleep pressure on circadian functioning. Behavioural studies show that sleep deprivation diminishes rest-activity phase shifting capacity. We want to resolve the neurophysiological mechanisms and investigate whether and how this can be influenced.

RELATIONSHIPS BETWEEN ADOLESCENTS’ TEST ANXIETY, STRESS AND SLEEP

J.F. Dewald, A.M. Meijer, F.J. Oort, S.M. Bögels

a Research Institute of Child Development and Education, University of Amsterdam

Introduction: This study aims to investigate the relationship between adolescents’ test anxiety, stress and different aspects of sleep.

Methods: 175 adolescents (70.8% girls, mean age 15.14 years) participated in the study. Test anxiety, stress and chronic sleep reduction were assessed at baseline using self-reports. Sleep parameters were subjectively (sleep diaries) and objectively (actigraphy) measured during the following five school nights.

Results: Stress fully mediated the relationship between test anxiety and self-reported sleep quality and test anxiety and chronic sleep reduction. Test anxiety predicted shorter subjectively and objectively measured sleep time; however, stress did not mediate these relationships.

Conclusion: We demonstrate that test anxiety is related to adolescents’ stress, negatively influencing sleep quality and chronic sleep reduction, whereas the relationship between test anxiety and sleep time is not mediated by stress. Our results highlight the need to address subjective indices of sleep, especially sleep quality or chronic sleep reduction, rather than objective sleep efficiency or total sleep time when studying the effects of emotional problems on sleep.

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


Research Institute of Child Development and Education, University of Amsterdam
Department of Medical Psychology, Academic Medical Center, University of Amsterdam
Department of Psychology, University of Amsterdam

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

Methods: Sleep was monitored over 3 consecutive weeks using actigraphy.

Results: Adolescents’ sleep was more fragmented during the high-stress time than during the low-stress time, meaning that individuals slept more restless during stressful times. However, sleep efficiency, total sleep time, and sleep-onset latency remained stable throughout the 3 consecutive weeks. High chronic sleep reduction was related to later bedtimes, later sleep-start times, later sleep-end times, later getting-up times, and more time spent in bed. Furthermore, low chronic sleep reduction and high baseline stress were related to more fragmented sleep during stressful times.

Conclusions: This study shows that stressful times can have negative effects on adolescents’ sleep fragmentation, especially for adolescents with low chronic 30 sleep reduction or high baseline stress.

WHY SLEEP MATTERS: DIFFERENCES IN DAYTIME FUNCTIONING BETWEEN ADOLESCENTS WITH LOW AND HIGH CHRONIC SLEEP REDUCTION AND SHORT AND LONG SLEEP DURATIONS.

J. F. Dewald-Kaufmann a,b, F. J. Oort a, S. M. Bögels a, A. M. Meijer a

 a Research Institute of Child Development and Education, University of Amsterdam
 b Department of Pediatric Endocrinology, Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University

Introduction: Sleep problems are prevalent in adolescents and can severely impair their daytime functioning. This study aims to investigate differences in daytime functioning (e.g., depressive symptoms, attention problems, school functioning, and school performance) between adolescents with high and low chronic sleep reduction and short and long sleep durations. With this approach we get a better idea of their vulnerability to impaired daytime functioning due to (chronic) sleep loss.

Methods: From a total sample size of 794 adolescents, we selected the lowest and highest quartiles of adolescents with either low or high chronic sleep reduction and either short or long sleep durations.

Results: We found significant differences in daytime functioning between the different groups, giving evidence of vulnerability to impaired daytime functioning due to (chronic) sleep loss.

Conclusion: The results are of high clinical relevance as they show that adolescents obtaining sufficient and/or good sleep show nearly no daytime functioning problems. Programs to improve adolescents’ sleep are therefore highly recommended.

THE EFFECTS OF SLEEP EXTENSION AND SLEEP HYGIENE ADVICE ON SLEEP AND DEPRESSIVE SYMPTOMS IN ADOLESCENTS: A RANDOMIZED CONTROLLED TRIAL

J.F. Dewald-Kaufmann a,b, F.J. Oort a,c, A.M. Meijer a

a Research Institute of Child Development and Education, University of Amsterdam

b Department of Pediatric Endocrinology, Dr. von Hauner Children’s Hospital, Ludwig-Maximilians-University

c Department of Medical Psychology, Academic Medical Center, University of Amsterdam

Introduction: Sleep problems are common and persistent during adolescence and can have negative effects on adolescents' mood. To date, studies that investigate the effects of sleep extension on adolescents' sleep and depressive symptoms are still lacking. This study aims to investigate the effects of gradual sleep extension combined with sleep hygiene advice in adolescents with chronic sleep reduction on objectively measured sleep, self-reported sleep problems and depressive symptoms.

Methods: Fifty-five adolescents with chronic sleep reduction (mean age: 15.44 years; 85.5% females) were included in the study. Participants were randomly assigned to either a sleep extension group (gradual sleep extension by advancing bedtimes in the evening and receiving sleep hygiene advice) or to a control group (no instruction). Sleep was measured with actigraphy during three weeks, the first week was the baseline week, and the last two weeks were the experimental weeks during which sleep was extended. Other outcome variables were self-reported sleep problems (daytime sleepiness, symptoms of insomnia and circadian rhythm sleep disorder) and depressive symptoms, which were assessed before and after the experimental manipulation.

Results: During the third week of the experiment, adolescents in the sleep extension group had earlier bedtimes, earlier sleep onsets, spent more time in bed and slept longer than adolescents in the control group. Their chronic sleep reduction, insomnia symptoms and depressive symptoms diminished significantly. In addition, there was a trend of improved circadian rhythm sleep disorder symptoms and sleep quality.

Conclusion: Gradual sleep extension combined with sleep hygiene advice seems to have beneficial effects on sleep, self-reported sleep problems and depressive symptoms of adolescents with chronic sleep reduction. Although we cannot distinguish between the effects of sleep extension and sleep hygiene advice, the results suggest that advancing bedtimes can extend sleep and improve depressive symptoms.

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

J.F. Dewald, M.A. Short, M. Gradisar, F.J. Oort, A.M. Meijer

a Research Institute of Child Development and Education, University of Amsterdam
b School of Psychology, Flinders University

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

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

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

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

CAFFEINE INCREASES LIGHT RESPONSIVENESS OF THE CIRCADIAN PACEMAKER

Hester C. van Diepen\textsuperscript{a}, Eliane A. Lucassen, MD\textsuperscript{a}, Roman Yasenkov, PhD\textsuperscript{a}, Inske Groenen\textsuperscript{a}, Adriaan P. Ijzerman, PhD\textsuperscript{b}, Johanna H. Meijer, PhD\textsuperscript{a}, Tom Deboer, PhD\textsuperscript{a}

\textsuperscript{a}Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, PO Box 9600 Mailbox S5-P, 2300 RC Leiden, The Netherlands
\textsuperscript{b}Leiden Academic Centre for Drug Research, Division of Medicinal Chemistry, PO Box 9502, 2300RA Leiden, The Netherlands

Objectives: Caffeine is the most used psychoactive stimulant. It reduces sleep and sleepiness by blocking adenosine receptors. Adenosine increases during sleep deprivation (SD) and is thought to induce sleepiness and initiate sleep. Light-induced phase shifts of the circadian rest-activity rhythm are mediated by light responsive suprachiasmatic nucleus (SCN) neurons. Previous studies showed that SD reduces circadian phase shifting capacity and decreases SCN neuronal activity. In addition, adenosine agonists and antagonists mimic and block the effect of SD on light-induced phase shifts in behaviour, suggesting a role for adenosine. Here, we examined the role of SD and the effect of caffeine on light responsiveness of the SCN.

Methods: We performed \textit{in vivo} electrical activity recordings of the SCN in freely moving mice subjected to light pulses in combination with sleep deprivation and adenosine injections (15 mg/kg i.p.). In additions, we undertook behavioural recordings in constant light and dark conditions with or without caffeine in the drinking water.

Results: The sustained response to light in SCN neuronal activity was attenuated by 51\% (± 14\% SEM) after a 6-hour SD prior to light exposure. Subsequent i.p. application of caffeine was able to restore the light response. The period length in constant light during caffeine treatment in drinking water was 36 minutes (± 10 min) longer.

