SLEEP-WAKE
Research in the Netherlands

Volume 29, 2018

29

This publication was sponsored by **UCB**

Gildeprint Drukkerijen, Enschede

ISBN 978-94-9301-470-1

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ISBN 978-94-9301-470-1

Volume 29, 2018

Published by
Dutch Society for Sleep-Wake Research

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PREFACE

As I am writing this, in my hotel room in Basel while attending the 2018 ESRS meeting, I am reminded of the state of sleep research in the Netherlands. As in previous years, Dutch sleep science is well-represented in the European sleep meeting, with talks, workshops and posters, and this nicely reflects the level of sleep science and medical practice that we have achieved in our country.

It is pleasing to see that sleep science continues to grow worldwide, with advances in fundamental and applied knowledge being published daily; and equally pleasing is to witness the dissemination of that knowledge with popular media reporting more and more on the positive effects of sleep on wellbeing and health.

We are fortunate to have an active and expansive body of Dutch sleep professionals, that interact and meet at the various events occurring throughout the year. In 2017 we had the second national sleep conference in Ermelo, that we organised together with our sister organisation, the Dutch medical sleep association, the SVNL. After a very successful meeting in 2016 it was encouraging to see that there remains sufficient interest and, frankly, a need, to stay updated and discuss novel issues. From 2019 the conference will be a biannual meeting, alternating with the ESRS and we hope this will remain the national hotspot for all information on ongoing fundamental scientific sleep projects, public-private partnerships, and clinical sleep science.

Other highlights of the year include the organisation in St. Michielsgestel of the 2018 international sleep medicine course, ISMC, that alternates between Belgium, the United Kingdom and The Netherlands. On November 2nd 2018, the NSWO will host the autumn meeting, with a focus on REM sleep in Amsterdam. On October 5th, the 'Kind&Slaap' association will host a symposium entitled 'Good night – sleep tight' in Zeist.

The novel website of NSWO hopes to be the portal for information on healthy and disordered sleep, for sleep professionals, media, the general public and anyone interested in the many facets of sleep; be sure to check it out. And finally, this yearbook highlights the ongoing work and investigation of the Dutch sleep professionals, made possible by a generous gift from UCB.

Enjoy!

Ysbrand van der Werf

EDITORIAL NOTE

This year we're delighted to see what we hope is a new trend. A great amount of contributions, delivered with only the minimum of encouragement from our side. This year we can boast of 64 abstracts. Looking back the last ten years, there is a change in the composition of the yearbook. In 2015, there was an all-time low, especially in abstracts - only 21 were submitted. In the years before we recieved on average 36 abstracts, but, also more than 10 mini-papers in each book. In 2016, the Scientific committee put in much effort to promote the yearbooks' potential to present one's abstracts. It paid off. The numbers of abstracts have been stable the last three years, with an average of 65 abstracts per year. The mini-papers, however, declined. The last three years we have received on average 5 papers. We believe that while this book is an excellent medium to present an overview of published work, it is also the scientific journal of our organization, to also present new findings and insights. After all, the yearbook offers a peer-reviewed, open-access, no-charge publication!

This edition contains 4 mini-papers, covering a wide range of topics. Professor Coenen has given us an original historical review on the research of dreaming, while Šuvak et al are presenting new insights into the metabolomics of sleep. Lammers-van der Holst et al present a model of factors leading to fatigue at work during shift work and lvarez-Estevez et al report on the reliability of an automatic algorithm for the analysis of the oxygen saturation levels.

We have a special section this year; Roelof Hut has written a beautiful piece on the life and work of professor Serge Daan, who passed away earlier this year. It is fascinating to read the contributions he has made to the field of chronobiology and sleep, the (other) great minds he worked with and to gain an insight into his personal life. Serge Daan inspired many throughout his long career, myself included.

We are proud to present the abstracts of three very diverse PhD theses. While Melanie Knufinke presents how top athletes sleep (spoiler alert – it isn't all that great), the effects of sleep in this population and how they can remedy this issue, Pedro Fonseca has explored how to monitor sleep (unobtrusively) at home and to improve the algorithms to classify sleep when not using a PSG. Henry Keijzer, on the other hand, has explored new genetic protocols and the use of melatonin as a biomarker to bring us closer to a personalized sleep medicine approach.

Two book reports this year: one which is aimed at the sleep professional; *Medications and their effects on sleep and wake*, from the Sleep Medicine Clinics series, and one for the general public: *Wat kun je doen aan dementie*?, with an entire chapter dedicated to the role of sleep.

This yearbook is the result of the joined efforts of the Scientific committee. I would like to express my gratitude to Cathalijn, Floor, Johan, Marijke, Peter, Annemarie and Sebastiaan for their help in the editorial process and as reviewers, to Arthur, for reminding you all of our deadlines and to UCB for making this publication possible. Of course, we are very grateful to all contributors for providing the content.

Els Møst
Editor

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In Memoriam

SERGE DAAN

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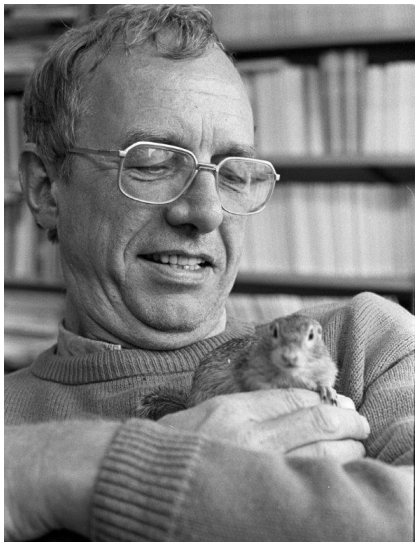

Figure 1. Serge with European ground squirrel
(1993, photo: Joost Tinbergen)

The fields of chronobiology and physiological ecology have lost a prominent member when Serge Daan, Emeritus Professor at the University of Groningen, passed away on February 9th, 2018. Serge was a clever and critical researcher, who inspired and trained many of us. He made seminal discoveries in hibernation research, ecological energetics, behavioral biology, sleep research, and sex-ratio adaptation. Serge was born in 1940, in the historical windmill 'De Plasmolen' in Mook, Limburg, the Netherlands. In 1944, during the Second World War liberation, the Daan family fled from the Plasmolen only hours before it was shelled by American troops. After the war, the family moved to the estate 'Het Schol' near Deventer, where Serge grew up with seven brothers and sisters. The family had a great interest in biology and together the children built an impressive collection of skulls for their museum. Many visitors may remember part of this collection displayed in the hall of Serge's house 'Villa Later' in Paterswolde. Serge studied biology at the University of Amsterdam and obtained his master's degree in 1966. During his studies he worked with evolutionary biologist Dick Hillenius at the Zoological Museum Amsterdam; at the time a meeting place of biologists, artists, writers and poets. Serge expanded the museum collections by catching amphibians in southern Limburg, using his Harley Davidson as field vehicle. In Greece he collected reptiles and to his surprise a newly discovered Agama lizard sub-species was named after him: Agama stellio daani[1]. Unwilling to spend the rest of his life in dusty museums, he returned his PhD grant to the Dutch Science Foundation and instead obtained stipends to investigate hibernation with Prof. dr. Punt in 1968[2]. It took him back to southern Limburg, where he discovered that hibernating bats would save energy by moving to colder parts of the cave[3]. To test whether this behavior was a temperature response, he carried large blocks of ice into the

cave to attract hibernating bats. The result of this experiment was that Serge caught pneumonia, but it also represents a landmark: Serge had changed from a descriptive taxonomist to an experimental biologist. Activity patterns during hibernation were further studied in garden dormice in the lab. Serge described that euthermic arousals clearly followed a circadian pattern, interrupted by multi-day torpor[4]. These patterns were the first free-running circadian data collected by Serge. It sparked his interest in biological rhythms, further boosted by Mike Menaker's early publication on circadian rhythms in hibernating bats[5]. It was many years later, in 2009, when Serge, as faculty Dean, was able to show his gratitude and admiration to Mike Menaker by awarding him an honorary professorship at the University of Groningen: 'For a generation of researchers into the biological clock, including those in Groningen, Michael Menaker is the giant on whose shoulders they stand'.

Serge wanted to learn more about the emerging field of circadian rhythms by visiting Jürgen Aschoff. In one day they wrote a successful Humboldt post-doc fellowship application allowing Serge to work with Aschoff at the famous Max Planck Institute in Andechs, Germany (1971-1973). At the time Aschoff was not only working on human chronobiology, but also on rhythms in mammals and birds. The concept of circadian adaptation to day length and latitude was studied by comparing calculated solar light intensity curves (using an equation obtained from his brother) with year-round activity patterns of several mammal and bird species at Erling-Andechs and locations on the Arctic Circle[6]. These measurements were performed in collaboration with Eino Erkinaro (University of Oulu), who not only taught Serge ice fishing, but also raised his interest in annual changes in vole activity patterns from diurnal to ultradian to nocturnal[7]. Much later, after Serge established his Chronobiology group at the University of Groningen in 1990, ultradian rhythms and flexibility in natural activity patterns were further developed by his PhD students Menno Gerkema and Roelof Hut, who continued these themes as independent professors in Groningen.

In 1973, Serge moved to Stanford University (1973-1975) where he worked with Colin Pittendrigh, who did his PhD with the famous evolutionary geneticist Theodosius Dobzhansky. Pittendrigh's evolutionary view on rhythms, wonderfully described in his oeuvre paper The Darwinian Clock Watcher[8], greatly affected Serge as a scientist and influenced his following career steps. They published the five famous Daan & Pittendrigh papers (the 'Bible of Chronobiology'), describing fundamental properties of circadian systems[9,10,11,12,13]. In an attempt to reconcile Aschoff's view of parametric circadian entrainment through period changes with Pittendrigh's view of non-parametric entrainment through phase shifts, Serge calculated velocity response curves from phase response curves. This showed that with increasing light pulse duration, the advance portion of the phase response curve would compress, while the delay portion would expand[10]. This was much later confirmed by Serge's PhD student Marian Comas[14], who confirmed that this would eventually lead to lengthening of the circadian period as described by 'Aschoff's rule'. Non-parametric and parametric entrainment was fully reconciled when Domien Beersma modelled natural entrainment of ground squirrels, diurnal burrowing rodents that never see dawn or dusk and therefore could only entrain by tuning intrinsic period to 24-h[15,16]. Serge was notably proud of this insight and presented the merger of Aschoff's and Pittendrigh's entrainment models during the memorable Pittendrigh lecture at the 1998 meeting of the Society for Research on Biological Rhythms. The lecture was a wonderful historic portrait of these 'founding fathers' of

Chronobiology and from that moment on the series came to be called the Pittendrigh-Aschoff lectures. After his lecture, Anna Wirz-Justice immediately jumped on Serge and hijacked the written text, only to give it back after Serge promised to publish it in the Journal of Biological Rhythms[17]. In the biography of Aschoff, Serge further elaborated on the mutual friendship and cross-fertilization between Aschoff and Pittendrigh[18]. This biography turned out to be Serge's last publication and he was emotionally touched holding its first copy in his hands, only two months before he died.

Serge was fascinated by the functional relevance of rhythms and he contacted Rudi Drent, an expert in field ecology at the University of Groningen. Serge was appointed at the University of Groningen in 1975, where he remained throughout his career despite several external offers. He aimed to quantify costs and benefits of rhythms in the field and to trace selective forces leading to rhythmicity. Drent and his group were unravelling reproductive behavior, quantifying energy income and expenditure of reproducing animals in the field. Drent and Daan teamed up, helped by a small army of PhD students (Tinbergen, Dijkstra, Gerkema, Masman and many others), and wrote the citation classic "The Prudent Parent"[19], evaluating the adaptive value of phenotypic variation in clutch size, laying date and chick growth. Following up on David Lack, they clarified how proximate and ultimate factors intertwine. An important conceptual step that Serge made was that, in a seasonal environment, the clutch size decision maximizing fitness must be linked to time of year because offspring fitness declines over the breeding season. Parents building up condition have to trade off the time it takes to produce an extra egg against the fitness loss of the whole clutch by laying later. This is the reason that animals should breed before, and not at the annual food peak; a consequence not often recognized.

Figure 2. Serge releasing a kestrel at Lauwersmeer (1980, photo: Anna Wirz-Justice)

After Serge became associate professor (1985) and founded his Chronobiology group (1990), the idea was refined by including seasonal variation in food, replacing time needed to build up condition by an energetic limit of 4 x BMR, and parental fitness cost of foraging based on experimental data of his kestrel system[20,21,22]. To learn quantification of energy expenditure, Serge and his family visited his friend and collaborator Jim Kenagy in 1982 (University of Washington, Seattle). They developed the theme of 'Time and Energy in Behaviour', which became central to Serge's further work and named the first Erasmus Summer School in

Chronobiology that he organized in Groningen (1991). Because animals have to rely on relevant parameters that they are able to measure, it is important to know their physiological possibilities and ecological situation. Therefore, Drent and Daan introduced the idea of capital and income breeders in the Prudent Parent paper, a concept stimulating many ecologists. Serge's group tested these basic ideas in kestrels experimentally at the Lauwersmeer area, close to his farm house in Morra, which served as a field station (Fig.2). These kestrel studies are amongst the most important ecological studies quantifying energy expenditure, time budgets, and fitness consequences of behavioral decisions related to clutch size, sex ratio, and lay date, and Serge's concepts stimulated the field of evolutionary eco-physiology tremendously.