Conclusions: The data suggest that increased homeostatic sleep pressure changes circadian pacemaker functioning by reducing SCN neuronal responsiveness to light. The electrophysiological and behavioural data together provide evidence that consuming caffeinated beverages may increase clock sensitivity to light.

CAFFEINE INCREASES LIGHT RESPONSIVENESS OF THE MOUSE CIRCADIAN PACEMAKER

Hester C. van Diepen\textsuperscript{a}, Eliane A. Lucassen, MD\textsuperscript{a}, Roman Yasenkov, PhD\textsuperscript{a}, Inske Groenen\textsuperscript{a}, Adriaan P. Ijzerman, PhD\textsuperscript{b}, Johanna H. Meijer, PhD\textsuperscript{a}, Tom Deboer, PhD\textsuperscript{a}

\textsuperscript{a}Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Centre, PO Box 9600 Mailbox S5-P, 2300 RC Leiden, The Netherlands
\textsuperscript{b}Leiden Academic Centre for Drug Research, Division of Medicinal Chemistry, PO Box 9502, 2300RA Leiden, The Netherlands

Caffeine is the most used psychoactive stimulant worldwide. It reduces sleep and sleepiness by blocking access to the adenosine receptor. Adenosine increases during sleep deprivation and is thought to induce sleepiness and initiate sleep. Light-induced phase shifts of the rest-activity circadian rhythms are mediated by light responsive neurons of the suprachiasmatic nucleus (SCN) of the hypothalamus, where the circadian clock of mammals resides. Previous studies showed that sleep deprivation reduces circadian clock phase shifting capacity and decreases SCN neuronal activity. In addition, application of adenosine agonists and antagonists mimic and block the effect of sleep deprivation on light-induced phase shifts in behaviour, suggesting a role for adenosine.

In the present study we examined the role of sleep deprivation and the effect of caffeine on light responsiveness of the SCN. We performed \textit{in vivo} electrical activity recordings of the SCN in freely moving mice and showed that the sustained response to light in SCN neuronal activity was attenuated after a 6-hour sleep deprivation prior to light exposure. Subsequent i.p. application of caffeine was able to restore the response to light. Finally, we undertook behavioural recordings in constant conditions and found an enhanced period lengthening during chronic caffeine treatment in drinking water in constant light conditions.

The data suggest that increased homeostatic sleep pressure changes circadian pacemaker functioning by reducing SCN neuronal responsiveness to light. The electrophysiological and behavioural data together provide evidence that caffeine enhances clock sensitivity to light.

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CAFFEINE ENHANCES LIGHT RESPONSIVENESS OF THE CIRCADIAN PACEMAKER

Hester van Diepen, Roman Yasenkov, Johanna H. Meijer, Tom Deboer

Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Centre, PO Box 9600 Mailbox S5-P, 2300 RC Leiden, The Netherlands

Caffeine is an adenosine antagonist which alters sleep in many mammals and is worldwide the most used psychoactive stimulant to reduce sleepiness. Adenosine levels in the brain increase in the course of sleep deprivation and decrease during recovery sleep, and is one of the substances thought to be involved in the regulation of sleep. Sleep deprivation is known to significantly decrease neuronal activity in the suprachiasmatic nucleus (SCN). These results suggest that circadian clock functioning is modified by changes in sleep pressure. Light induced phase shifts are mediated by light responsive SCN neurons, which respond with a sustained increase in electrical activity for the full duration of the light pulse, with characteristic fast transient components occurring at light onset and offset. Sleep deprivation is known to significantly attenuate the phase-shifting effect of light on behavioral activity. In addition, application of adenosine agonists and antagonists mimic and block the effect of sleep deprivation on light-induced phase shifts.

In the present study we examined the effect of sleep deprivation and caffeine on light responsiveness of the SCN. We performed in vivo electrical activity recordings of the SCN in freely moving mice. The electrophysiological recordings showed that the sustained response to light in SCN neuronal activity was attenuated after a 6-hour sleep deprivation prior to light exposure. Subsequent i.p. application of caffeine was able to restore the response to light. Finally, we undertook behavioral recordings in constant light and found an enhanced period lengthening during chronic caffeine treatment in drinking water.

The data suggest that increased homeostatic sleep pressure changes circadian pacemaker functioning by reducing SCN neuronal responsiveness to light input. Both the electrophysiological and behavioral data provide evidence that caffeine is able to enhance light sensitivity of the circadian system. Consuming caffeinated beverages may therefore increase clock sensitivity to light.

Presented at the SRBR meeting in Big Sky, Montana, June 2014.
ORAL APPLIANCE VERSUS CPAP IN OBSTRUCTIVE SLEEP APNEA SYNDROME; A TWO-YEAR FOLLOW-UP

Michiel H.J. Doff\textsuperscript{a}, Aarnoud Hoekema\textsuperscript{a}, Peter Wijkstra\textsuperscript{b}, Johannes H. van der Hoeven\textsuperscript{c}, James J.R. Huddleston Slater\textsuperscript{a}, Lambert G.M. de Bont\textsuperscript{a}, Boudewijn Stegenga\textsuperscript{a}

\textsuperscript{a}Department of Oral and Maxillofacial Surgery
\textsuperscript{b}Department of Home Mechanical Ventilation
\textsuperscript{c}Department of Clinical Neurophysiology

University Medical Center, University of Groningen, Groningen, The Netherlands

\textbf{Introduction:} We hypothesized that oral appliance therapy is not inferior to CPAP in treating mild-to-severe OSAS in a two-year follow-up regarding the proportions of successful treatments. In this study we report about the two-year follow up of a cohort (n=103) of a previously conducted randomized controlled trial.

\textbf{Methods:} Objective and subjective parameters were assessed after two months, one year and two years of treatment. Treatment was considered “successful” when the apnoea-hypopnoea index (AHI) was <5 or showed ‘substantial reduction’, defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient who had no symptoms while using therapy.

\textbf{Results:} Regarding the percentage of successful treatments, oral appliance therapy was not inferior to CPAP in treating mild-to-severe OSAS in a two-year follow-up. CPAP was still successful in 67.3% of the patients and oral appliance therapy in 52.9% of the patients (p=0.14) after two years of treatment. Significantly more patients (p=0.04) dropped out under oral appliance therapy (47%) compared to CPAP (33%).

\textbf{Conclusion:} Both therapies showed substantial improvements in polysomnographic and neurobehavioral outcomes. However, CPAP was more effective in lowering the AHI and showed higher oxygen saturation levels compared to oral appliance therapy (p<0.05).

\textbf{Figure 1.} Individual values of the apnoea-hypopnoea index (AHI) of the patients who completed the entire follow-up in the randomized treatment group. CPAP, continuous positive airway pressure

\textit{Doff MHJ, Hoekema A, Wijkstra PJ, van der Hoeven JH, Huddleston Slater JJ, de Bont LG, Stegenga B. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. SLEEP. 2013 Sep 1;36(9):1289-96.}
AGING OF THE SUPRACHIASMATIC CLOCK

Sahar Farajnia, Tom Deboer, Jos H. T. Rohling, Johanna H. Meijer, and Stephan Michel

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

More than half of the elderly in today’s society suffer from sleep disorders with detrimental effects on brain function, behavior, and social life. A major contribution to the regulation of sleep stems from the circadian system. The central circadian clock located in the suprachiasmatic nucleus of the hypothalamus is like other brain regions subject to age associated changes. Age affects different levels of the clock machinery from molecular rhythms, intracellular messenger, and membrane properties to neuronal network synchronization. While some of the age-sensitive components of the circadian clock, like ion channels and neurotransmitters, have been described, little is known about the underlying mechanisms. In any case, the result is a reduction in the amplitude of the circadian timing signal produced by the suprachiasmatic nucleus, a weakening in the control of peripheral oscillators and a decrease in amplitude and precision of daily rhythms in physiology and behavior. The distortion in temporal organization is thought to be related to a number of serious health problems and promote neurodegeneration. Understanding the mechanisms underlying age-related deficits in circadian clock function will therefore not only benefit rhythm disorders but also alleviate ageassociated diseases aggravated by clock dysfunction.

SLEEP STRUCTURE AND EMOTIONAL MEMORY PROCESSING IN POLICE OFFICERS AND COMBAT VETERANS WITH PTSD

W.F. Hofman\textsuperscript{a,b}, M. de Boer\textsuperscript{a,b}, M.J. Nijdam\textsuperscript{c}, R.A. Jongedijk\textsuperscript{d,e}, M. Olff\textsuperscript{c,d}, L.M. Talamini\textsuperscript{a,b}

\textsuperscript{a}Dept. of Psychology, \textsuperscript{b}Amsterdam Brain and Cognition, University of Amsterdam, \textsuperscript{c}Centre for Psychological Trauma, Department of Psychiatry, Academic Medical Centre at University of Amsterdam, Amsterdam, \textsuperscript{d}Arq Psychotrauma Expert Group, Diemen, \textsuperscript{e}Foundation Centrum '45, Oegstgeest, The Netherlands

\textbf{Introduction:} Disturbed sleep is a key symptom of posttraumatic stress disorder (PTSD). In a previous study in healthy subjects we found adaptive changes in sleep architecture after emotional experiences, benefitting emotional housekeeping and the attenuation of emotional responses. Little is known, however, about the relation between sleep and emotional memory processing in PTSD. The current study assesses the impact of an emotional stressor on sleep parameters in PTSD patients.

\textbf{Methods:} Traumatized police officers and combat veterans with and without PTSD are compared. The experimental setup involves the presentation of neutral or distressing film fragments in the evening, followed by full polysomnography of undisturbed, whole night sleep, and cued recall of film content on the next evening. The order of the film conditions is counterbalanced across subjects. Emotional state before and after film viewing and during recall is assessed with psychological and physiological measures.

\textbf{Results:} Contrary to many previous studies that found only mildly disrupted (macro)sleep architecture in PTSD, our preliminary results on 13 patients show significantly more N1 sleep (p< 0.001), less N3 sleep (p< 0.001) and, in addition, significant lower subjective sleep quality (p< 0.01). There was a trend towards a higher REM sleep percentage (p=0.07) and a longer duration of rapid eye movement bursts (p=0.051) after the emotional stressor.

\textbf{Conclusion:} Contrary to the literature, sleep architecture appears to be altered in PTSD patients towards a more superficial sleep, with lower subjective sleep quality. Patients tend to respond to an acute non-trauma-related emotional stressor with more 'intense' REM sleep.

\textit{22nd Congress of the European Sleep Research Society, Tallinn, 16-20 September 2014.}
ACTIVATION OF THE METABOTROPIC GLUTAMATE RECEPTOR (MGLUR2/3) ATTENUATES ABERRANT EEG NETWORK OSCILLATIONS IN THE SALICYLATE RAT MODEL OF TINNITUS

H. Huysmans, A. Ahnaou, W.H.I.M. Drinkenburg

Dept. of Neurosciences, Janssen R&D, a Division of Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium.

Aim: Tinnitus is a distressful condition characterized by phantom auditory sensations that can experimentally be induced by high doses of sodium salicylate, the active component of aspirin. The neural generator for tinnitus is assumed to be located in the cochlea, while an elevated glutamate excitatory neurotransmission has been recognized to play a role in the salicylate-induced tinnitus model. The present study investigated whether activation of the mGlu2 receptor, which is also distributed in the cochlea, could influence the neural activity that underlies tinnitus related aberrant EEG network oscillatory pattern.

Methods: Animals were chronically implanted with six microwire electrodes and measurements of EEG were obtained from different auditory cortical areas over 2 hrs after acute subcutaneous (s.c.) administration of salicylate (250 mg/kg) and saline. Next, we investigated the potential of mGluR2/3 agonist LY404039 (10 mg/kg s.c.) to attenuate salicylate-induced aberrant EEG oscillatory pattern.

Results: Salicylate elicited persistent pathological EEG network gamma-frequency oscillations in auditory and hippocampal areas, which may indicate that animals could experience tinnitus up to 2 hrs after the administration. Pre-treatment with LY404039 consistently attenuated salicylate-induced aberrant EEG network gamma oscillations.

Conclusions: The findings indicate that salicylate-induced stimulation of cortical areas triggers abnormal cortical EEG gamma oscillations that can be related to the mechanisms underlying the generation and sensation of tinnitus. The pronounced cortical network EEG gamma activity, likely derived from hyperactive glutamatergic neural signaling, suggest that strategies that modulate glutamatergic pathways through mGluR2 might open up novel avenues for tinnitus pharmacotherapy.

FENS2014, Milan, Italy.
LACK OF DISRUPTIVE EFFECTS OF THE CANNABINOID CB1 AGONIST WIN55,212-2 ON HIGH-LEVEL NEURONAL NETWORKS IN RATS

H. Huysmans, R. Biermans, WHIM Drinkenburg, A. Ahnaou

Dept. of Neurosciences, Janssen R&D, a Division of Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium.

Aims: The endocannabinoid system has been proposed to modulate a variety of physiological processes, including those that underlie cognition. Given the well-established role of the hippocampus in learning and memory processes, and a high expression of hippocampal cannabinoid CB1 receptors, the present studies explored the utility of CB1 receptor agonism as a pharmacological challenge model of dysfunctional high-level brain network functionality in rats.

Methods: The influence of subcutaneous administration of WIN55,212-2 (0.03, 0.1 and 0.3 mg/kg) was characterized on: 1/ sleep-wake architecture in freely moving rats during 20 hours recording session, 2/ functional network oscillations and connectivity recorded from six different cortical areas in freely moving rats during two hrs of the dark phase, 3/ mismatch negativity (MMN) response typically elicited in the auditory, frequency-deviant oddball paradigm, which indexes attention and sensory memory processing in conscious rats.

Results: WIN55,212-2 at the doses of 0.03 and 0.1 mg/kg had no major effect on sleep-wake organization, whereas at a dose of 0.3 mg/kg passive waking was slightly enhanced without leading to drastic disruption of the sleep wake cycle. WIN55,212-2 did not alter cortical network oscillations and connectivity at any of the doses tested, while also MMN-like activity was not affected.

Conclusions: Overall, acute administration of the CB1 agonist WIN55,212-2 did not disrupt functional network connectivity and cognitive information processing in this study. The findings do not support the use of the endocannabinoid agonist WIN55,212-2 at the doses tested here as a valid pharmacological challenge model of dysfunctional high-level neuronal network activity in rats.

FENS2014, Milan, Italy.
E-MAIL SUPPORT IMPROVES THE EFFECTIVENESS OF INTERNET-DELIVERED SELF-HELP TREATMENT FOR INSOMNIA: A RANDOMIZED TRIAL

Jaap Lancee\textsuperscript{a}, Jan van den Bout\textsuperscript{b}, Marjolijn Sorbi\textsuperscript{b}, & Annemieke van Straten\textsuperscript{c}

\textsuperscript{a}University of Amsterdam \\
\textsuperscript{b}Utrecht University \\
\textsuperscript{c}VU University and EMGO institute

Introduction
Internet-delivered treatment is effective for insomnia, but little is known about the beneficial effects of support. The aim of the current study was to investigate the additional effects of low-intensity support to an internet-delivered treatment for insomnia.

Methods
Two hundred and sixty-two participants were randomized to an internet-delivered intervention for insomnia with ($n=129$) or without support ($n=133$). All participants received an internet-delivered cognitive behavioral treatment for insomnia. In addition, the participants in the support condition received weekly emails. Assessments were at baseline, post-treatment, and 6-month follow-up.

Results
Both groups effectively ameliorated insomnia complaints. Adding support led to significantly higher effects on most sleep measures ($d=0.3-0.5$; $p<0.05$), self-reported insomnia severity ($d=0.4$; $p<0.001$), anxiety, and depressive symptoms ($d=0.4$; $p<0.01$). At the 6-month follow-up, these effects remained significant for sleep efficiency, sleep onset latency, insomnia symptoms, and depressive symptoms ($d=0.3-0.5$; $p<0.05$).

Discussion
Providing support significantly enhances the benefits of internet-delivered treatment for insomnia on several variables. It appears that motivational feedback increases the effect of the intervention and encourages more participants to complete the intervention, which in turn improves its effectiveness.

THE EFFECT OF SUPPORT ON INTERNET-DELIVERED TREATMENT FOR INSOMNIA: DOES BASELINE DEPRESSION SEVERITY MATTER?

Jaap Lancee, Marjolijn Sorbi, Maarten Eisma, Annemiek van Straten, & Jan van den Bout

a University of Amsterdam
b Utrecht University
c VU University and EMGO institute

Introduction
Internet-delivered cognitive-behavioral treatment (CBT) is effective for insomnia. However, little is known about the beneficial effects of support. Recently we demonstrated that motivational support moderately improved the effects of internet-delivered treatment for insomnia. In the present study, we tested whether depressive symptoms at baseline moderate the effect of support on internet-delivered treatment for insomnia.