Figure 3. Serge at Kapp Martin, Svalbard (1978, photo: Joost Tinbergen)

Serge also followed his interest in circadian rhythms. When he joined Drent's goose expedition on Svalbard, he studied the daily timing of cliff jumping in young Brunnich's Guillemots[23] (Fig.3). He showed that young guillemots found safety in numbers by synchronizing their jumping. Predators thus promote an evolutionary basis for circadian timing of behavior! Serge further explored similar examples of adaptive daily timing[24]. Voles turned out to have a short term (2-3h), ultradian activity rhythm, which is synchronized in the field[25,26]. Possibly, voles could also profit from 'safety in numbers' for their predator: the kestrel! It marks Serge's view on science that such hypotheses should not remain 'adaptive story telling', but should be experimentally tested. A large group of researchers from two institutes, including Serge's wife Ruth Hohe, took on an ambitious project. They observed hunting success of raptors while simultaneously measuring above-ground vole densities every 15 min. The data showed that predators increase their efficiency by synchronizing to the vole rhythm and hence voles did not find 'safety in numbers' (at the time it was unusual to put many authors on a paper)[27].

In 1980, Serge and Aschoff organized a crucial symposium for chronobiology, at the Ringberg castle[28]. Jürgen Zulley (Munich) presented data on sleep timing under conditions of temporal isolation, and Alex Borbély (Zürich) showed data on increased sleep intensity after sleep deprivation. This inspired intense discussion with Serge's later collaborators Gerard Groos and Anna Wirz-Justice (Basel), resulting in the basic concept of the two-process model of sleep

regulation (Fig.4). The need for sleep was suggested to increase during waking and to decrease during sleep, and the termination of sleep was thought to be influenced by a circadian clock.

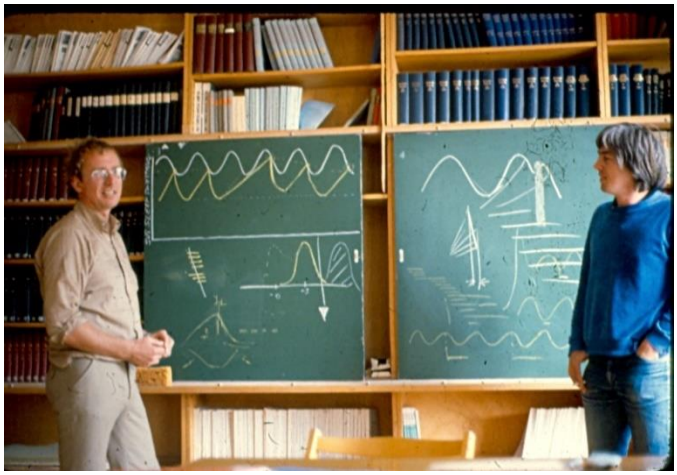

Figure 4. Serge discusses his first diagram of the two-process model with Gerard Groos in Andechs, Germany, the day after the Ringberg meeting where Alex Borbély introduced the idea (1980, photo: Anna Wirz-Justice)

Unaware of these developments, the Biological Psychiatry group of Rudi van den Hoofdakker in Groningen was searching for explanations for the positive mood effects of sleep deprivation in depressed patients. At a meeting in Munich, Anna Wirz-Justice told Domien Beersma, a member of Rudi's group, that "Serge Daan at Groningen University had a model that could explain everything". Upon return to Groningen, Domien contacted Serge, and they started intensive collaboration. The Psychiatry group owned one of the few computers in Groningen and Serge and Domien had weekly meetings discussing model simulations. The conceptual model was extended with an upper threshold and many datasets were included. In collaboration with Alex Borbély, Irene Tobler and Peter Achermann in Zürich a quantitative two process sleep model developed[29]. Anna Wirz-Justice and Rudi van den Hoofdakker saw the possibilities of the model to understand mood responses of depressed patients by sleep restriction and deprivation. Derk-Jan Dijk, a PhD student of Serge, performed crucial experiments to fill in important aspects of the model. Marijke Gordijn worked on clinical aspects of sleep and circadian rhythms and later founded an applied chronobiology company. Annual meetings between Zürich, Groningen and Basel were feasts of inspiration, but Serge was also known to have strong opinions in the scientific debate. Discussions with the Harvard group of Chuck Czeisler (one vs. two oscillators; strong vs. weak resetting) were good examples of this. These discussions made a long lasting impression on both Serge and Chuck. In his 2017 EBRS lecture Chuck referred to this as an 'important learning experience', while kindly reminding the audience of the scholarly capacity of Serge. Although it certainly strengthened the research quality of both groups, it also must have caused considerable discomfort to the people involved.

The success of sleep research was partly fueled by Serge's old love: hibernation. At the time, the function of sleep was unknown and some considered it to be just 'wasting time'. If one could show that animals pay a large amount of energy in order to sleep, then sleep must serve an important evolutionary benefit. Inspired by Sara Hiebert's work on hummingbirds, showing a few hours of euthermic 'rest' after torpor, Serge hypothesized that the birds might actually

be sleeping to recover from sleep deficit during torpor. This idea could not only functionally explain the enigmatic euthermic arousals from torpor, but it could also show that hibernators are 'warming up to sleep'. Brian Barnes (University of Alaska) and PhD student Arjen Strijkstra measured the first EEG during hibernation in Arctic ground squirrels and indeed showed that euthermic arousals were mainly spent sleeping with deeper sleep after longer torpor[30]. Craig Heller's group (Stanford University) worked on the same hypothesis independently, which generated many papers and friendships.

To find an evolutionary benefit of circadian organization, Serge determined fitness of mice with clock malfunctions together with Kamiel Spoelstra and his son Moritz and daughter Berte. They released hundreds of mice in enclosures in Bubonizi (Russia)[31] and Princeton (USA)[32]. While the data showed that a functional clock clearly had fitness benefits, the mice also showed temporal niche switching. Serge and Roelof hypothesized that limited food could have triggered diurnality. Could there be a metabolic sensitive slave oscillator downstream from the SCN? Could there be two oscillators after all? The old data from the Andechs bunker studies, archived in Serge's office, might contain a clue: Aschoff and Wever always used body temperature as a phase marker, but never as an indicator of metabolic rate. It turned out that the human sleep-wake cycle indeed slowed down with lower body temperature, suggesting that metabolic rate may affect human circadian organization[33]. Serge had re-analyzed those data together with Ken-Ichi and Sato Honma, whom he knew well from the many Sapporo meetings and who became long standing collaborators and friends of Serge and Ruth.

Serge was not only a clever scientist, but also a generous person. Together with his wife Ruth, he created a warm atmosphere for his group members by organizing numerous garden dinners. Many colleagues attended, and Serge would thank specific people for their contributions with presents and flowers. In addition, Ruth and Serge had many colleagues staying over at 'Villa Later', where rich dinners formed the center of unforgettable scientific discussions. He also served the academic community with endless energy. He was a member of more than 90 boards and committees for journals, societies, funding agencies and evaluations. He was associate editor of the Journal of Biological Rhythms (1984-1995) and he was very grateful to remain in its Advisory board until he died. For the University of Groningen he served as Director of the BCN-Master Program, Faculty Vice-Dean (2001-2004), Dean (2007-2009), and Prorector (2008-2009). He modernized the University by installing a tenure-track system, and the Rosalind Franklin program for women in science, from which Martha Merrow received her appointment in Groningen.

Serge received many awards, but he was notably proud of 'Aschoff's rule' (which he received from Chuck Czeisler in 2002), the University of Groningen Silver Medal (2006), and most of all, the International Prize for Biology (Japanese Society for the Promotion of Science), which he received from the Emperor of Japan. Serge was also very excited when colleagues would receive a prize. This was especially true when he heard that Rosbash, Hall and Young received the 2017 Nobel Prize for their work on circadian rhythms. Serge Daan was Professor of Chronobiology and Professor of Ethology and held the Niko Tinbergen Distinguished Chair in Behavioral Biology. He was a member of the Hollandsche Maatschappij der Wetenschappen, Fellow of the Royal Society of Canada, and Knight in the Order of the Dutch Lion. He supervised 42 PhD students and 16 post-docs, most of whom went on to scientific careers. He connected

chronobiology and ecophysiology from an evolutionary perspective, including the mutual dependency of mechanism and function. His work created opportunities for many of us and will influence future generations of biologists. The world has lost a great scientist, and many of us have lost a dear colleague, mentor and friend.

Published in Journal of Biological Rhythms 2018; 33(2):111-116.

REFERENCES

[1] Beutler A and Frør E. Agama stellio daani, a Greek lizard, named after S. Daan, Mitt. Zool. Ges. Braunau 1980; 3: 255-290.

[2] Daan S. Activiteit en lethargie van winterslapende zoogdieren. PhD thesis Cum Laude, University of Amsterdam (promotor Prof.dr. A. Punt). http://permalink.opc.uva.nl/item/000312225, 1973.

[3] Daan S. Activity during natural hibernation in three species of Vespertilionid bats. Netherlands Journal of Zoology 1973; 23: 1-71.

[4] Daan S. Periodicity of heterothermy in the garden dormouse, Eliomys quercinus (L.). .Netherlands Journal of Zoology 1973; 23: 237-265.

[5] Menaker M. Endogenous rhythms of body temperature in hibernating bats. Nature 1959; 184: 1251-1252.

[6] Daan S and Aschoff J. Circadian rhythms of locomotor activity in captive birds and mammals: their variations with season and latitude. Oecologia 1975; 18: 269-316.

[7] Erkinaro E. The seasonal change of the activity of Microtus agrestis. Oikos 1961; 12: 157-163.

[8] Pittendrigh CJ. Temporal organisation: reflections of a Darwinian clock-watcher. Annual Reviews in Physiology 1993; 55: 17-54.

[9] Daan S and Pittendrigh CJ. A functional analysis of circadian pacemakers in nocturnal rodents. II. The variability of phase response curves. Journal of Comparative Physiology A 1976; 106: 253-266.

[10]Daan S and Pittendrigh CJ. A functional analysis of circadian pacemakers in nocturnal rodents. III. Heavy water and constant light: homeostasis of frequency? Journal of Comparative Physiology A 1976; 106: 267-290.

[11]Pittendrigh CJ and Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. I. The stability and lability of spontaneous frequency. Journal of Comparative Physiology A 1976; 107: 223-252.

[12]Pittendrigh CJ and Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. IV. Entrainment: pacemaker as clock. Journal of Comparative Physiology A 1976; 106: 291-331.

[13]Pittendrigh CJ and Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. V. Pacemaker structure: a clock for all seasons. Journal of Comparative Physiology A 1976; 106: 333-355.

[14]Comas M, Beersma DG, Spoelstra K and Daan S. Phase and period responses of the circadian system of mice (Mus musculus) to light stimuli of different duration. Journal of Biological Rhythms 2006; 21: 362-372.

[15]Hut RA, Van Oort BEH, Daan S. Natural entrainment without dawn and dusk: the case of the European ground squirrel (Spermophilus citellus). Journal of Biological Rhythms 1999; 14: 290-299.

[16]Beersma DGM, Daan S and Hut RA. Accuracy of circadian entrainment under fluctuating light conditions: contributions of phase and period responses. Journal of Biological Rhythms 1999; 14: 320-329.

[17]Daan S. Colin Pittendrigh, Jürgen Aschoff and the natural entrainment of circadian systems. Journal of Biological Rhythms 2000; 15: 195-207.

[18]Daan S. Die Innere Uhr des Menschen. Jürgen Aschoff (1913-1998), Wissenschaftker in einem bewegten Jahrhundert. Reichert Verlag, Wiesbaden, Germany, 2017.

[19]Drent RH and Daan S. The prudent parent – Energetic adjustments in avian breeding. Ardea 1980; 68: 225-252.

[20]Daan S, Dijkstra C, Drent R. and Meijer T. Food supply and the annual timing of avian reproduction. In: Acta XIX Congressus Internationalis Ornothologic, Vol 1 (ed. H.Quellet) pp. 392-407 University of Ottawa Press, Ottawa, 1989.

[21]Daan S, Deerenberg C and Dijkstra C. Increased daily work precipitates natural death in the Kestrel. Journal of Animal Ecology 1996; 65: 539-544.

[22]Daan S and Tinbergen JM. Adaptation of life histories. In: J.R.Krebs & N.B.Davies, Behavioral Ecology. 4th Edition, Blackwell, 311-333, 1997.

[23]Daan S and Tinbergen J. Young guillemots (Uria lomvia) leaving their Arctic breeding cliffs – A daily rhythm in numbers and risk. Ardea 1979; 67: 96-100.

[24]Daan S. Adaptive daily strategies in behaviour. In: Handbook of Behavioral Neurobiology 4, Biological Rhythms (ed. Jürgen Aschoff). ISBN 0-3-6-40585-7, 1981.

[25]Daan S and Slopsema S. Short-term rhythms in foraging behavior of the common vole, Microtus arvalis. Journal of Comparative Physiology 1978; 127: 215-227.

[26]Gerkema MP and Daan S. Ultradian Rhythms in Behavior: The Case of the Common Vole (Microtus arvalis). In: H. Schulz & P. Lavie (eds.) Ultradian Rhythms in Physiology and Behavior, Springer, Berlin, pp 11-31, 1985.

[27]Raptor group RUG/RIJP. Timing of vole hunting in aerial predators. Mammal Reviews 1982; 12: 169-181.

[28]Aschoff J, Daan S and Groos GA, eds. Vertebrate Circadian Systems: Structure and Physiology. The theme of a meeting in October 1980 at Schloss Ringberg, Proceedings in Life Science, Springer, Berlin, 1982.

[29]Daan S, Beersma DG and Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. American Journal of Physiology - Regul.Integr.Comp.Physiol. 1984; 246: R161-R183.

[30]Daan S, Barnes BM and Strijkstra AM. Warming up for sleep – ground-squirrels sleep during arousals from hibernation. Neuroscience Letters 1991; 128: 265-268.

[31]Daan S, Spoelstra K, Albrecht U, Schmutz I, Daan M, Daan B, Rienks F, Poletaeva I, Dell'Omo G, Vyssotski A, Lipp HP. Lab Mice in the Field: Unorthodox Daily Activity and Effects of a Dysfunctional Circadian Clock Allele. Journal of Biological Rhythms 2011; 25: 118-129.

[32]Spoelstra K, Wikelski M, Daan S, Loudon A, Hau M. Natural selection against a circadian clock gene mutation in mice. Proceedings of the National Academy of Sciences 2016; 113: 686-691.

[33]Daan S, Honma S, Honma K. Body temperature predicts the direction of internal desynchronization in humans isolated from time cues. Journal of Biological Rhythms 2013; 28: 403-411.

SLEEP-WAKE
Research in The Netherlands

Volume 29, 2018

PhD theses

HOME SLEEP MONITORING

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Sleeping habits have changed throughout history following human progress and technological development. While we slept an average of nine hours per day in 1900, today we hardly get six and a half. To make matters worse, epidemic stress and obesity are contributing to the quick rise of sleep disorders such as insomnia and sleep apnea, with an important percentage of the population either suffering from a clinically relevant disorder, or nonetheless reporting dissatisfaction with sleep.

Luckily, perception and recognition of the importance of sleep is changing. Many of the symptoms of sleep deprivation and other sleep disorders are now recognized as actual sleep-related issues, leading to an earlier diagnosis and timely treatment. The assessment of sleep disorders is traditionally performed in dedicated sleep laboratories, where trained technicians apply a plethora of sensors to monitor overnight physiological processes of the subjects under investigation. However, it has some limitations, such as lack of applicability for extended periods of time, or difficulty to use in a home environment. Progress in sensor technology over the last decades has partially alleviated this problem, with the development of ambulatory monitors for some sleep-related parameters. The simplest and arguably most popular of such ambulatory monitors, actigraphy, consists of the measurement of gross body movements by means of a limb-worn accelerometer. Given its relative comfort and ease of use, actigraphy has met relative success in the clinical assessment of sleep-wake disturbances. Interestingly, it was also the first technique to make its way to non-clinical, consumer-grade sleep tracking (CST) devices.

The recent and growing interest in sleep by the general public has led to an increasing demand for sleep tracking devices which can be used without assistance or intervention of a physician. Although the attempt to provide users with information about a period mostly characterized by unconsciousness can seem commendable, there is light and shadow when it comes to the widespread use of these devices. They have the potential to play an invaluable role in educating consumers on the importance of having enough sleep time, and on how to introduce and maintain healthy sleep routines. But the fact remains that they are based on a surrogate measure of sleep, and furthermore that most of their marketing claims lack proper validation or are outright implausible. This aspect in particular may have seriously negative consequences for individuals with sleep-related concerns - but yet undiagnosed disorders - who will seek an explanation with these devices before consulting with medical professionals, or worse, for asymptomatic individuals with a hidden primary sleep disorder.

Despite the low level of evidence for CST devices, the physiological basis behind modern sensors which have the ability to measure cardiorespiratory activity during the night is, in theory, solid. Research has shown a strong link between sleep, sleep disorders, and autonomic

nervous system (ANS) activity, which is, in turn, correlated with measures such as heart rate variability (HRV) and respiratory rate variability (RRV) that could be derived from such sensors. In particular, the topic of automatic detection of different sleep stages, usually divided in Wake, REM sleep, `light sleep' (N1 and N2) and `deep sleep' (N3) has received increasing attention over the last decade, but performance remains modest.

Accordingly, the first objective of this thesis is to develop methods to increase the performance of sleep stage classification and bring it closer, for healthy subjects, to the gold standard polysomnography (PSG). This work is separated in three parts.

The first part deals with the analysis of physiological signals that allow features discriminative of sleep stages to be extracted. Chapter 2 describes a method to precisely localize QRS complexes in electrocardiography (ECG) signals, essential for the accurate measurement of HRV. The proposed algorithm achieves a very low localization error, and is robust to severe signal degradation, common in ambulatory acquisitions of ECG. Chapter 3 describes a method which allows body movements to be estimated from artifacts in ECG and respiratory inductance plethysmography (RIP) signals. It alleviates the need to wear an additional sensor in case cardiac and/or respiratory measures are performed. Equally important, it allows retrospective data sets for which actigraphy was not registered to be used in the development and validation of sleep staging algorithms which make use of body movement information.
The second part focuses on methods for automatic sleep stage classification. Chapter 4 describes an algorithm which uses a large set of HRV and RRV features extracted from ECG and RIP, achieving a moderate agreement for four-class sleep stage classification (Wake/REM/N1 and N2/N3) of healthy subjects.

The third part explores the use of advanced probabilistic methods to further improve classification performance. Chapter 6 explores the use of Markov chains which exploit the structured nature of sleep and can use features discriminative not only of different sleep stages, but also of stage transitions and sleep stage continuity. This chapter shows that discriminative models like conditional random fields (CRF) are better suited for this task when compared to other popular probabilistic classifiers such as the simple epoch-based linear discriminants used in Chapter 4, and Hidden Markov Models (HMM) often described in literature. CRF classifiers are further extended in Chapter 7 to the problem of sleep stage classification, achieving a performance improvement over the classifier described in Chapter 4. In addition, this chapter shows how these classifiers are better suited for the more complex task of five-class classification (Wake/N1/N2/N3/REM), the standard for sleep scoring in traditional PSG.

The second objective of the thesis is to prove that these methods can work with sensors that are less obtrusive. Although ECG and RIP provide the means to measure ANS characteristics during sleep, they are not exactly compatible with long-term, unassisted monitoring. Chapter 5 validates a sleep stage classifier which uses HRV features derived from a photoplethysmography sensor, achieving a reasonable performance on four-class classification of healthy middle aged adults and better performance than actigraphy for Sleep/Wake classification.

Finally, and given the limited amount of evidence regarding the use of this technology in clinically relevant populations, the third and final objective of the thesis is to evaluate whether these methods can be applied in subjects suffering from a sleep disorder. This will provide first evidence of whether the technology has the potential to ever be used in clinical practice. Chapter 7 explores the performance of CRF using HRV and RRV features on patients diagnosed with obstructive sleep apnea, achieving a reasonable performance for four-class classification. With a veritable explosion in the offer and adoption of wearable monitors, many of which emphasize sleep and sleep quality as one of the key health factors, together with an increasing awareness that sleep is a fundamental element in balanced living, it is inevitable that home sleep monitoring technology will reach widespread use in the next few years, perhaps before it is even adopted and endorsed by (medical) sleep associations. The research agenda in this area should focus on validating and further improving it on a wider patient population and also on understanding its fundamental limitations. Furthermore, it should be redirected from a simple monitoring and reporting function to a tool that can give users in general, and disordered patients in particular, actionable suggestions, providing the means to help the millions of people suffering from sleeping disorders or complaints.

P. Fonseca. Home Sleep Monitoring. PhD thesis, Eindhoven University of Technology, 2018

MELATONIN TREATMENT IN CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS: TOWARDS PERSONALIZED SLEEP MEDICINE

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Personalized sleep medicine seeks to improve the tailoring and timing of preventive and therapeutic measures using genetic, biomarker, phenotype and psychosocial characteristics. This information is used to give the right patient the right drug at the right dose at the right time. This thesis evaluated and developed different methods to improve personalized sleep medicine.

In chapter 2, we reviewed the literature on personalized sleep medicine for circadian rhythm sleep-wake disorders (CRSWD). Particularly within sleep medicine, the genetic and biomarker pillars are less developed compared to other medical disciplines, mainly because sleep is a very complex phenotype with multiple genetic regulation mechanisms. In a clinical setting, genetics are not yet used, and biomarkers are used only sporadically and are limited to melatonin. However, the other two pillars are very established within the sleep medicine field. In particularly, the use of PSG, actigraphy and questionnaires yields much information for the diagnosis and optimal treatment of a variety of sleep disorders. To strengthen further the (pharmaco-)genetic and biomarker pillars, technology must further evolve, applied medical sleep research must reveal a clear medical benefit to diagnosis and treatment options for patients, and the costs of analysis must be reduced. Although several studies have been performed indicating that certain genetic factors are associated with specific sleep problems, more research is absolutely needed to implement the findings of these studies in clinical practice.

In chapter 3, we retrospectively analyzed 1848 diagnostic 5-point curves to evaluate these DLMO calculations, and we studied the correlations between sleep onset as measured by diaries or polysomnography (PSG) and DLMO. DLMO could be determined in 76.2% (n=1408) and could be reliably measured in saliva conveniently collected at home. DLMO significantly differed between different age groups, and it increased with age. Pearson's correlations between DLMO and sleep onset measured with PSG or with a diary were moderate, and diaries and PSG sleep onset time should not be used to estimate DLMO. The determination of DLMO before treatment is further discussed in chapter 4. Treatment of CRSWD can include light therapy, chronotherapy and melatonin. Exogenous melatonin is increasingly being used in patients with insomnia or CRSWD. Although pharmacopoeias and the European Food Safety Authority (EFSA) recommend administering melatonin 1 or 2 h before the desired bedtime, several studies have shown that melatonin is not always effective if administered according to this recommendation. Crucially for the optimal treatment of CRSWD, melatonin and other treatments should be administered at a time related to the individual circadian phase. If not administered according to the individual patient's circadian timing, melatonin and other treatments might not only be ineffective, but they might even result in contrary effects. In

chapter 5 a follow-up study was performed to see if sleep timing can predict DLMO in patients with a possible CRSWD and if this differ in the various types of CRSWD, age en gender. Correlations were only moderate between DLMO and sleep onset in the complete dataset, but increased in patients with delayed sleep-wake phase disorder (DSWPD), DSWPD patients with a regular sleep pattern and in patients with advanced sleep-wake phase disorder (ASWPD), respectively r= 0.542, 0.657, 0.728 and 0.814. In DSWPD patient with a regular sleep pattern mid-sleep correlated very strong r=0.839 with DLMO. Correlation in other CRSWD were not significant. DLMO, sleep-onset and age were discriminated most between sleep-wake disorders.

In chapter 6, we performed an observational study of melatonin treatment satisfaction using self-reported, online melatonin treatment satisfaction questionnaires (MTSQs) about patient perspectives regarding their treatment satisfaction. The majority of patients, 78.8% (n= 160), were satisfied with their melatonin treatment satisfaction, although this number significantly diminished with increased age. Patient treatment satisfaction increased with improvement of sleep onset, sleep maintenance, sleep-offset, improved mood, less daytime sleepiness and less tiredness. Patients with prior headache complaints reported significantly fewer headaches during melatonin treatment. The melatonin dose increased significantly with increased age. Questionnaire outcomes were used to optimize treatment further if necessary. More research is necessary in older adults to optimize melatonin treatment because the melatonin dose used might be too high.

Genetic research is an important pillar of personalized medicine. In chapter 7, we developed a protocol for the automated extraction of genomic DNA from saliva samples using the QIAxtractor. These samples were collected on Salivettes, which are also used for DLMO measurements. Normally, genomic DNA is acquired by venipuncture, but this is an invasive procedure not always suitable for children and persons with intellectual disabilities. The developed, fully automated method provided genomic DNA of a sufficient quantity and quality to perform downstream real-time PCR tests. In chapter 8, we tested the hypothesis that inter-individual metabolization of exogenous melatonin depends on the occurrence of a specific single nucleotide polymorphism (SNP) in the *CYP1A2* gene. In a pilot study, we found that individuals with the *CYP1A2*1F* C/C genotype had higher circulating melatonin levels, compared to other genotypes. These results warranted the start of a follow-up to test clinically poor metabolizers to determine whether they also have these SNPs in the *CYP1A2* gene, which was performed in chapter 9. In some of the patients with intellectual disabilities (IDs) and sleep problems, the initial good response to melatonin disappeared within a few weeks after starting treatment. In these patients, the melatonin levels at noon were extremely high (>50 pg/mL). We hypothesized that the disappearing effectiveness was associated with slow metabolization of melatonin because of an SNP of the *CYP1A2* gene. In all of the patients, the salivary melatonin levels at noon were >50, or the melatonin half time was >5 h. An SNP was found in eight of 15 patients. The *1C allele was found in two patients, and in six patients, the *1F allele was found. Of 15 patients with diminishing effectiveness of melatonin, seven were diagnosed with autism spectrum disorder, and in four of these patients, an SNP was found. The other eight patients were known to have genetic syndromes. In six of these patients, their behavior was considered to be the autistic type, and in three of them, an SNP was found. This

finding could provide a new direction for research into the genetic background of autism. It is very likely that epigenetic factors control the expression of the *CYP1A2* gene.