Methods
The current article reports on a secondary data analysis of a trial in which people with insomnia were randomly assigned to an internet-delivered treatment with support \( n = 129 \) or without support \( n = 133 \). We performed an intention-to-treat multilevel regression analysis to test for within-group (time: baseline vs. post-treatment, baseline vs. 6-month follow-up) and between-group (support, depression, and depression \( \times \) support) effects.

Results
We found that baseline depressive symptoms moderate the effect of support on sleep efficiency, total sleep time, and sleep onset latency (but not on wake after sleep onset, number of nightly awakenings and the Insomnia Severity Index). This means that for these variables, people with high levels of depressive symptoms benefit from support, whereas people with low levels of depressive symptoms improve regardless of support.

Conclusions
The data show that baseline depression severity plays an important role in the way internet treatments need to be delivered. These findings open up opportunities to personalize the support offered in internet-delivered treatments. Furthermore, support seems to enhance the benefit of treatment. In a stepped care model, providing support to internet-delivered treatment may be the first step up after pure online self-help treatment.

LONG TERM SLEEP AND FATIGUE AT SEA: A FIELD STUDY

Wessel M.A. van Leeuwen\textsuperscript{a}, Mike Barnett\textsuperscript{b}, Göran Kecklund\textsuperscript{a}, Torbjörn Åkerstedt\textsuperscript{a}

\textsuperscript{a} Stress Research Institute, Stockholm University, Stockholm, Sweden; \textsuperscript{b} Warsash Maritime Academy, Southampton, United Kingdom

Introduction
Although anecdotic reports are frequent, real field studies on long-term fatigue and sleep at sea are lacking. This will be the first such study.

Methods
2 European shipping companies participate with the entire crew of in total 8 ships during their routine operations for a period of on average 15 weeks at sea. Sleep is assessed using sleep diaries in combination with actigraphy, sleepiness (Karolinska Sleepiness Scale, KSS) is rated two-hourly during a full day every week. Fatigue (Multiple Fatigue Inventory, MFI-20) is measured weekly. Preliminary analysed background questionnaires of participants (n=23) reveal what is typical sleep/wake-behaviour in the seafarer.

Results
Average working-time is 69 ± 11 hours/week and 83\% of seafarers do overtime work at least once a week. 50\% of seafarers report having split sleep (2 sleep episodes of >1.5 hours per 24h). Self reported daily sleep need is 8.2 ± 1.1 hours, self reported daily sleep duration only 7.7 ± 1.5 hours. 70\% naps once a week or more. Twice as many report being morning type as compared to evening type. 43\% report higher fatigue levels at the end of a journey at sea compared to the start. Coffee consumption is considerably higher during working days (2.8 ± 1.9 cups) than during days off (1.0 ± 1.2 cups).

Conclusion
Preliminary analyses give a highly interesting insight in sleeping habits at sea. Full analyses of the field studies including long-term fatigue, sleep and sleepiness at sea will be carried out and presented later.

ESRS 2014, Tallin, Estonia.
SLEEP AND SLEEPINESS DURING CUMULATIVE SLEEP RESTRICTION AND SUBSEQUENT RECOVERY SLEEP

Wessel M.A. van Leeuwen\textsuperscript{a,b,c}, Tarja Porkka-Heiskanen\textsuperscript{b}, Mikael Sallinen\textsuperscript{c,d}, Mikko Härmä\textsuperscript{c}

\textsuperscript{a} Stress Research Institute, Stockholm University, Stockholm, Sweden; 
\textsuperscript{b} Sleep Team Helsinki, University of Helsinki, Helsinki, Finland; 
\textsuperscript{c} Centre of Expertise on Human Factors at Work, FIOH, Helsinki, Finland; 
\textsuperscript{d} Agora Center, University of Jyväskylä, Jyväskylä, Finland.

Introduction
This study investigates sleep and sleepiness during successive nights with restricted sleep and how those recover when habitual sleep length is regained.

Methods
After 2 baseline nights of 8 hours time in bed (TIB), 14 healthy young men had 4 hours TIB per night for 5 nights, followed by 3 recovery nights with 8 hours TIB (EXP). 7 control subjects had 8 hours TIB per night throughout the experiment (CON). Sleep stages were scored and repeated measures ANOVA used to detect changes across nights with restricted sleep and across nights with recovery sleep. In addition, subjects rated their sleepiness (Karolinska Sleepiness Scale, KSS) 140 times throughout the experiment. Ratings were longitudinally correlated to sleepiness as predicted by the three-process model of alertness regulation (TPMA).

Results
During the 4h TIB nights, sleep efficiency (from .95 to .98) and total sleep time (228 to 234 min.) increased, whereas stage 1 (S1) sleep (from 15 to 10 min.), time awake (11 to 5 min.) and sleep latency (6 to 2 min.) decreased. During the recovery nights S1 sleep increased (from 28 to 35 min.) whereas slow wave sleep (SWS) decreased (from 72 to 57 min.) and sleep latency increased (from 3 to 7 min.). In CON, no changes were observed except reduced sleep efficiency towards the end of the experiment. Individuals sleepiness ratings correlated significantly to model predicted sleepiness (ranging from r=.20 (p<.05) to .72 (p<.001).

Conclusion
Sustained short sleep reduces the amount of S1 sleep without increasing SWS. The TPMA is well capable of predicting sleepiness levels under such conditions.

ESRS 2014, Tallin, Estonia.
DOES ANTI-EPILEPTOGENESIS AFFECT SLEEP IN GENETIC EPILEPTIC RATS?

G van Luijtelaar a, M Wilde a, R Citraro b, F. Scicchitano b, C. van Rijn a

aBiological Psychology, Donders Institute of Cognition, Brain and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands
bDepartment of Experimental and Clinical Medicine, School of Medicine, University of Catanzaro, Catanzaro, Italy

Introduction: Recently it was established that early long lasting treatment with the anti-absence drug ethosuximide (ETX) delays the occurrence of absences and reduces depressive-like symptoms in a genetic model for absence epilepsy, rats of the WAG/Rij strain. Here it is investigated whether anti-epileptogenesis (chronic treatments with ETX for 2 and 4 months) affects REM sleep in this model.

Methods: Four groups of weaned male WAG/Rij rats were treated with ETX for 4 months, two groups for 2 months (at 2-3 and 4-5 months of age), the fourth group was untreated. Next, the rats were recorded 6 days after the last day of the treatment for 22.5 h. Non-REM sleep and REM sleep parameters and delta power were analyzed in four characteristic and representative hours of the recoding period.

Results: Four months treatment with ETX reduced the amount of REM sleep (Figure) and REM sleep as percentage of total sleep time. Other sleep parameters were not affected by the treatment. Clear differences between the various hours of the light-dark phase in amounts of non-REM and REM sleep and delta power were found, in line with commonly reported circadian sleep patterns.

Conclusion: It can be concluded that the reduction of REM sleep is unique for the early and long lasting chronic treatment. The outcomes may explain our earlier finding that a reduction of REM sleep might alleviate depressive like symptoms.

Figure. Hourly mean (and s.e.m.) of REM sleep for four hours of the 24h day of chronically treated and control WAG:Rij rats in minutes. Begin and end of the light period is followed by begin and end of the dark period. ETX 2-5 were treated for 4 months (n=6), ETX 2-3 (n=9) for 2 months, ETX 4-5 (n=10) for 2 months, while the control group (n=8) was untreated.

INTRODUCTION: Homeostatic and circadian changes that occur during adolescence can result in chronic sleep reduction. This may particularly be true for adolescents with Delayed Sleep Phase Disorder (DSPD), which is associated with late Dim Light Melatonin Onset (DLMO). This study assessed the influence of melatonin treatment on chronic sleep reduction in adolescents with DSPD and examined whether adolescents with DSPD suffer from more chronic sleep reduction than adolescents from the general population before and after melatonin treatment.

METHODS: Adolescents with DSPD (n = 145; 55.9% boys; mean age 15,5 years; mean DLMO = 22:32 h) completed a questionnaire concerning chronic sleep reduction at baseline. From these, 53 adolescents also completed this questionnaire after on average 10 weeks of melatonin treatment.