General conclusions

We are going towards personalized medicine in CRSWD and the contribution from this thesis are: melatonin is an effective biomarker from which reliable DLMO calculations can be obtained. Sleep parameters can only be used to determine DLMO in patients with advanced sleep-wake phase disorder and patients with delayed sleep-wake phase disorder which have a regular sleep pattern. DLMO should be determine and used in addition to the sleep parameters for diagnosis and CRSWD. Questionnaires can be used to evaluate melatonin treatment. Genomic DNA can be isolated with an automated method from a non-invasive sample that is also used for DLMO measurements. SNPs in the *CYP1A2* gene influence the metabolization rate of exogenous melatonin. However these SNP's are not solely responsible for the loss of melatonin treatment response.

SLEEP IN ELITE ATHLETES

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Elite athletes have high activity profiles and thus depend rather heavily on the recovery and performance benefits that can be attained from good quality sleep. Considering that sleep is the recovery strategy par excellence and indispensable for overall health and performance capacity, the aim of the thesis was to (1) shed light on sleep quantity and quality in elite athletes, (2) identify factors that adversely affect their sleep, (3) extend knowledge on the effects of sleep on performance, and (4) investigate promising interventions to optimize sleep.

Aim 1: Characterizing sleep of elite athletes

Initial evidence of objective estimates of actigraphy-based sleep quantity and sleep quality indicated that athletes' sleep is inferior to that of non-athlete controls and potentially insufficient for adequate recovery and optimal performance[1]. In order to provide a more complete picture of sleep in elite athletes, we sought to extend this information by (1) also assessing subjective estimates of sleep quantity and quality (questionnaire and diary-based), (2) using an actigraphy threshold with higher sensitivity to sleep in assessing objective sleep quantity, and (3) providing preliminary insight in (EEG-based) sleep stage distributions. Sleep was monitored among a large cohort of 98 elite athletes during seven consecutive days of habitual training using daily morning- and evening diaries, wrist-worn actigraphy and a wireless one-channel EEG headband sensor.

In general, elite athletes were found to be healthy sleepers. However, based on sub-clinical questionnaires, the study reported in **Chapter 2** showed that a vast minority of 41% did classify as poor sleeper (PSQI cutoff poor sleeper ≥ 5[2]) and that 12% was identified as having a potential sleep disorder (HSDQ cutoff ≥ 2.02[3]). Restless leg symptom / periodic limb movement disorder (RLS/PLMD) was the most frequently reported sleep disturbance. Daily self-reports revealed an average sleep duration of 8 hours, well within the recommended range of 7-9 hours[4,5]. Yet, self-reported sleep onset latency (20 minutes) and wake after sleep onset (13 minutes) revealed areas for improvement. Finally, diary studies revealed that, with the given amount of sleep, athletes felt only moderately refreshed, alert, and vigorous in the morning[6].

The actigraphy-based sleep estimates reported in **Chapter 3** depicted a similar pattern. As may be expected, absolute values did differ from subjective measures[7-9]. The seven-day average sleep duration was close to 8 hours. Wake after sleep onset can be improved (33 minutes) and sleep efficiency (88%) was lower than the average for this age group (i.e., 92%)[10]. The latter finding indicates relatively fragmented sleep. During 22% of the nights, sleep efficiency scores were below 85%, a threshold that is considered the upper limit for poor sleep[11].

Analysis of the EEG-based sleep stage distributions revealed typical values for the amount of light and REM sleep[10,12] (Chapter 3). However, in line with the high activity level of elite

athletes[13], the amount of deep sleep was relatively high (21%). According to the recovery hypothesis of sleep, deep sleep adapts to the body's current need for recovery. That is, the amount of deep sleep typically increases with sustained wakefulness or following strenuous exercise[14]. As such, the relatively high proportion of deep sleep may reflect an elevated recovery need in elite athletes.

Aim 2: Identifying sleep jeopardizing factors

In the literature, individual and environmental factors such as jet lag[15], psychological and physiological pre-sleep arousal[16-18], training and competition schedules[16,19-21], have all been related to compromised sleep quantity and quality in athletes. However, a broad assessment of elite athletes' general sleep hygiene practices (i.e., daytime behaviors and environmental conditions that facilitate good quality sleep) is lacking. Quantifying the presence (or absence) of such practices – and calculating their association with sleep quality – can aid in the development of tailored sleep hygiene guidelines for elite athletes. Therefore, **Chapter 2** reported self-reported estimates of sleep hygiene and sleep in 98 elite athletes during seven consecutive days of training.

Results of a general questionnaire showed that athletes' sleep hygiene practices were generally adequate. Still, athletes reported difficulties to keep a regular sleep-wake pattern, experienced psychological strain in the evening (e.g., bedtime stress and worry), and engaged in activating pre-sleep activities. These general questionnaire results were complemented by a detailed seven-day diary assessment of sleep hygiene practices, where again, only a few behaviors appeared to be suboptimal. These suboptimal behaviors included late-evening consumptions of heavy meals and caffeinated beverages, as well as engagement in sedentary activities that involved artificial light exposure in the evening (75% of nights). A notable observation was that athletes infrequently engaged in daytime sleep (naps; 18% of days). Correlation analyses indicated that adequate sleep hygiene was indeed associated with better sleep quality and less disordered sleep among athletes. This is in line with reports among non-athletes[22].

Another factor that may impact sleep of elite athletes is training load. Athletes follow intense training programs that are designed to stimulate psychophysiological adaptation, so that performance capacity can be enhanced. The relation between exercise and sleep appears to be inconclusive. On the one hand, exercise can improve sleep quality[23]. On the other hand, there is evidence suggesting that prolonged periods of extreme exercise intensity may worsen sleep quantity and quality[13,24,25]. To further the understanding of whether increases in training benefit or jeopardize sleep quantity and quality in elite athletes, **Chapter 3** investigated how day-to-day variations in self-reported training load were reflected in actigraphy-based sleep estimates and one-channel EEG-based sleep staging. Self-reports of training load and sleep estimates were collected during seven consecutive days of training among a cohort of 98 elite athletes. Results revealed moderate training load (mean = 5.4, scale 1-10) across all seven days of assessment. Large intra-individual differences showed that low, medium and sometimes high levels of training load were covered. Despite relatively large variation within individuals, day-to-day differences in self-reported training load were not reflected in actigraphy-based sleep measures (e.g., sleep duration, sleep efficiency), nor in EEG-based sleep stage distributions.

Aim 3: Establishing the effects of sleep on athletic performance

While still in its infancy, prior research suggests a deterioration of cognitive and athletic performances following (partial) sleep deprivation[26], while performance appears to improve following sleep extension[27,28]. Importantly, in their daily life, athletes usually encounter subtle day-to-day changes in sleep that are smaller than the changes employed in experimental studies (e.g., ± 4 hours). Given the lack of research, the extent to which such small changes in sleep may indeed be reflected in (sport-specific) performance as yet remains unclear. Against this background, **Chapter 4** investigated the extent to which rather mild, naturally occurring day-to-day variations in sleep quantity and sleep stages (sleep quality) are reflected in the cognitive and sport-specific performance of elite athletes. The effect of (changes in) actigraphy-based sleep quantity and one-channel EEG-based sleep stage duration on psychomotor performance as well as performance of fine- and gross motor skills was assessed among 98 elite athletes during three non-consecutive occasions. Results revealed that small changes in total sleep time were immediately reflected in small but significant changes in psychomotor vigilance (i.e., reaction time) the following day. Additionally, small and inconsistent effects of sleep quantity and sleep stages on gross motor skill performance were observed, but no effects were established for fine motor skill performances.

Aim 4: Optimizing Sleep

While there is good reason to believe that optimized sleep may benefit recovery, overall health and well-being, and performance capacity in athletes, the number of interventions tested among a healthy population such as elite athletes, is limited. Thus far, the few studies aiming at sleep optimization in athletes concern interventions focusing on nutrition[29], specific sleep hygiene practises[30-32], brain-wave entrainment[33], or sleep extension[27,28]. Based on the analyses of elite athletes sleep and potential sleep-disturbing factors reported in Chapters 2 and 3, Chapters 5a, 5b, 5c and 6 present practical sleep hygiene guidelines (Chapter 5a) and report experimental tests of several chronobiological sleep interventions (Chapters 5b, 5c and 6).

For many, adequate sleep hygiene practices are the very foundation for good quality sleep. Sleep hygiene are the “conditions and practices that promote continuous and effective sleep” (p. 347, American Academy of Sleep Medicine 2001[34]). To that end, in **Chapter 5a** sleep hygiene guidelines that are tailored to the unique demands that elite athletes face in their daily routines are provided. These sleep hygiene recommendations were organized around regularity, stimulants and substances, psychological strain, active (pre-) sleep behavior and environment. Furthermore, sleep as well as sleep hygiene practices may differ considerably during periods of training and competition and may depend on the sleep location. Therefore, a smartphone application was developed that athletes can use to self-monitor their sleep hygiene and sleep quality during different periods (training versus competition) and environmental circumstances (e.g., sleep location).

One of many factors involved in sleep initiation and maintenance is thermoregulation. Body temperature fluctuates during the 24 hour day. Close to sleep onset, skin temperature increases which causes vasodilatation and a drop in core body temperature. More specifically, research has shown that increasing the distal to proximal gradient in skin temperature (DPG)

before bedtime predicts sleep onset latency under strict experimental conditions[35-38]. **Chapter 5b** provides the results of a field-based pilot study that was conducted among sub-elite athletes to examine the effectiveness of distal skin warming by means of heated bed socks on DPG and its potential effect om sleep latency. Results revealed that wearing heatable socks (vs. conventional socks) during the last 30 minutes before bedtime effectively increased distal to proximal skin temperature gradient (DPG) in sub-elite athletes. However, against expectations, the augmented DPG did not result in shorter sleep onset latency or improvement of the remaining actigraphy- and one-channel EEG-based sleep estimates.

Besides temperature, the initiation and consolidation of sleep is predominantly regulated by the circadian system, which requires periodic light-dark exposure for stable entrainment to the 24 hour day[39,40]. Exposure to light in the evening, and especially to short wavelength light (e.g., emitted by electronic screens), delays circadian phase by suppressing melatonin secretion by the pineal gland[41]. In humans, melatonin indicates the biological night and is crucial for sleep initiation and maintenance[42]. In line with this observation, prior studies have shown that blocking short-wavelength light in the evening can preserve melatonin secretion and potentially improve sleep[43,44]. In **Chapter 5c**, a pilot study is described in which the effectiveness of blocking short-wavelength light in the evening on sleep under natural conditions was assessed among a group of recreational athletes. Results showed that wearing amber-lens (short wavelength blocking) glasses during three hours before bedtime had no effect on actigraphy-based sleep estimates. However, subjective estimates revealed shorter sleep onset latencies, improved sleep quality and alertness in the morning, as compared to habitual evening light exposure.

Proceeding from the promising evidence provided in Chapter 5c, **Chapter 6** showed the results of an intervention study in which evening light restriction was combined with bright light exposure in the morning. Effects of the intervention were compared to a condition that involved no light regulation. Although athletes had difficulties to keep strict bed- and wake times, which was a requirement in both conditions, results of the intervention were promising, indicating a significant reduction of 8 minutes in sleep onset latency following light regulation. When athletes kept a stricter sleep-wake schedule during both conditions, self-reported sleep onset latency was even shorter (ΔSOL = 17 minutes), and accompanied by a significant improvement in self-rated sleep quality.

Conclusion

While elite athletes appear to sleep an average of almost eight hours per night, their sleep tends to be fragmented and ratings of feeling refreshed and alert were modest at best. Subtle changes in sleep quantity were immediately visibly in cognitive performance. The current thesis shows that good sleep hygiene practices and light regulation are promising strategies in optimizing athletes' sleep and increasing their performance capacity. Reducing light exposure in the evening combined with increasing light exposure in the morning, helps to facilitate sleep onset and improve perceptions of sleep quality.

References

1. Leeder J, Glaister M, Pizzoferro K, Dawson J, Pedlar C. Sleep duration and quality in elite athletes measured using wristwatch actigraphy. J Sport Sci. 2012; 30 (6): 541-545.

2. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28 (2): 193-213.
3. Kerkhof GH, Geuke MEH, Brouwer A, Rijsman RM, Schimsheimer RJ, Van Kasteel V. Holland Sleep Disorders Questionnaire: a new sleep disorders questionnaire based on the International Classification of Sleep Disorders-2. J Sleep Res. 2013; 22 (1): 104-107.
4. Watson NF, Badr MS, Belenky G, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. Sleep. 2015; 38 (6): 843-844.
5. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's updated sleep duration recommendations. Sleep Health. 2015; 1 (4): 233-243.
6. Knufinke M, Nieuwenhuys A, Geurts SAE, Coenen AML, Kompier MAJ. Self-reported sleep quantity, quality and sleep hygiene in elite athletes. J Sleep Res. 2018; 27 (1): 78-85.
7. Baker FC, Maloney S, Driver HS. A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women. J Psychosom Res. 1999; 47 (4): 335-341.
8. Chae KY, Kripke DF, Poceta JS, et al. Evaluation of immobility time for sleep latency in actigraphy. Sleep Med. 2009; 10 (6): 621-625.
9. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. J Sleep Res. 1999; 8 (3): 175-183.
10. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004; 27 (7): 1255-1273.
11. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. Sleep. 2004; 27 (8): 1567-1596.
12. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger M, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. 6th ed. Elsevier; 2017: 15-24.
13. Driver HS, Taylor SR. Exercise and sleep. Sleep Medicine Reviews. 2000; 4 (4): 387-402.
14. Shapiro CM, Bortz R, Mitchell D, Bartel P, Jooste P. Slow-wave sleep: a recovery period after exercise. Science. 1981; 214 (4526): 1253-1254.
15. Lee A, Galvez JC. Jet lag in athletes. Sports Health. 2012; 4 (3): 211-216.
16. Lastella M, Lovell GP, Sargent C. Athletes' precompetitive sleep behaviour and its relationship with subsequent precompetitive mood and performance. Eur J Sport Sci. 2014; 14: S123-S130.
17. Juliff LE, Halson SL, Peiffer JJ. Understanding sleep disturbance in athletes prior to important competitions. J Sci Med Sport. 2015; 18 (1): 13-18.
18. Erlacher D, Ehrlenspiel F, Adegbesan OA, Galal El-Din H. Sleep habits in German athletes before important competitions or games. J Sport Sci. 2011; 29 (8): 859-866.
19. Sargent C, Roach GD. Sleep duration is reduced in elite athletes following night-time competition. Chronobiology International. 2016; 33 (6): 667-670.
20. Lastella M, Roach GD, Halson SL, Martin DT, West NP, Sargent C. Sleep/wake behaviour of endurance cyclists before and during competition. J Sport Sci. 2015; 33 (3): 293-299.
21. Fullagar HH, Skorski S, Duffield R, Julian R, Bartlett J, Meyer T. Impaired sleep and recovery after night matches in elite football players. J Sport Sci. 2016; 34 (14): 1333-1339.
22. Mastin DF, Bryson J, Corwyn R. Assessment of sleep hygiene using the sleep hygiene index. J Behav Med. 2006; 29 (3): 223-227.
23. Youngstedt SD. Effects of exercise on sleep. Clinics in Sports Medicine. 2005; 24 (2): 355-365.
24. Thornton HR, Duthie GM, Pitchford NW, Delaney JA, Benton DT, Dascombe BJ. Effects of a two-week high intensity training camp on sleep activity of professional rugby league athletes. International Journal of Sports Physiology and Performance. 2017; 12 (7): 928-933.
25. Killer S, Svendsen I, Jeukendrup A, Gleeson M. Evidence of disturbed sleep and mood state in well-trained athletes during short-term intensified training with and without a high carbohydrate nutritional intervention. J Sport Sci. 2017; 35 (14): 1402-1410.
26. Fullagar HHK, Skorski S, Duffield R, Hammes D, Coutts AJ, Meyer T. Sleep and athletic performance: the effects of sleep loss on exercise performance, and physiological and cognitive responses to exercise. Sports Med. 2015; 45 (2): 161-186.
27. Mah CD, Mah KE, Kezirian EJ, Dement WC. The effects of sleep extension on the athletic performance of collegiate basketball players. Sleep. 2011; 34 (7): 943-950.
28. Schwartz J, Simon RD. Sleep extension improves serving accuracy: A study with college varsity tennis players. Physiol Behav. 2015; 151: 541-544.
29. Halson SL. Nutrition, sleep and recovery. Eur J Sport Sci. 2008; 8 (2): 119-126.
30. Halson SL. Sleep in elite athletes and nutritional interventions to enhance sleep. Sports Med. 2014; 44 (1): 13-23.
31. Fullagar H, Skorski S, Duffield R, Meyer T. The effect of an acute sleep hygiene strategy following a late-night soccer match on recovery of players. Chronobiology international. 2016; 33 (5): 490-505.
32. Nédélec M, Halson S, Delecroix B, Abaidia A-E, Ahmaidi S, Dupont G. Sleep hygiene and recovery strategies in elite soccer players. Sports Med. 2015; 45 (11): 1547-1559.

33. Abeln V, Kleinert J, Strüder HK, Schneider S. Brainwave entrainment for better sleep and post-sleep state of young elite soccer players – A pilot study. Eur J Sport Sci. 2014; 14 (5): 393-402.
34. American Academy of Sleep Medicine. *ICSD - International Classification of Sleep Disorders, revised: diagnostic and coding manual.* Chicargo, Illinois: American Academy of Sleep Medicine; 2001.
35. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Functional link between distal vasodilation and sleep-onset latency? American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2000; 278 (3): R741-R748.
36. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Physiology: warm feet promote the rapid onset of sleep. Nature. 1999; 401 (6748): 36-37.
37. Romeijn N, Raymann RJ, Møst E, et al. Sleep, vigilance, and thermosensitivity. Pflügers Archiv-European Journal of Physiology. 2012; 463 (1): 169-176.
38. Raymann RJ, Swaab DF, Van Someren EJ. Skin temperature and sleep-onset latency: changes with age and insomnia. Physiol Behav. 2007; 90 (2): 257-266.
39. Duffy JF, Wright KP. Entrainment of the human circadian system by light. J Biol Rhythm. 2005; 20 (4): 326-338.
40. Czeisler CA, Allan JS, Strogatz SH, et al. Bright light resets the human circadian pacemaker independent of the timing of the sleep-wake cycle. Science. 1986; 233 (4764): 667-671.
41. West KE, Jablonski MR, Warfield B, et al. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. J Appl Physiol. 2011; 110 (3): 619-626.
42. Brainard GC, Hanifin JP, Greeson JM, et al. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci. 2001; 21 (16): 6405-6412.
43. Burkhart K, Phelps JR. Amber lenses to block blue light and improve sleep: a randomized trial. Chronobiol Int. 2009; 26 (8): 1602-1612.
44. Sasseville A, Paquet N, Sévigny J, Hébert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production. Journal of Pineal Research. 2006; 41 (1): 73-78.

SLEEP-WAKE
Research in the Netherlands

Volume 29, 2018

Research papers

OBJECTIVE VALIDATION OF AN AUTOMATIC OXYGEN DESATURATION DETECTOR ON A CLINICAL POLYGRAPHIC DATABASE

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INTRODUCTION

We are presenting results on the validation of an automatic oxygen saturation analysis algorithm for the scoring of desaturation events on polysomnographic (PSG) recordings. Sleep-Related Breathing Disorders (SRBD), such as Obstructive Sleep Apnea (OSA), are common sleep disorders whose diagnosis requires considerable human resources in relation to the manual review of the PSG. Moreover manual review is prone to errors due to tiredness and scoring subjectivity. Clinical findings over the last years have uncovered the impact of SRBD on health (e.g. increased development of hypertension, heart disease or diabetes) contributing to the general awareness, and thus to an increase in the demand of PSG investigations. This represents a challenge for the already congested sleep centers. On this regard one of the main lines of development is focused towards more efficient patient screening to prioritize the available resources.

Respiratory pauses characteristic of SRBDs are usually associated with a drop in the oxygen saturation levels. One promising screening approach is thus to estimate the SRBD severity by subrogating the count of apneic events by the number of desaturation events present in the recording. Literature provides of some clinical studies investigating the feasibility of predicting SRBD severity by using the so-called Oxygen Desaturation Index (ODI)[1,2].

In this study we are reporting on the reliability of an automatic algorithm for the analysis of the oxygen saturation levels and the assessment of ODI. We compare automatic desaturation scorings against the corresponding human clinical scorings. Specifically on this study a dataset of ambulatory polygraphic recordings (APGs) was gathered by retrospectively examining our clinical sleep center database. The development of automatic screening tools is of interest as it represents an opportunity for potential great savings in costs, less invasive patient monitoring, and improved efficiency and quality in the diagnosis.

METHODS

Data selection

A dataset of 180 APGs was gathered from patients attending our sleep center in the period from July 2017 to July 2018. Patients were referred to our center for screening the possibility of OSA. The polygraphic montage included standard recording of respiratory activity, but not sleep EEG. Selection was done randomly and no exclusion criteria was applied a priori as the intention was to assess the reliability of the algorithm on the related general patient phenotype. Table 1 shows the general characteristics of the involved subjects.

Table 1. General descriptors of the 180 APG recordings included in the validation. Respiratory Disturbance Index (RDI) is here defined as the number of respiratory events (apnea, hypopnea) divided by the Total Analysis Period (lights off-on period). Oxygen Desaturation Index (ODI) is analogously calculated by considering the number of desaturations in the same time period. Results are shown using the median (Q2) and the corresponding inter-quartile ranges (Q1 – Q3). Mean values are also shown for reference. Gender data is shown as the percentage of male subjects

	Q2 (Q1, Q3)	*Mean*	*Min – Max*
Age	50 (41, 60)	51.04	18 - 86
Gender	58.89% males	---	---
RDI	6.33 (2.13, 14.02)	13.12	0.00 – 89.50
ODI3	7.28 (2.48, 14.15)	13.08	0.12 - 84.23

Clinical scoring procedure

Manual scoring of respiratory events was performed during clinical routine examination and in general accordance with the standard clinical rules of the American Association of Sleep Medicine (AASM). Specifically only desaturation events of 3% or more are considered. Percentage of desaturation is calculated as the difference in the oxygen saturation levels between the point where the signal starts to drop (desaturation start) and the beginning of plateau preceding the subsequent oxygen resaturation (desaturation end).

Clinical scoring of desaturations in our department takes place by using a semi-automatic approach. Clinicians run a first pass of our automatic algorithm (referenced below) and then edit the results were necessary by adding, removing or moving possible misscorings. This scoring procedure saves already considerable scoring time, as the clinician just needs to focus on reviewing the results of the automatic scoring. Finally scorings are digitally stored using the EDF+ format[3]. The results of this clinical semi-automatic scoring procedure are taken as reference for the validation of our automatic algorithm.

Automatic analysis

The automatic analysis of the oxygen saturation signal is based on a method described elsewhere[4]. This method has been re-adapted and implemented within the visualization and analysis software Polyman[5]. Thus each patient recording is reanalyzed purely using this method (no human intervention) and the resulting desaturation annotations are compared to the corresponding clinical scorings.

Validation method

Validation is carried out at two different levels. First a time-based validation is performed for each recording by dividing it into 1s or 30s scorable periods. Each period is classified to contain a desaturation if it overlaps with a marked desaturation event, and otherwise it does not. Using these markings as reference we construct a confusion matrix comparing the clinical and the automatic scorings. From the confusion matrix validation indices are obtained which are shown in Table 2.

Second at a diagnostic level, for each recording the respective oxygen desaturation indexes (ODIs) are obtained. Indexes are calculated separately by considering desaturation events equal or greater than 3% (ODI3), 4% (ODI4), and 5% (ODI5). On each case the index is obtained by counting the number of corresponding desaturations divided by the Total Analysis Period

(TAP). TAP is calculated as the period between the lights off-on markings, obtained from the manual annotations of the clinical scorers.
Differences between the respective manual and automatic ODIs are then analyzed using statistical analysis.

RESULTS AND DISCUSSION

Tables 2 summarizes the results from the above-described validation procedure. As data are in general non-normally distributed, the median and the corresponding interquartile ranges are used as general descriptors. For the same reason non-parametric hypothesis testing is used for analyzing the results.

Table 2. Summary of validation results. Upper part shows results from the time-based validation using 1s and 30s epochs. Bottom part shows analyses regarding the diagnostic ODI indices. Distributions are characterized using the median and inter-quartile ranges.

Time-based validation					
Metric	*1 s*		*30 s*		
Accuracy	0.99 (0.98, 1.00)		0.99 (0.96, 1.00)		
Sensitivity	0.99 (0.97, 1.00)		0.99 (0.97, 1.00)		
Specificity	0.99 (0.98, 1.00)		0.99 (0.96, 1.00)		
Precision	0.97 (0.73, 1.00)		0.97 (0.72, 1.00)		
F1-score	0.96 (0.83, 0.99)		0.97 (0.83, 0.99)		
Kappa	0.95 (0.82, 0.99)		0.95 (0.80, 0.99)		
Diagnostic index validation					
Diagnostic index	ODI_{ref}	ODI_{auto}	*Kruskal-Wallis p-value*	ODI_{ref} - ODI_{auto}	R^2
ODI3	7.28 (2.48, 14.15)	8.25 (3.84, 15.69)	0.180	0.20 (0.00, 1.62)	0.992
ODI4	2.86 (0.74, 8.52)	3.54 (1.15, 9.37)	0.285	0.00 (0.00, 0.54)	0.996
ODI5	1.31 (0.28, 5.41)	1.53 (0.35, 5.66)	0.439	0.00 (0.00, 0.15)	0.997

Results in Table 2 show no big differences when changing the granularity on the time-based analysis. Accuracy values in Table 2 indicate that on a median basis the corrections needed by the technicians involve less than 1% of the analysis period. As with respect to the resulting ODI indices, results from the Kruskal-Wallis statistic show that no significant differences can be found among the medians of the different reference and automatic distributions. When comparing the difference distributions (ODI_{ref}-ODI_{auto}), on the other hand, results show that automatic analysis tends to slightly subestimate the reference ODI value. At alpha = 0.05, two-tailed Wilcoxon analysis confirms that medians of the differences are significantly different from zero ($p < 0.05$) in all the three cases (not shown in Table 2). To statistically quantify the actual deviation bias we further performed a one-tailed analysis assuming a certain bias, and checking against the alternative hypothesis that the absolute median differences are over the chosen threshold. Using this analysis it turns out that the null hypotheses cannot be rejected ($p > 0.05$) when assuming biases of around 0.68, 0.24, and 0.08 respectively for ODI3, ODI4 and ODI5. Taking into account the respective reference ODI distributions, this leads to relative deviations of about 9%, 8% and 6% from the median reference ODI. Put into plain words, for the median patient with reference ODI3 = 7.28, an output of around 7.71 would be expected by the automatic algorithm.