RESULTS: At baseline adolescents with DSPD reported significantly more symptoms of chronic sleep reduction than adolescents from the general population, whereas after treatment they reported significantly less symptoms. DLMO did not influence the effect of treatment.

CONCLUSION: The improvement of chronic sleep reduction after treatment is an important finding, considering the negative consequences of chronic sleep reduction for adolescents’ daytime functioning.

SLEEP IN CHILDREN WITH ASTHMA:
RESULTS OF THE PIAMA STUDY


Introduction: Children with asthma are thought to have impaired sleep quality and quantity. In this study, we investigated which of the many sleep aspects are associated with asthma.

Methods: Our sample consisted of 2529 children (aged 11 years) who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. Parents reported about asthma symptoms (wheezing, dyspnea, prescription of inhaled corticosteroids and asthma diagnosis) and children reported about different aspects of sleep (bedtime, rise time, sleep quality and daytime sleepiness/tiredness). Results were analyzed with (logistic) regression analysis.

Results: Children with frequent asthma symptoms significantly more often reported that they felt sleepy or tired during the day (34.4% experienced daytime sleepiness/tiredness at least once a week) than children without asthma symptoms (22.2%) and children with infrequent asthma symptoms (21.9%). This association was not confounded by sex, age of the child, parental educational level or smoking inside the house; the effect was also not modified by sex. There were no associations between asthma and bedtime, time spent in bed or sleep quality.

Conclusions: Children with frequent asthma symptoms experienced daytime sleepiness/tiredness more often than children with infrequent or no asthma symptoms. Otherwise, children with asthma did not differ much from children without asthma with regard to sleep.

THE SLEEP POSITION TRAINER: A NEW TREATMENT FOR POSITIONAL OBSTRUCTIVE SLEEP APNOEA.


a Department of Otolaryngology/Head Neck Surgery, Jan Tooropstraat 164, St. Lucas Andreas hospital, 1061 AE Amsterdam, the Netherlands
b Department of Clinical Neurophysiology, St. Lucas Andreas Hospital, Amsterdam, the Netherlands
c Department of Epidemiology and Biostatistics, VU Medical Centre, Amsterdam, The Netherlands

Introduction
Positional obstructive sleep apnoea (POSA), defined as a supine apnoea-hypopnoea index (AHI) twice or more as compared to the AHI in the other positions, occurs in 56% of obstructive sleep apnoea patients. Positional therapy (PT) is one of several available treatment options for these patients. So far, PT has been hampered by compliance problems, mainly because of the usage of bulky masses placed in the back. In this article, we present a novel device for treating POSA patients.

Methods
Patients older than 18 years with mild to moderate POSA slept with the Sleep Position Trainer (SPT), strapped to the chest, for a period of 29 ± 2 nights. SPT measures the body position and vibrates when the patient lies in supine position.

Results
Thirty-six patients were included; 31 patients (mean age, 48.1 ± 11.0 years; mean body mass index, 27.0 ± 3.7 kg/m(2)) completed the study protocol. The median percentage of supine sleeping time decreased from 49.9% [20.4-77.3 %] to 0.0 % [range, 0.0-48.7 %] (p < 0.001). The median AHI decreased from 16.4 [6.6-29.9] to 5.2 [0.5-46.5] (p < 0.001). Fifteen patients developed an overall AHI below five. Sleep efficiency did not change significantly. Epworth Sleepiness Scale decreased significantly. Functional Outcomes of Sleep Questionnaire increased significantly. Compliance was found to be 92.7 % [62.0-100.0 %].

Conclusion
The Sleep Position Trainer applied for 1 month is a highly successful and well-tolerated treatment for POSA patients, which diminishes subjective sleepiness and improves sleep-related quality of life without negatively affecting sleep efficiency. Further research, especially on long-term effectiveness, is ongoing.

LONG-TERM EFFECTIVENESS AND COMPLIANCE OF POSITIONAL THERAPY WITH THE SLEEP POSITION TRAINER IN THE TREATMENT OF POSITIONAL OBSTRUCTIVE SLEEP APNEA SYNDROME

J. Peter van Maanen\textsuperscript{a}, Nico de Vries\textsuperscript{b}.

\textsuperscript{a} Department of Otolaryngology/Head Neck Surgery, Jan Tooropstraat 164, St. Lucas Andreas hospital, 1061 AE Amsterdam, the Netherlands

Introduction
To investigate effectiveness, long-term compliance, and effects on subjective sleep of the Sleep Position Trainer (SPT) in patients with position-dependent obstructive sleep apnea syndrome (POSAS).

Methods
Prospective, multicenter cohort study. Adult patients with mild and moderate POSAS were included. Patients were asked to use the SPT for 6 mo. At baseline and after 1, 3, and 6 mo, questionnaires would be completed: Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), and questions related to SPT use.

Results
One hundred forty-five patients were included. SPT use and SPT data could not be retrieved in 39 patients. In the remaining 106 patients, median percentage of supine sleep decreased rapidly during SPT’s training phase (day 3 to 9) to near-total avoidance of supine sleep. This decrease was maintained during the following months of treatment (21\% at baseline versus 3\% at 6 mo). SPT compliance, defined as more than 4 h of nightly use, was 64.4\%. Regular use, defined as more than 4 h of usage over 5 nights/w, was 71.2\%. Subjective compliance and regular use were 59.8\% and 74.4\%, respectively. Median ESS (11 to 8), PSQI (8 to 6), and FOSQ (87 to 103) values significantly improved compared with baseline.

Conclusion
Positional therapy using the Sleep Position Trainer (SPT) effectively diminished the percentage of supine sleep and subjective sleepiness and improved sleep related quality of life in patients with mild to moderate position-dependent obstructive sleep apnea syndrome. SPT treatment appeared to have sustained effects over 6 months. SPT compliance and regular use rate were relatively good. Subjective and objective compliance data corresponded well. The lack of a placebo-controlled group limited the efficacy of conclusions.

THEORETICAL APPROACH TOWARDS INCREASING EFFECTIVENESS OF PALATAL SURGERY IN OBSTRUCTIVE SLEEP APNEA: ROLE FOR CONCOMITANT POSITIONAL THERAPY?

J. Peter van Maanen\textsuperscript{a}, Birgit I. Witte\textsuperscript{b}, Nico de Vries\textsuperscript{a}.

\textsuperscript{a} Department of Otolaryngology/Head Neck Surgery, Jan Tooropstraat 164, St. Lucas Andreas hospital, 1061 AE Amsterdam, the Netherlands
\textsuperscript{b} Department of Epidemiology and Biostatistics, VU Medical Centre, Amsterdam, The Netherlands

Introduction
The aims of this study are to evaluate the effect of palatal surgery (uvulopalatopharyngoplasty (UPPP) or Z-palatoplasty (ZPP)) with or without (+/-) concomitant radiofrequent ablation of the base of the tongue (RFTB) on body position-specific apnea-hypopnea index (AHI) values in patients with obstructive sleep apnea (OSA) and to compare this treatment outcome to the theoretical effect of (addition of) positional therapy (PT).

Methods
Retrospective analysis of pre- and posttreatment polysomnographies in 139 patients who had undergone UPPP/ZPP +/- RFTB was performed. Hypothetical evaluation of the effects of (addition of) ideal PT on AHI in positional OSA (POSA) patients was carried out.

Results
Median AHI significantly decreased from 18.0 to 11.2 ($p < 0.001$). Median AHI in all separate positions decreased significantly as well. Sixty-eight patients suffered from POSA and showed a significant decrease in median AHI from 15.5 to 11.5 ($p = 0.002$). In the 71 non-positional OSA (NPOSA) patients, the significant AHI decrease was more outspoken, from 23.0 to 11.0 ($p < 0.001$). Our hypothetical model to treat POSA patients with an ideal PT (as monotherapy or in addition to surgery) resulted in a significant median AHI decrease from 18.0 to 4.5 ($p < 0.0001$).

Conclusion
UPPP/ZPP +/- RFTB significantly reduces AHI and all body position-specific AHI values. This reduction is significantly higher in NPOSA than in POSA patients. When considering UPPP/ZPP +/- RFTB, the effect of body position needs to be taken into account. PT, either as monotherapy or in addition to surgery, theoretically has shown to improve treatment results dramatically in POSA patients. Prospective, controlled trials focusing on the effects of this combination of treatments should further evaluate this hypothetical conclusion.