CONCLUSIONS

According to the obtained results our automatic desaturation detector shows good performance in comparison to the respective reference clinical scorings. It is able to accurately score desaturations and approximate the true ODI with minimal human intervention. Ultimately, the decision threshold in order to classify the performance as 'good enough' should be established in the context of the corresponding expected intra- and inter-rater (human) deviations. Indeed, in the absence of a more objective scoring reference, the ultimate goal of automatic scoring is to match the reliability between human experts. Such an assessment is momentary missing for this dataset and therefore is left as future work.

REFERENCES

[1] Alvarez-Estevez D, Moret-Bonillo, V. Computer-assisted diagnosis of the sleep apnea-hypopnea syndrome: a review. Sleep Disorders 2015; Article ID 237878, 2015:1-33.

[2] Fabius TM, Benistant JR, Bekkedam L, van der Palen J, de Jongh FHC, Eijsvogel MMM. Validation of the oxygen desaturation index in diagnostic workup of obstructive sleep apnea. Sleep and Breathing, 2018; 1-7.

[3] Kemp B, Olivan J. European data format 'plus' (EDF+), an EDF alike standard format for the exchange of physiological data. Clinical Neurophysiology 2003; 114(9):1755-1761

[4] Moret-Bonillo V, Alvarez-Estevez D, Fernandez-Leal A, Hernandez-Pereira E. Intelligent approach for analysis of respiratory signals and oxygen saturation in the sleep apnea/hypopnea syndrome. The Open Medical Informatics Journal, 2014; 8:1-19

[5] Kemp B, Roessen M. Polyman: a free(ing) viewer for standard EDF(+) recordings and scorings. In Sleep-Wake Research in The Netherlands, Ruijgt GSF, de Boer T, van Kasteel V, van Luijtelaar G, Overeem S, 2007; 18:71-73.

THE MYSTERY OF REM SLEEP AND DREAMING

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THE DISCOVERY OF REM SLEEP

The year 1953 marks a turning point in the research on sleeping and dreaming. Graduate student Eugene Aserinsky and his professor Nathaniel Kleitman, the grandfather of sleep research, both affiliated to the University of Chicago, published their discovery of sleep periods which were associated with atypical rapid eye movements. Aserinsky watched the eyes of his son so carefully that he sometimes noticed jerky, large and rapid eye movements. These eye movements were associated with a low tone in the main body muscles and an EEG pattern that had similarities with the waking pattern. The researchers also obtained preliminary evidence that dreaming occurred during these sleep periods. It is evident that the discovery of this type of sleep, called 'rapid eye movement', or REM sleep, is one of the most important findings in modern sleep and dream research, since it was the hope to find a new paradigm to study the enigmatic dream phenomenon. The paper of Aserinsky and Kleitman [1] is therefore regarded as a genuine milestone in sleep and dream studies and one of the most cited papers in this field.

ANCIENT VIEWS ON DREAMING

Until that time there were many speculative opinions and meanings about dreams and dreaming. In several ancient cultures people believed that dreams were messages of supernatural beings such as gods, angels and demons. Dreams contained, often hidden, messages; warning the sleeper for danger, predicting the future, clarifying situations, or rewarding or punishing the sleeper. Many Christian people assumed that God preached through dreams. Aristotle (384-322 BC) was the first to believe that dreams were produced by ourselves and that they were not of an external origin [2]. He had the idea that dreams were the remains of the waking experiences and that the dreaming mind could communicate with the body. As such, dreams could analyze illnesses and predict diseases and function as a diagnostic means. Original was the dream view of the ancient Chinese culture, distinguishing the soul from the body. The soul would move out of the body of a sleeping person during the dream and visits places and persons the sleeper would see in his dream. A careful awakening was required, since the soul needed time to return into the body and a too fast awakening could be fatal. Elements of this view can still be found in 'near-death-experiences'.

PSYCHOANALYSIS

In the 19th century the Austrian psychiatrist Sigmund Freud (1856-1939), who extensively studied dream theories and dream interpretations, took over several elements of Aristotle's dream opinions. He integrated these elements in his dream theory, which he laid down in his impressive work 'Die Traumdeutung' ('The Interpretation of Dreams') published in 1900 [3]. Based on the dream recall of several of his psychiatric patients, he came to the view that dreams were expressions of profound desires and fears, often related to repressed childhood

memories and obsessions. The content of the dream was driven by the fulfillment of deep, often inappropriate, unconscious wishes. According to Freud, the dream formed an access to the unconscious mind: 'dreams are the royal road to the unconscious'. Dreams had both a manifest and a latent content. The manifest content was that what a dreamer later could recall of a dream, often bizarre and meaningless stories, while the latent content included the real meaning, related to the unconscious wishes or fantasies. It was the goal to extract the latent content from the manifest content, by careful analyzing the dream. This formed the basis of psychoanalysis, and many versions of this therapy are still in use, although the scientific basis is regularly under discussion.

REM SLEEP AND DREAM RECALL

William Dement (1928 –), another graduate student of the earlier mentioned Kleitman, was also highly interested in dreaming. It seemed evident to him, and the entire research group he belonged to, that REM sleep was the sleep for dreaming. However, Dement wondered whether dreaming would take place exclusively during REM sleep. His hope was that he could find a strict relation between the two phenomena. Rigorous attempts to test this idea were carried out. Many people came to the sleep lab and were aroused during REM sleep. Of course, also control experiments were performed by arousing sleeping subjects from non-REM sleep. The Kleitman lab published the first well-controlled recall study in 1957 [4]. In 80% of the awakenings from REM sleep a vivid dream recall was obtained, but this occurred only in 7% of the arousals from non-REM sleep. The team was excited by the high percentage of REM recall, though this was not 100%, but simultaneously frustrated by the low, but not zero, percentage of non-REM recalls. Especially this latter finding jeopardized the idea that REM sleep was the exclusive sleep for dreaming, but also that REM sleep and dreaming were two sides of the same coin. A bulk of studies were performed to understand the percentage of recalls from slow-wave sleep. That those were remains from dreams from an earlier REM period could be excluded directly. However, it was a problem that a dream could not be defined exactly and people could perhaps indicate a dream when in reality something just flashed through their minds. That issue was finally tackled by Gene Orlinsky, a graduate student of Allan Rechtschaffen [4]. He tried to solve this problem by performing an experiment in which he used an eight-point scale for the judgment of dream reports. Indeed, Orlinsky found clear differences between non-REM and REM reports in the sense that a non-REM recall is generally poorer, less vivid and less dreamlike as compared to a REM recall. But he also found that occasionally a long, vivid dream was reported after a non-REM arousal. In about 5% of cases he found a dream report that could not be differentiated from a REM dream report. To their disappointment the sleep scientists had to come to the conclusion that REM sleep cannot be considered as exclusively synonymous with dreaming!!

The dream recall studies revealed two facts which are not directly in line with the view that REM sleep and dreaming are the expressions of the same process; the occasional absence of a recall by awakenings from REM sleep and the sometimes vivid recall by arousals from non-REM sleep. Despite these findings, the general public's opinion of REM sleep is that this is the dreaming sleep and that the minor exceptions are caused by the vague and slippery nature of the dream.

HYPNAGOGIC HALLUCINATIONS

Hypnagogic hallucinations are vivid, frequently frightening dreams that occur at sleep onset. Many have experienced these visual, tactile or auditory images that occur at the transition from waking to sleep. Sometimes they are accompanied by sleep paralysis or by an intense muscle shock. Feelings of falling in a hole, or flying, can also be experienced in these hallucinations. When they take place upon awakening these hallucinations are called hypnopompic. The Dutch physician Ysbrand van Diemerbroeck (1609 – 1674), who worked as a doctor during the black death epidemic raging in Nijmegen in 1635/1636 and who later became a professor of medicine at Utrecht University, was the first who described these dream hallucinations[5]. Mostly, these experiences are called dreamlike, for the reason that they occur at the transition from waking to sleep. The EEG pattern is active, but the type of sleep cannot be qualified as REM sleep. In narcoleptic patients, suffering from the intrusion of REM sleep when they are awake, similar hallucinatory phenomena occur. During a narcoleptic attack, frightening and dreamlike hallucinations can emerge, associated with sleep paralysis and cataplexy. In these hypnagogic hallucinations at sleep onset and at narcoleptic attacks, reality and dream fantasies are often mixed. The story of 'The devil's thrill' started with a hypnagogic hallucination. The composer Giuseppe Tartini (1692–1770) dreamed that he had handed the devil his violin to test the devil's musical skills, and the devil played a song with exceptional virtuosity! Tartini tried to recollect the music afterwards, and composed based on the beautiful devil's music a sonata known as 'the devil's thrill'. In a similar way, the German chemist August Kekulé dreamed of a snake with his tail in his mouth and found thereby the circular molecular structure of benzene.

THE ACTIVATION - SYNTHESIS HYPOTHESIS

It is now convincingly demonstrated that dreaming can take place outside REM sleep. A dream can emerge in slow-wave sleep, presumably when the fluctuating brain activity is high enough, and further at sleep onset in hypnagogic hallucinations and upon awakening in hypnopompic hallucinations. A common feature of all these states is associated with a degree of consciousness almost reaching waking consciousness. It was originally proposed by Harvard scientists Allan Hobson and Robert McCarley that dreaming is the result from the attempts of the brain to make sense of the high neural activity during sleep. They called this the 'activation-synthesis' hypothesis [6]. The neurophysiologists knew that circuits in the brain stem are activated, leading to REM sleep. The produced activity ascends by PGO waves to higher brain areas involved in sensations, emotions and memories, and the cortex synthesizes these internal processes, together with the limited external information into a story to create a meaning from all these signals. This results in dreaming images and since the brain has difficulties to produce an acceptable story of all signals, this leads to chaotic scenes, objects and stories, forming an often surreal, illogical, emotional and bizarre narrative, which is curiously enough felt by the dreamer as a lifelike reality. This implies that the dream itself is a byproduct of the activity associated with REM sleep, initially originating in the brainstem and spreading to higher cortical areas. In this view the REM sleep must have an important, still unknown, function, while the dream is an unintentionally, senseless byproduct.

But, does this indeed mean that dreams are completely meaningless? Perhaps not completely. If it is assumed that the brain contains memories full of important information, it can be accepted that even when areas of the brain are randomly activated, important memory

information is reactivated. The more impact this information has for a person, the more memory space is occupied. And thereby is the likelihood greater that these impact containing areas are activated. Thus, situations and events often appearing in dreams seem to have had a strong impact to the sleeper, and it is not the detailed story which is relevant, but the events and the persons often appearing in dreams, evoking emotional reactions. In this view, the psychoanalytical dream theory obtains to some degree a scientific basis. Allan Hobson said it in an alternative way: 'Dreaming may be our most creative conscious state, one in which the chaotic, spontaneous recombination of cognitive elements produces novel configurations of information in new ideas. While many or even most of these ideas may be nonsensical, if even a few of its fanciful products are truly useful, our dream time will not have been wasted' [7].

THE INFORMATION PROCESSING THEORY

It has long been known that sleep forms a favorable condition for memory consolidation. New information is better consolidated after a period of sleep, compared to a period of waking. Research to this sleep-dependent memory processing started soon after the discovery of REM sleep. I began around 1975, with my group at the Radboud University, research concerning the view that REM sleep, with dream flashes frequently containing residues of daily experiences, could be directly involved in this positive effect of sleep on memory. Ten years of intensive research later, after the dissertations of Zach van Hulzen [8] and Gilles van Luijtelaar [9], the disappointing conclusion was that we had no single result pointing towards a positive role of REM sleep in memory consolidation. To our surprise, after a period of silence, the search to confirm this attractive hypothesis was resumed with the enthusiastic approach of the group of Robert Stickgold of Harvard University. This group found indeed some positive evidence for the role of REM sleep in off-line memory reprocessing, in a few forms of learning, but the evidence is still not convincing. Stickgold created even a model for the strengthening of associations by REM dreaming, but the model has speculative traits [10]. Furthermore, more and more recent evidence suggests that sleep-dependent memory consolidation is not favored by REM sleep but on the contrary by non-REM sleep.

CONCLUSIONS

The most important notion that emerges from the literature is that the general assumption that REM sleep is the equivalent of dreaming needs a thorough revision. REM sleep and dreaming are not identical processes and REM sleep has to be divorced from dreaming [11]. REM sleep and dreaming are dissociable states: brain stem mechanisms are controlling REM sleep, while dreaming is controlled by forebrain mechanisms [12]. Dreams are the expression of high-amplitude brain activity during sleep and that explains why dreaming occurs at sleep onset and at sleep ending, and, almost always during REM sleep, since this type of sleep is generally associated with a high brain activity. It only seems and looks therefore that REM sleep and dreaming are highly connected.

Taking all evidence together, it is more likely that REM sleep serves an own unknown function. Moreover, in this perspective, the dream is a random byproduct of REM sleep, caused by the high brain activity, with no direct meaning. Nevertheless, based on the content of the dream, frequently consisting of memory images with a mix of remote and recent memory traces, a certain interpretation of a dream seems sometimes possible. This is especially done in the psychoanalytical dream theory. However, the dream interpretation is often regarded as

speculative with a limited scientific basis. The original enthusiasm around the discovery of REM sleep has now two sides: it has delivered new, important and interesting questions concerning the function of the mysterious REM sleep phenomenon, but it has unfortunately not brought more insight into the nature of dreams, the most intriguing experiences in life.

REFERENCES

[1] Aserinsky, E., Kleitman, N.: Regularly occurring eye motility, and concomitant phenomena, during sleep. Science 118, 273-274, 1953

[2] van der Eijk, Ph.: Aristoteles: Over het geheugen, de slaap en de droom. Groningen: Historische Uitgeverij, 2003

[3] Sulloway, F.J.: Freud: Biologist of the mind. New York: Basic Books, 1983

[4] Dement, W.C.: Some must watch while some must sleep. San Francisco: W.H. Freeman and Company, 1972

[5] Kompagne, E.J.: 'The devil lay upon her and held her down'. Hypnagogic hallucinations and sleep paralysis described by the Dutch physician Isbrand van Diemerbroeck (1609-1674) in 1664. Journal of Sleep Research 17: 464-467, 2008

[6] Hobson, J.A., McCarley, R.W.: The brain as a dream state generator: An activation-synthesis hypothesis of the dream process. American Journal of Psychiatry 134: 1335-1368, 1977

[7] Hobson, J.A.: Sleep. New York: Scientific American Library, 1989

[8] van Hulzen, Z.J.M.: Paradoxical sleep deprivation and information processing in the rat. Meppel: Krips Repro, 1986

[9] van Luijtelaar, G.: Paradoxical sleep: deprivation studies revisited. Meppel: Krips Repro, 1986

[10] Stickgold, R., Hobson, J.A., Fosse, R., Fosse, M.: Sleep, learning, and dreams: Off-line memory reprocessing. Science 294, 1052-1057, 2001

[11] Coenen, A.: The divorce of REM sleep and dreaming. Sleep and Dreaming. Cambridge University Press, 133-135, 2003

[12] Solms, M.: Dreaming and REM sleep are controlled by different brain mechanisms. Sleep and Dreaming. Cambridge University Press, 51-58, 2003

FATIGUE, RECOVERY AND SLEEP IN ROTATING SHIFT WORKERS

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INTRODUCTION

Approximately 20% of the workforce in Europe are shift workers[1]. Shift work, resulting in circadian misalignment and disrupted sleep-wake schedules, negatively impacts workers' health, safety and productivity. Acute detrimental effects are poor sleep quality, sleep loss and less consolidated sleep, which in turn result in sleepiness and fatigue at the work place, and in the long run may develop into shift work disorder[2,3-8]. Next to sleep problems and fatigue, shift workers also report a higher 'Need for Recovery', compared to day workers[3]. Working night shifts, where the misalignment of circadian and homeostatic sleep processes is most prominent, are related to most sleep problems and the highest Need for Recovery compared to evening or day shifts[4,5]. Even more, the potential risk for fatigue-related injuries or errors is higher for night shifts (28 %) and evening shifts (15 %) compared with day shifts[6]. Most research has focused on work decrements and sleep during shift days, little is known about the recuperation time between shifts, more particular on days off. The aim of this paper is to investigate how sleep on days off and recovery are associated with fatigue during the night shifts.

METHODS

A cross-sectional survey was conducted in the Netherlands as part of the 'Managing a shift work lifestyle' training program implementation (Circadian®) at four industrial company sites in the chemical sector. All participants worked the same continuous fast forward rotating 5-shift schedule, each shift cycle comprised (in order) two morning shifts 07:00-15:00 (M), two evening shifts 15:00-23:00 (E), two night shifts 23:00-07:00 (N) and four days off (O); i.e. MM-EE-NN-OOOO, MM-EE-NN, and so forth. Participation to the survey was anonymous and voluntary. The participants were asked during which shift type (morning, evening or night) their work was most affected by fatigue. The total sample size consisted of 251 participants (all men), of which 141 men indicated to be most affected by fatigue during the night shift, 92 during the morning shift and 12 during the evening shift. Six participants were excluded due to incomplete data. The results of the subgroup who stated that their work was most affected by fatigue during the night shift are reported here (20-62 years old, mean age 45 years).

Sleep was measured as subjective sleep quality and sleep duration on days off. Quality of sleep was quantified on a 1-100 scale, where 1 = absolute worst and 100 = could not be better; 100 reflecting sleep that is of sufficient duration and depth resulting in one feeling awake and refreshed. For Sleep duration subjects indicated their hours and minutes asleep.

Recovery was measured with the subscales 'Need for Recovery' and 'Ability to Recover', on 5-point Likert scales ranging from 1 'rarely to never' to 5 'almost always'. Need for Recovery refers to the immediate need to recuperate from a work period. The Need for recovery scale

consisted of 4 statements concerning lethargy, affect and mood problems, where higher scores indicate more Need for Recovery. The Ability to Recover scale also consisted of 4 statements, but concerning work-life balance and restoration of normal sleep/wake cycle, where higher scores indicate a good ability to recover from shift work.

Fatigue at work was assessed with 6 statements regarding different aspects of fatigue, i.e. motivation, attention, energy, working on 'autopilot', coordination/clumsiness and irritability. Subject were instructed to indicate to what extent the statements applied to them during their night shifts again by using a 5-point Likert scale.

To examine the associations between fatigue at work and sleep and recovery during days off, the Spearman's Rho correlations were used as non-parametric analysis.

RESULTS AND DISCUSSION

Descriptive analyses of fatigue, sleep and recovery, including all correlation coefficients, are shown in table 1. The model in Figure 1 shows the observed correlations with fatigue. Need for recovery had a moderate correlation with fatigue at work (r^2= .47; p <.001). Ability to Recover had a smaller correlation with fatigue at work, (r^2= - 0.33; p <.001), and Sleep quality on days off had a weak correlation with fatigue at work (r^2= -.25; p <.01). No significant correlation has been found with sleep duration on days off (r^2= 0.06).

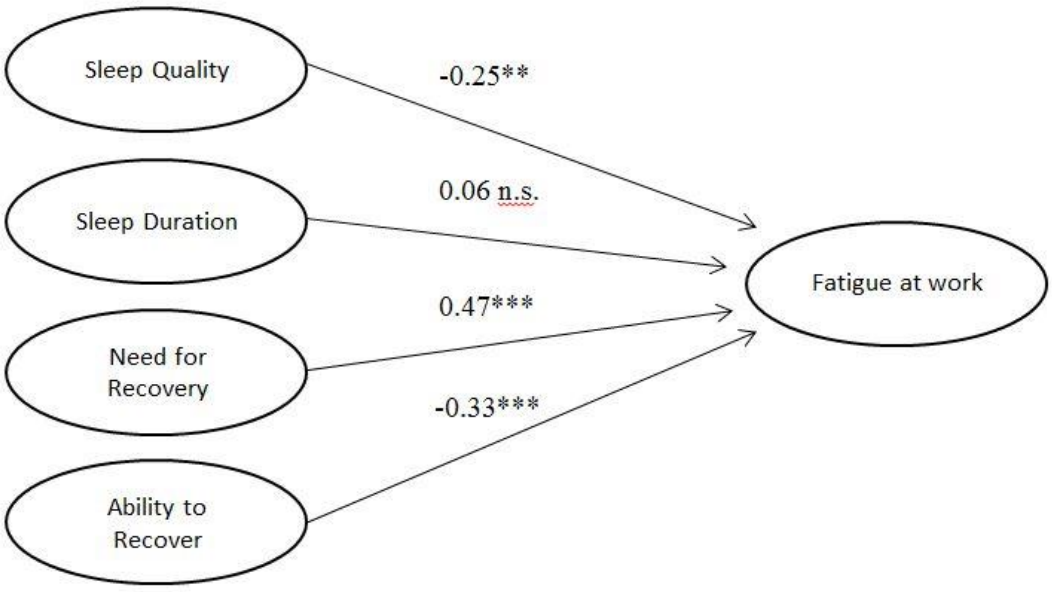

Figure 1: Model of associations between sleep, recovery and fatigue at work.
*= p <.05, **= p <.01, ***=p < .001, n.s.=not significant

These results suggest that the restorative function of time off from work, is not primarily defined by sleep but the immediate need to recuperate from a work period (i.e. Need for Recovery). This is consistent with the result that the Ability to Recover is negatively related with fatigue, meaning that the less shift workers are able to have a good work/life balance the higher the fatigue at work (or vice versa). It is known that, compared to day workers, shift

workers do have more work/life conflicts. For instance, Bonnefond and colleagues showed that particularly night shifts negatively affect shift workers' social life[7]. When Need for Recovery perpetuates, it may result in poor health and increase in sickness absence[8], for which elevated risks have been shown in shift work populations[9].

Table 1. Descriptive analyses (means and standard deviations) and Spearman's Rho correlation matrix for fatigue, sleep and recovery.

	Mean (SD)	*Fatigue*	*SQ*	*SD*	*NfR*
Fatigue at Work	2.12 (0.70)				
Sleep quality days off (SQ)	80 (14)	- 0.25[b]			
Sleep duration days off (hr:m)	7:47 (1)	0.06	0.35[a]		
Need for Recovery (NfR)	1.87 (0.5)	0.47[a]	- 0.29[a]	- 0.07	
Ability to Recover	3.74(0.8)	- 0.33[a]	0.27[b]	- 0.04	- 0.57[a]

[a]p= < .001, [b]p= < .01

This dataset propound that shift workers' perception of their recovery from work might be an admissible indicator for their performance at work.

To conclude, this study indicates that shift workers' functioning at work is affected by conditions outside work, i.e. other than sleep. When it comes to managing workplace health and safety through shift schedule optimization, the focus has mainly been on shift length, as well as speed and direction of shift rotations. It can be postulated that providing for sufficient and guaranteed recovery time after a work period may be the better option, since previous studies on the relation between health and shift schedule features, such as direction and speed of rotation, have shown inconsistent results[10]. Therefore, Human Resources and Occupational Health professionals should focus on recovery as part of their strategies to keep shift workers productive and healthy at work, and to reduce their absence rates.

REFERENCES

[1] European foundation for the improvement of living and working conditions. Changes over time – First findings from the fifth European Working Conditions Survey. Dublin: Publications Office of the European Union; 2015.

[2] Wright Jr, KP, Bogan, RK, & Wyatt, JK. Shift work and the assessment and management of shift work disorder (SWD). Sleep Medicine Reviews 2013; 17:41-54.

[3] Jansen NWH, Kant I, van Amelsvoort LGPM, Nijhuis FJN, van den Brandt PA. Need for recovery from work: evaluating short-term effects of working hours, patterns and schedules. Ergonomics 2003;46:664–680.

[4] Åkerstedt T. Shift work and disturbed sleep/wakefulness. Occupational Medicine 2003; 53: 89-94.

[5] Van De Ven HA, van der Klink JCL, Vetter C, et al. Sleep and need for recovery in shift workers: do chronotype and age matter?. Ergonomics 2016; 59:310-324.

[6] Caruso CC. Negative impacts of shiftwork and long work hours. Rehabil Nurs 2014; 39:16–25.

[7] Bonnefond A, Härmä M, Hakola T, Sallinen M, Kandolin I, Virkkala J. Interaction of age with shift-related sleep-wakefulness, sleepiness, performance, and social life. Experimental Aging Research 2006; 32:185-208.

[8] Sluiter JK, De Croon EM, Meijman TF, Frings-Dresen MHW. Need for recovery from work related fatigue and its role in the development and prediction of subjective health complaints. Occupational and Environmental Medicine 2003; 60:62-70.

[9] De Croon, EM, Sluiter JK, Frings-Dresen, MH. Need for recovery after work predicts sickness absence: a 2-year prospective cohort study in truck drivers. Journal of Psychosomatic Research 2003; 55:331-339.

[10] Health Council of the Netherlands. Shiftwork and health risks: possibilities for prevention. The Hague: Health Council of the Netherlands, 2015; publication no. 2015/25. *ISBN 978-94-6281-057-0.*

METABOLOMICS OF INSOMNIA

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INTRODUCTION

In the modern society, prolonging its activities into the night-time can cause sleep deprivation[1]. The use of electrical devices, different work shifts, demand for high performance at work, and other activities affect sleeping. Sleep deprivation may result in an increased risk of type 2 diabetes, metabolic syndrome, obesity, arterial hypertension and glucose intolerance[1,2], but it can also affect working memory, attention, and cognitive function, as well as plenty of other effects. A century ago, an average time of sleep was 9 hours, nowadays we sleep on average 6.5 hours, which makes insufficient sleep a public health problem. The mechanisms underlying sleep disorders are not well understood. Research in this field progresses quite slow, and many patients are not treated efficaciously[3]. Previously, metabolomics approaches have never been used to describe the metabolic pathways involved in sleep disorders. The aim of this study was to describe the metabolic composition in saliva samples in people having insmonia. The focus was on quantitative changes in primary (polar) metabolites. Saliva is a good biofluid for monitoring biological responses, and it was used in this study, because it changes quite fast due to different stressors, stimuli, insults, and physiological state[4]. Another reason why saliva represents a good candidate for monitoring biological responses is its easily available and a non-invasive source.