CHRONIC INSOMNIA: NOT ALWAYS PSYCHOPHYSIOLOGICAL

Nicole E. Neerings-Verberkmoes, Monique H.M. Vlak, Lonneke M.L. de Lau, Hans L. Hamburger

Amsterdam Centre for Sleep and Wake Disorders, Slotervaart Medical Center, Amsterdam, The Netherlands

OBJECTIVE: To determine the sensitivity, specificity and the positive and negative predictive value of taking a detailed sleep history for making the diagnosis of psychophysiological insomnia.

DESIGN: Retrospective case file study.

METHOD: We examined 767 patients referred to the Amsterdam Centre for Sleep and Wake Disorders, and who underwent polysomnography for the first time between 1 January and 31 December 2010. We compared the probable diagnosis made following history-taking with the final diagnosis made after polysomnography. In this we differentiated between organic and non-organic insomnia. The sensitivity, specificity, positive and negative predictive values of the sleep history were calculated.

RESULTS: In 24.8% of the 303 patients whose histories did not indicate organic insomnia, polysomnography showed there to be an organic cause. Primary causes were obstructive sleep apnoea (13.2%), upper airway resistance syndrome (5.4%), and periodic limb movement disorder (4.0%) or a combination of these. In the histories of 464 patients there were indications that the insomnia had an organic cause and in 325 of them this was confirmed by polysomnography. The sensitivity of detailed history taking to psychophysiological insomnia was 62.1%, the specificity 81.3%, the positive predictive value was 75.2% and the negative predictive value was 70.0%. In patients under the age of 40 with a score on the Epworth sleepiness scale < 10 (i.e. no hypersomnolence), a BMI < 25 kg/m2 and indications of psychophysiological insomnia, organic insomnia could not be demonstrated, with the exception of one parasomnia.

CONCLUSION: History-taking only meant that the organic cause was missed in a substantial percentage of patients with insomnia, in particular in older patients with hypersomnolence and a high BMI.

PERSONALIZED LIGHT THERAPY FOR IMPROVED CIRCADIAN RHYTHM MANAGEMENT

V. Pronk, E. Møst

Philips Research, Eindhoven, the Netherlands

Introduction
Successful application of light therapy in an ambulatory care setting requires the integration of the therapy with, in particular, ambient light levels. The combination of these two factors is expected to enable a more efficient regulation of the circadian rhythm. The beneficial effects of a proper alignment between a person’s circadian rhythm and the light-dark cycle to which that person is exposed, continue to be endorsed in the literature. Yet, practical light therapies that sustain this alignment in a flexible and adaptive way remain largely elusive today.

Methods
The mathematical model of the human circadian pacemaker introduced by Kronauer et al. [1982], provides a useful tool to evaluate the integrative effect of light on the human circadian system. In particular, it allows the timing of the core-body temperature (CBT) minimum to be estimated with an accuracy of, typically, plus or minus one hour. We have used this tool to design and evaluate a heuristic algorithm that, on a daily basis, computes a personalized light ‘recipe’, aimed at entraining and stabilizing a person’s circadian rhythm. The algorithm enables a rapid shift of the CBT minimum to a predefined position in time, and aims to keep it at that position. The recipe is computed in the early evening and consists of an evening light or light deprivation therapy and a morning light therapy. Each therapy is described in terms of timing and intensity. The algorithm takes ambient light into account.

Results
Using an existing dataset comprising a fortnight of light exposure data of 20 participants, we provide a proof of concept, illustrating that the algorithm renders successful circadian stabilization, expressed in the context of the model used. Being adaptive, the algorithm is inherently resilient to a certain degree of non-adherence to the therapy. The evaluation provides numerous hints for refinements and improvements.

Conclusions
We have shown the feasibility of providing a personalized light therapy to stabilize a person’s circadian rhythm in an ambulatory care setting, wherein the ambient light levels to which this person is exposed have been incorporated.


Presented at the SLTBR - society for Light therapy and biological Rhythm

NSWO 25, 2014
ENHANCED PHASE RESETTING IN THE SYNCHRONIZED SUPRACHIASMATIC NUCLEUS NETWORK

Ashna Ramkisoensing, Changgui Gu, Heleen M.D. van Engeldorp Gastelaars, Stephan Michel, Tom Deboer, Jos H.T. Rohling and Johanna H. Meijer

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

The suprachiasmatic nucleus (SCN) adapts to both the external light-dark (LD) cycle and seasonal changes in day length. In short photoperiods, single-cell activity patterns are tightly synchronized (i.e., in phase); in long photoperiods, these patterns are relatively dispersed, causing lower amplitude rhythms. The limit cycle oscillator has been used to describe the SCN’s circadian rhythmicity and predicts that following a given perturbation, high-amplitude SCN rhythms will shift less than low-amplitude rhythms. Some studies reported, however, that phase delays are larger when animals are entrained to a short photoperiod. Because phase advances and delays are mediated by partially distinct (i.e., nonoverlapping) biochemical pathways, we investigated the effect of a 4-h phase advance of the LD cycle in mice housed in either short (LD 8:16) or long (LD 16:8) photoperiods.

In vitro recordings revealed a significantly larger phase advance in the SCN of mice entrained to short as compared to long photoperiods (4.2 ± 0.3 h v. 1.4 ± 0.9 h, respectively). Surprisingly, in mice with long photoperiods, the behavioral phase shift was larger than the phase shift of the SCN (3.7 ± 0.4 h v. 1.4 ± 0.9 h, respectively). To exclude a confounding influence of running-wheel activity on the magnitude of the shifts of the SCN, we repeated the experiments in the absence of running wheels and found similar shifts in the SCN in vitro in short and long days (3.0 ± 0.5 h v. 0.4 ± 0.9 h, respectively). Interestingly, removal of the running wheel reduced the phase-shifting capacity of mice in long days, leading to similar behavioral shifts in short and long photoperiods (1.0 ± 0.1 h v. 1.0 ± 0.4 h).

As the behavioral shifts in the presence of wheels were larger than the shift of the SCN, it is suggested that additional, non-SCN neuronal networks in the brain are involved in regulating the timing of behavioral activity. On the basis of the phase shifts observed in vitro, we conclude that highly synchronized SCN networks with high-amplitude rhythms show a larger phase-shifting capacity than desynchronized networks of low amplitude.

THE UNDERVALUED POTENTIAL OF POSITIONAL THERAPY IN
POSITION-DEPENDENT SNORING AND OBSTRUCTIVE SLEEP
APNEA – A REVIEW OF THE LITERATURE

Madeline J. Ravesloot\textsuperscript{a}, J. Peter van Maanen\textsuperscript{a}, Lideke N. Dun\textsuperscript{a}, Nico de Vries\textsuperscript{a}

\textsuperscript{a} Department of Otolaryngology/Head Neck Surgery, Jan Tooropstraat 164, St. Lucas Andreas hospital, 1061 AE Amsterdam, the Netherlands

Introduction
Research during the past 10-20 years shows that positional therapy (PT) has a significant influence on the apnea-hypopnea index. These studies are predominantly performed as case series on a comparably small number of patients. Still, results have not found their way into the daily diagnostic and treatment routine. An average of 56% of patients with obstructive sleep apnea (OSA) have position-dependent OSA (POSA), commonly defined as a difference of 50% or more in apnea index between supine and non-supine positions. A great deal could be gained in treating patients with POSA with PT. The aim of this paper was to perform a thorough review of the literature on positional sleep apnea and its therapy.

Methods
A broad search strategy was run electronically in the MEDLINE and EMBASE databases using synonyms for position and sleep apnea.

Results
Sixteen studies were found which examined the effect of PT on OSA. In this literature review, we discuss the various techniques, results, and compliance rates.

Conclusion
Long-term compliance for PT remains an issue, and although remarkable results have been shown using innovative treatment concepts for PT, there is room for both technical improvement of the devices and for further research.

MEDICAL TECHNOLOGY ASSESSMENT OF POLYSOMNOMOGRAPHY, TYPE 2: FULL PSG AT HOME; ARE THERE DIFFERENCES IN PERFORMANCE BETWEEN UNATTENDED PSG SYSTEMS AT HOME?


Sleep-Wakecenter SEIN, Dr. Denekampweg 20, 8025 BV Zwolle, The Netherlands.

Polysomnography (PSG) in a clinical setting (PSG, type 1) is time consuming and expensive. Type 2, i.e. full PSG at home, is thought to be a good alternative, but has never been evaluated in terms of a medical technology assessment (MTA). In some countries this lack of MTA precludes reimbursement for PSG type 2. This communication is part of a series of posters which add up to a medical technology assessment of PSG, type 2, and deals with technical failures when recording full PSG at home. This study is designed to evaluate the technical reliability of two different full PSG systems at home, Titanium (Embla) and Siesta (Compumedics Limited).

A retrospective study over 2012 was set up to evaluate two full PSG systems at home. The population which used the Titanium system (T) consisted of 366 patients (age: 45 ± 17 yrs) and for the Siesta (S) of 100 patients (age: 43 ± 17 yrs). All patients underwent two consecutive days type 2 PSG at home with one system. After 24 hours, patients returned to the clinic for a check-up. The following signals were evaluated within both systems: EEG (including eye movements and chin EMG), EMG_{m.tibialis}, nasal pressure, inductive belts_{thorax and abdomen} and oxygen saturation. A measurement fault was indicated when there was limited recording time or a technical interruption. We also estimated the amount of interruptions within the recorded signals.

Both systems were similar in percentages of patients without any faults in both nights (T:93.2%; S:90.0%, p=0.28). The T-system failed in 3.8% of the patients on the first night, and 3.0% on the second night. Faults within the first and second night (5.0%) were similar for the S-system. It turned out, that there was no system where both nights had failed. Within the successful recordings there were more inductive belts interruptions with the S-system. This resulted for the inductive belts in T:3.5% and S:10% (p=0.01). See Table.

It is reliable to perform full PSG type 2 at home with both PSG systems. To minimize the errors in particular for the inductive belts there is a preference for the Titanium system. Despite some failures, reliable diagnoses could be made. We postulate that similar results will be seen when testing other PSG type 2 systems. This would imply that the brand of the equipment has no or little influence on the results of the PSG.

<table>
<thead>
<tr>
<th>Signal</th>
<th>Titanium (T)</th>
<th>Siesta (S)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal pressure</td>
<td>30.4%</td>
<td>35.1%</td>
<td>0.98</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>26.7%</td>
<td>26.6%</td>
<td>0.38</td>
</tr>
<tr>
<td>Inductive belts_{thorax and abdomen}</td>
<td>3.5%</td>
<td>10.0%</td>
<td>0.01*</td>
</tr>
<tr>
<td>EEG</td>
<td>2.9%</td>
<td>4.4%</td>
<td>0.47</td>
</tr>
<tr>
<td>EMG_{m.tibialis}</td>
<td>3.5%</td>
<td>1.1%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* p-value < 0.05

SLEEP AND FATIGUE AMONG OFFICERS ON BOARD GAS TANKERS

Elianne F.E.R. Rongen\textsuperscript{a,b}, Audrey E.W.G. Rost-Ernst\textsuperscript{a,b}, Remko Kloos\textsuperscript{c}, Wessel M.A. van Leeuwen\textsuperscript{d}

\textsuperscript{a}Netherlands Maritime University, Rotterdam, The Netherlands  
\textsuperscript{b}STC Group, Rotterdam, The Netherlands  
\textsuperscript{c}Anthony Veder Group, Rotterdam, The Netherlands  
\textsuperscript{d}Stress Research Institute, Stockholm University, Stockholm, Sweden

Introduction
Fatigue is a growing safety concern in the maritime industry; especially on board gas tankers, safety is of crucial importance. Therefore, this field study investigates sleep and fatigue levels on board routinely operating gas tankers.

Methods
22 officers working on 2 gas tankers from a Dutch shipping company participated on a 10-day voyage through European waters, working either day work (n=16) or on 4h on/8h off watch system (n=6). Sleepiness (Karolinska Sleepiness Scale, KSS) was rated hourly, neurobehavioral performance (Sustained Attention to Response Task, SART) at the start and end of each work period. Sleep and sleep quality was assessed using actigraphy and diaries. Sleepiness ratings were also correlated to predictions based on the three-process model of alertness regulation.

Results
Sleepiness peaked around 4 AM in both watch keepers (KSS=5.5) and day workers (KSS=6.2) and correlated well with model predictions (average r=.60, p<.001). Average sleep efficiency was 88\% - with no difference between watch keepers and day workers. Daily sleep duration was shortest in those working 08-12 (6 h), and longest in those working 00-04 (8 h). Day workers slept about 6.5 hours/day. Errors on the SART were most frequent at night and were 35\% more frequent at the end of a working period compared to the beginning.

Conclusion
Highest sleepiness is reached in line with model predictions (i.e. around 4 AM). Although no sleep on duty was observed, the fact that neurobehavioral performance declined with time at work may be of risk.

ESRS 2014, Tallin, Estonia.
MEDICAL TECHNOLOGY ASSESSMENT OF POLYSOMNOGRAPHY, TYPE 2: FULL PSG AT HOME; NIGHT TO NIGHT SLEEP VARIABILITY


a Sleep-Wakecenter SEIN, Dr. Denekampweg 20, 8025 BV Zwolle, The Netherlands.

Polysomnography (PSG) in a clinical setting (PSG, type 1) is time consuming and expensive. Type 2, i.e. full PSG at home, is thought to be a good alternative, but has never been evaluated in terms of regular Medical Technology Assessment (MTA). In some countries this lack of MTA precludes reimbursement for PSG type 2. This communication is part of a series of posters which add up to MTA of PSG, type 2, and deals with night to night sleep variability. This study investigates the differences between the first and the second night, during two consecutive full PSG’s type 2, on all sleep parameters.

Retrospective study of 339 patients (49.1% male, mean age=45.0, SD=16.7) who underwent full PSG type 2 for two consecutive days. Their final diagnoses were (according to ICSD-2) Insomnia (n=201), Sleep Related Breathing Disorder (SRBD) (n=49), Circadian Rhythm Sleep Disorder (CRSD) (n=20), Sleep Related Movement Disorder (SRMD) (n=43), Idiopathic Hypersomnia (IH) or Narcolepsy (n=12), Parasomnia (n=6) and No Diagnosis (n=8). The subjects with the diagnosis Insomnia, SRBD, SRMD and the total group were compared on all sleep parameters of the first and the second night. We also compared two age groups: patients aged up to 45 years (n=156) and a group over 45 years (n=183).

The results of the total group indicate significant differences in the sleep variables: Time in Bed (TIB), Sleep efficiency (SE), Awakenings (AW), and Sleep Onset (SO) (table 1).

Patients diagnosed with Insomnia have a significant higher PLM index in the second night (p=0.04). The night-to-night sleep variability for the SRBD and SRMD groups showed no significant differences in all sleep parameters. The results of the group ≥45 years, have significant differences in various sleep parameters: SO and AW decreased resulting in increasing SE and NREM stage 3. Significant differences for the group under 45 years showed a higher NREM stage 2 (p=0.02) and REM (p=0.03) sleep during the first night. Like the Insomnia group the PLM Index of the younger group (p=0.04) also increased during the second night.

For the total group of 339 patients there are some significant differences between the first and the second night during two PSG’s at home. However, the clinical relevance of the significant differences is limited considering that they are not high. More remarkable differences between both recordings were found in the group ≥ 45 years. They appear to have some greater adaptation problems as many sleep parameters were disturbed and their sleep quality decreased when assessed over two nights.

INTERNAL DESYNCHRONIZATION FACILITATES SEIZURES

Magda K Smyk\textsuperscript{a}, Anton Coenen\textsuperscript{b}, Marian H Lewandowski\textsuperscript{a}, Gilles van Luijtelaar\textsuperscript{b}

\textsuperscript{a}Dep. of Neurophysiology and Chronobiology, Chair of Animal Physiology, Institute of Zoology, Jagiellonian University, Kraków, Poland; \textsuperscript{b}Department of Biological Psychology, Donders Centre for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands

INTRODUCTION: The occurrence of spike-wave discharges (SWDs) in WAG/Rij rats is modulated by the circadian timing system and is shaped by the presence of a light-dark cycle, motor activity, and state of vigilance. Here it is investigated whether the response to a phase shift is different between the SWDs and general motor activity rhythm. The process of reentrainment of both rhythms and its effect on number of absences was compared after a phase shift in the light-dark cycle, a condition known to induce internal desynchronization in the circadian timing system.

METHODS: Chronic electroencephalographic and motor activity recordings were made in adult WAG/Rij rats, kept in the 12:12 h light-dark cycle. After four baseline days, rats were exposed to an 8-h phase delay by shifting the light onset. Recordings were continuously made for another 10 consecutive days.

RESULTS: An immediate effect of the phase shift on both rhythms was observed: the acrophases were 7.5 h advanced. Next, they gradually returned to the baseline level, however, with a different speed. The more robust motor activity rhythm stabilizes first, whereas the weaker rhythm of SWDs adapted more slowly. The phase shift caused a prolonged aggravation of epileptic activity, observed mostly during the light phase.

DISCUSSION: Different speed and character of reentrainment suggests that the occurrence of seizures and motor activity are controlled by distinct circadian oscillators. The prolonged increase in absences after the phase shift has immediate practical consequences for patients.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Mean and SEM of the acrophase of the rhythm of general motor activity (A) and SWDs rhythm (B) during 3 baseline days and after a 8 hr phase delay. Y axis: degrees (360 degrees = 24 h, 0–180 degrees – the light phase, 181–360 degrees – the dark phase), X axis: experimental days. *p < 0.05, mean baseline vs postshift day.}
\end{figure}

EEG SLOW-WAVE CHARACTERISTICS IN SLEEP AFTER DAILY TORPOR IN DJUNGARIAN HAMSTERS

V.V. Vyazovskiy\textsuperscript{a}, I. Tobler\textsuperscript{b}, T. Deboer\textsuperscript{c}

\textsuperscript{a}Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK; \textsuperscript{b}Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland; \textsuperscript{c}Laboratory for Neurophysiology, Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, The Netherlands.

Objectives: In Djungarian hamsters the initial slow-wave activity (EEG power in the 0.5-4.0 Hz band; SWA) immediately following an episode of daily torpor is consistently enhanced above values obtained during a day without torpor, reminiscent to the SWA increase after sleep deprivation (SD). It is unknown whether the mechanisms are similar.

Methods: Individual EEG slow-waves recorded from the parietal cortex in adult male Djungarian hamsters (n=8, 8:16 LD) during the initial NREM sleep after torpor were analyzed. For comparison, a baseline day period with a similar amount of NREM sleep (50.0±3.4 vs 44.9±4.9 min, n.s.) and brain temperature (34.9±0.2 vs 34.9±0.2 °C, n.s.) was chosen. We identified slow-waves as negative deflections of the filtered (0.5-4 Hz) EEG below a zero-line.

Results: SWA during NREM sleep was higher after torpor (150.1±11.2 vs 108.0±7.1, % of a mean 8-h light period value, p=0.017). Slow-wave incidence, amplitude and duration were higher after torpor compared to baseline (by 22, 7 and 4% respectively, p<0.05), suggesting that the SWA increase is mainly due to more frequent incidence of EEG slow-waves. We then matched baseline and torpor slow-waves according to amplitude and compared their up- and down-ward slopes. Interestingly, the slopes during baseline and after torpor were virtually identical (p=0.83 and p=0.24 for up- and down-slopes respectively).

Conclusions: This finding is in contrast with the steeper slope of slow-waves after SD reported earlier in rats and humans. Therefore, our data suggest that mechanisms underlying increased NREM sleep SWA after torpor may differ from those after SD.

SLEEP DISORDERS OTHER THAN PARASOMNIAS OR PNES DURING THE NIGHT, AS MIMICS OF EPILEPSY

Al W. de Weerd
Sleep-wake center and KNF, SEIN Zwolle-Groningen, Zwolle, The Netherlands

Introduction: Next to parasomnias, other disturbances of sleep are thought to be exceptional as mimics of epilepsy. However, in our third line clinic dedicated to epilepsy and sleep disorders, these mimics are regularly encountered and are described here.

Methods. In our clinic long term (>24 hrs) video-EEGs always contain sensors which make global polysomnography (PSG) possible (respiration and EMG/muscle tone). In case this recording suggests a sleep disorder, a full PSG, (AASM rules) is done in order to get more details. We are aware that our patient group is a selection from the general population which may give bias in the prevalence figures.

Results. In 1650 consecutive patients video-EEG recordings suggested a serious sleep disorder in N=255 (15%). Most of them had an AASM defined insomnia or parasomnia. Some had pseudo non epileptic seizures (PNES) during the night. At consecutive PSG, in the remaining 19 patients (1.1%) a sleep disorder was found with characteristics similar to the clinical description of the events during the night without any video-EEG prove of epilepsy, PNES or parasomnia.

The final diagnoses in this group of 19 patients were obstructive or central apneas (O/CSA) in 9, sleep myoclonia in 5 and excessive periodic limb movements in the other 5 patients. In addition to these 19 patients, two patients (0.1%) had a status cataplecticus during day-time as part of not detected narcolepsy. Elsewhere, this was thought to be an epileptic disorder. Therapy for the sleep disorders resulted in substantial improvement. Examples are given below.

Conclusion. In 1.2% of our population a sleep disorder other than parasomnia or PNES, proved to be a mimic of epilepsy. This finding has major impact on the therapy.

Legend fig. 1a and b. Male 51 y/o. Healthy up to 2011. From then on attacks with a duration of 10-20 s, but sometimes for one hour or longer. He remains conscious, but can’t speak understandable and has waxing and waning loss of muscular tone of axial muscles in the neck and mandibular muscles. Sleepy during daytime which was attributed to moderate OSAS (AHI 20). CPAP did not help. In another clinic epilepsy was mentioned but not proven. AEDs did not improve the symptoms. The figs. show his hypnogram and multiple sleep latency test (MSLT). We diagnosed narcolepsy with recurrent status narcolepticus. Therapy with sodium oxybate combined with clomipramine gave complete remission.

Legend fig 2. Male 21 y/o, suspected to have frontal lobe epilepsy. AEDs worked each or in combinations for limited time. At examination healthy, but 130 kg and height 1.95 m. The fig. shows his hypnogram which proves that the frequent major attacks during the night were severe apneas with impressive motor phenomena sometimes mimicking a tonic seizure. CPAP eliminated the “epileptic” events during the night.
Fig. 1a. Hypnogram

Fig. 1b. MSLT

Fig. 2. Hypnogram, apneas/hypopneas and SpO2

Poster presented at European Epilepsy Congress, June 30, 2014, Stockholm and ESRS, September 2014, Tallinn
INTRODUCTION

Seclusion rooms in psychiatry wards are focused on being low-stimuli and high safety, but are often not designed to improve patient wellbeing and thereby do not facilitate the recovery process. Furthermore, there is often no alternative in between housing patients in the general ward or the seclusion room. Using dynamic lighting and an interactive wall in an intermediate room between these two housing options can potentially reduce the number of seclusions, increase the staff and client interaction, reduce trauma in patients and increase staff safety in acute psychiatric wards.

METHODS

A workflow analysis was conducted with both staff and (ex-) patients of a crisis unit for psychosis where seclusion occurs to find inefficiencies, needs, and room for improvement. The five most important needs were extracted and these were translated into lighting and interaction applications; i.e. allow the patient to have (some) control over room features, provide structure and information, facilitate contact with caregivers, allow personalization of the room and to provide distraction. The complete intervention was built around an interactive touch screen to be installed in the wall and has tempered glass to assure safety. The needs were translated into applications that the patient could control through a touch screen. The applications included the treatment program, adjust the room lighting (indirect cove lighting; white and color), show dedicated themes and pictures, video calls with caregivers, and a choice of games. Interviews were conducted to establish patient and staff evaluation.

RESULTS

Two intermediate step rooms (support rooms) and one seclusion room were equipped with the intervention at a new intensive care unit of the crisis unit at the Geestelijke Gezondheidszorg Eindhoven (GGzE). Both patients as well as caregivers indicated being able to control room features such as the lighting enhances patient empowerment and they rated these room control options as valuable. Also, patients reported that being able to view the treatment program on demand helped to create a predictable environment.

CONCLUSIONS

Both patients and staff were very satisfied with the intervention. Patient control of the environment showed to be an important of both patient and staff wellbeing and can aid the recovery of psychiatric patients. Implementing ambient (colored) lighting can be an easy to implement technology to establishing this; app based lighting control can provide patient, and if needed staff, control of the environment and help create a healing environment.

Presented at the Society for Light Treatment and Biological Rhythms conference, Vienna, 2014.
HONORARY MEMBERS

Dr. A.C. Declercq

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

Prof. Dr. H.A.C. Kamphuisen (1931-2013)