METHODS

Collection of saliva samples

Saliva samples were collected from healthy volunteers (n=4) and hospital patients (n=16) according to the standardized procedure of Gelderse Vallei hospital (Ede, the Netherlands). Hospital patients were both male (n=9) and female (n=7), age varied from 8-70 years, all with diagnosed sleep disorders (insomnia, also including 8 patients with delayed sleep phase disorder (DSPD)). Saliva samples were collected in the period from last five hours before sleep to the last hour before sleep. Salivette® tubes were used for saliva collection. Upon delivering the samples to the Biochemistry department at Wageningen University, the samples were prepared for measurement on LC-QQQ-MS and 1H NMR according to the protocol described by Wei et al. (Scientific Reports in press 2018). Preparing samples included centrifugation (Eppendorf Centrifuge 5427 R), with the supernatant filtered by using Pall 3K nanosep devices. The flow-through contained the metabolites of interest, while proteins and larger molecules were discarded. After filtration samples were frozen to -80° and thawed at room temperature before measuring. The Medical Ethical Reviewing Committee of Wageningen University (METC-WU) approved saliva metabolite measurements.

Table 1. Metabolites (from QQQ-MS or NMR based measurements) that show an increase or a decrease in intensity in insomniacs in the last three hours before bedtime.

Metabolite	*Change in the last three hours before sleep*
Aspartic acid	Decrease
Glycine	Decrease
Threonine	Decrease
Glutamic acid	Decrease
Ornitine	Decrease
Acetate	Decrease
Formic acid	Decrease
Tyrosine	Decrease
Phenylalanine	Decrease
Adenine	Increase
Acetylcarnitine	Increase
4-hydroxybenzoate	Increase
Choline	Increase
Ethanol	Increase
Leucine	Increase
GABA	Increase
Creatinine	Increase
Succinic acid	Increase

Table 2. Metabolites (from QQQ-MS or NMR based measurements) that are increased or decreased in insomniacs compared to healthy volunteers. Percentage is calculated according to % = (1-(LS/HS)*100), where LS is lower signal, and HS is higher signal.

Metabolite detected by MS	*Change in percentage*	*Signal in patients*
Lactic acid	74,4	Higher
Pantothenic acid	71,0	Higher
Succinic acid	63,3	Higher
Adenosine	60,9	Lower
Lysine	60,2	Lower
Glutamine	59,2	Lower
Proline	59,1	Lower
Arginine	54,8	Higher
Aspartic acid	51,0	Lower
Citrulline	50,1	Lower
Ornitine	49,7	Lower
GABA	48,0	Higher
Methionine	45,9	Lower
Tryptophan	45,2	Lower
Serine	45,1	Lower
Glutamic acid	44,9	Lower
Isoleucine	44,7	Lower
Glycine	44,3	Lower
Ethanol	43,5	Higher
Valine	41,6	Lower
Aconitic acid	39,9	Higher
Leucine	38,4	Lower
Cystine	38,3	Higher
Inosine	36,1	Higher
Histidine	31,9	Lower
Choline	30,9	Higher
Threonine	30,7	Lower
Hypoxanthine	30,1	Lower
Alanine	29,9	Lower
Creatinine	27,7	Higher
Methanol	26,0	Lower
Guanosine	24,8	Lower
Creatine	22,6	Higher
Tyrosine	20,3	Lower
Fumaric acid	20,1	Higher
Uric acid	19,8	Higher
Glycerol	18,3	Higher
Cytidine	18,0	Higher
Acetylcarnitine	17,9	Higher
Adenine	15,7	Lower
Citrate	15,4	Lower
Acetate	14,0	Lower
Isobutyrate/butyrate	13,5	Higher
Phenylalanine	13,2	Lower

LC-QQQ-MS and 1H NMR System

For the metabolite analyses LCMS-8040 triple quadrupole mass spectrometer (MS), and Shimadzu software were used. This method has been previously tested on different samples (cow milk, plant, microbial, and pig and cow blood) by the Biochemistry department. To measure metabolites by using nuclear magnetic resonance (NMR), one-dimensional nuclear

Overhauser enhancement spectroscopy (1-D-NOESY) spectra were obtained. Bruker spectrometer Avance III with a 600 MHz/54 mm UltraShielded Plus magnet equipped with a CryoPlatform cryogenic cooling system, a BCU-05 unit (Bruker, Rheinstetten, Germany) was used. To assign saliva nonoverlapping metabolite resonances, comparisons were made with internal standards, the Human Metabolome Database version 4.0 online library (http://www.hmdb.ca), as well as with published literature (Velitchka et al. 2014). The peak area of each assignment was relative to the calibration standard maleic acid at 6.00 ppm, resulting in arbitrary units that were used for statistical analyses. Correlation between two methods was confirmed by strong Pearson's correlation (> 0.7) in several metabolites (Valine, Leucine, Isoleucine, Tyrosine, and Phenylalanine)

Statistical analyses

Statistical analyses were performed in RStudio (RStudio Desktop version 1.1.423), Microsoft Excel (Microsoft Office 365 ProPlus, Excel version 1801) and IBM SPSS Statistics 22.0 (Statistical Product and Service Solutions: IBM Corp.). Differences were considered significant at the level of $P < 0.05$.

RESULTS

The last three hours before bedtime, individuals with sleep disorders were examined to determine which metabolites are increasing or decreasing in signal intensity. Table 1 shows which metabolites give an increase or decrease pattern within a 3 hours interval in insomniacs. We used the average of the metabolites in all patients to observe the differences within this three hour time interval. Nine metabolites showed a decrease in the signal before sleep occur nine metabolites showed an increase.

An overview of metabolites which decreased or increased, in insomniacs compared to healthy volunteers is displayed in Table 2. In total, 18 metabolites increased and 26 metabolites decreased in insomniacs compared to healthy volunteers.

The largest decrease in samples of hospital patients is seen in Adenosine with a significant difference (60,9 % higher signal in healthy volunteers than in insomniacs). The largest increase is observed in Lactic acid (74,4 % lower signal in healthy volunteers than in insomniacs).

DISCUSSION

This is the first study where metabolite composition was described in insomniacs. Adenosine shows a significant difference between healthy people and insomniacs ($p<0.05$). Previously, adenosine has been described as an important metabolite, participating in the sleep wake regulation[5,6]. Radulovacki[7] described the adenosine sleep theory, a possible mechanism and related experiments, in support to the theory. Our study shows an important role of adenosine in sleep disorders and corroborates previous findings. Histidine together with alanine is the precursor to carnosine, and both are observed to be decreased in insomniacs. Ornithine is found to be decreased (48%) as well and shows a significant difference ($p<0.05$). The decrease of ornithine and metabolites which make up carnosine, is in agreement with a recent study from Maeda et al.[8] showing that carnosine and ornithine were decreased by poor sleep quality. An interesting observation is that acetylcarnitine shows an increasing pattern in the last three hours before sleep, indicating an important association between sleep and fatty acid metabolism. Free fatty acids are observed to be increased after sleep deprivation in studies from Davies et al[9] (humans) and Hinard et al[10] (in vitro/in vivo) indicating higher lipid

metabolism during wakefulness or cell stimulation which was consistently accompanied by increased oxygen consumption and lactate production. Our metabolomic approach indeed shows an increased lactate production in hospital patients (74 %) compared to healthy volunteers. However, there was no significant difference ($p>0.05$). Branched chain amino acids (valine, leucine, isoleucine) are found to be decreased in hospital patients priorsleep. It is known that these three essential amino acids participate in metabolic pathways whose intermediates result in TCA cycle and give energy. They can contribute to the TCA cycle through Acetyl-CoA (leucine) and Succinyl-CoA (valine and isoleucine). Succinic acid that participates in the same metabolic pathway as Succinyl-CoA shows increase in hospital patients. This observation leads to the assumption that the TCA cycle is more active in insomniacs, indicating more metabolic activity prior to sleep in these patients.

CONCLUSION

A first conclusion coming from this study is that saliva is a simple, easily available source for observing metabolic changes. Changes in the signal of metabolites are observed in insomniacs in the last three hours before sleep. The results indicate an increase in a total of 9 metabolites and a decrease in 9 metabolites. When a comparison is made with healthy volunteers, significant changes in signals of metabolites are observed in the last hour before sleep. Specific metabolites as adenosine, lysine, proline, glutamine, and BCAA were found to be decreased in patients, while lactate, succinate, and GABA were found to be increased. It is suggested based on these findings that fatty acid metabolism is influenced in insomniacs. The TCA cycle is more active in insomniacs, because metabolites participating in it (isoleucine, valine, leucine) are lower in the signal. That leads to the conclusion that insomniacs can have higher metabolic activity. Further studies might reveal if treatment of insomnia is associated with a decrease of metabolic activity. Since several metabolites, like Adenosine, are significantly decreased in patients with insomnia, supplementation of these metabolites might be considered.

REFERENCES

[1]Troxel WM, Buysse DJ, Matthews K, et al. Sleep symptoms predict the development of the metabolic syndrome. Sleep. 2010;33(12):1633-1640.

[2]Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care. 2003;26(2):380-384.

[3]Spitzer AR. Reclassification of clinical sleep disorders using traditional models of syndromic, neuroanatomic, pathophysiological and etiological diagnosis. Med Hypotheses. 2014;83(3):391-397.

[4]Takeda I, Stretch C, Barnaby P, et al. Understanding the human salivary metabolome. NMR Biomed. 2009;22(6):577-584.

[5]Basheer R, Strecker RE, Thakkar MM, McCarley RW. Adenosine and sleep–wake regulation. Prog Neurobiol. 2004;73(6):379-396.

[6]Rathmacher JA, Fuller JC, Baier SM, Abumrad NN, Angus HF, Sharp RL. Adenosine-5'-triphosphate (ATP) supplementation improves low peak muscle torque and torque fatigue during repeated high intensity exercise sets. J Int Soc Sports Nutr. 2012;9.

[7]Radulovacki M. Adenosine sleep theory: how I postulated it. Neurol Res. 2005;27(2):137-138.

[8]Maeda S, Shimojo N, The mechanism underlying sleep disorder-induced decrease in athletic performance and its improvement available at https://kaken.nii.ac.jp/en/grant/KAKENHI-PROJECT-26282181/ Accessed August 31, 2018

[9]Davies SK, Ang JE, Revell VL, et al. Effect of sleep deprivation on the human metabolome. *Proc Natl Acad Sci*. 2014;111(29):10761-10766.

[10]Hinard V, Mikhail C, Pradervand S, et al. Key Electrophysiological, Molecular, and Metabolic Signatures of Sleep and Wakefulness Revealed in Primary Cortical Cultures. *J Neurosci*. 2012;32(36):12506-12517.

SLEEP-WAKE
Research in the Netherlands

Volume 29, 2018

Book Presentations

WAT KUN JE DOEN AAN DEMENTIE?
HOW CAN YOU DEAL WITH DEMENTIA?

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This book was written for, and is directed at, people who have recently been diagnosed with dementia or mild cognitive impairment, and their family members. The book covers evidence-based lifestyle interventions, medication, cognitive training, as well as practical tips on how to deal with dementia in everyday life. There is a separate chapter devoted entirely to the role of sleep in the etiology and prevention of dementia, specifically Alzheimer disease. This chapter summarizes recent scientific observations on the relationship between poor sleep and the risk of Alzheimer, and provides suggestions on how to improve sleep. A chapter on physical activity also points out the beneficial effects of physical activity and being outdoors during the day on sleep.
Jurgen Claassen is a geriatrician at Radboudumc and clinical investigator. His studies focus on cerebrovascular causes of cognitive decline and Alzheimer, and the role of sleep in development and progression of Alzheimer. Roy Kessels is professor of clinical neuropsychology at Radboud University and Radboudumc, and an expert on cognitive aging and cognitive training. Petra Spies is a geriatrician and clinical pharmacologist at Gelre Ziekenhuizen, with expertise in diagnosis and treatment of dementia and in pharmacotherapy in aging.

Figure 1. Book cover.

Wat kun je doen aan dementie? Jurgen Claassen, Roy Kessels, Petra Spies. LannooCampus. ISBN 9789401451116

MEDICATIONS AND THEIR EFFECTS ON SLEEP AND WAKE
FROM SLEEP MEDICINE CLINICS

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This book is a recent edition in the Sleep Medicine Clinics series, and offers a comprehensive overview on current drug therapy in sleep medicine, and on the complex relationship between drugs and sleep-wake. Novel and more effective treatments of common sleep disorders are highlighted. The topics chosen in this issue represent most relevant aspects in this field, in relation to the varied disorders of sleep. Among them, neurochemistry of sleep and wake (Sebastian Holst et al, Denmark); side effects of drugs on sleep with emphasis on insomnia and excessive daytime sleepiness (Ann Van Gastel, Belgium); sleep-disordered breathing and ventilatory impairment due to drug use (Ludger Grote, Sweden); pharmacologic treatment of insomnia (Sylvie Dujardin et al, The Netherlands); current pharmacologic approach of narcolepsy and hypersomnia (Gert Jan Lammers, The Netherlands); treatment of parasomnias, and their pharmacologic management (Paola Proserpio et al, Italy); pharmacologic management of sleep-disordered breathing, and its future perspectives (Jan Hedner, Sweden); drug therapy in restless legs syndrome (Galia Anguelova et al, The Netherlands); drugs in circadian sleep-wake rhythm disorders (Helen Burgess et al, USA); specific drug regimes in pregnant women (Laura McLafferty et a l, USA); pediatric aspects (Paschalis Steiropoulos et al, Greece); hypnotic discontinuation (Jonathan Hintze et al, USA), and finally a last one on chronic opioid use and their effect on sleep and wake (Michelle Cao et al, USA).

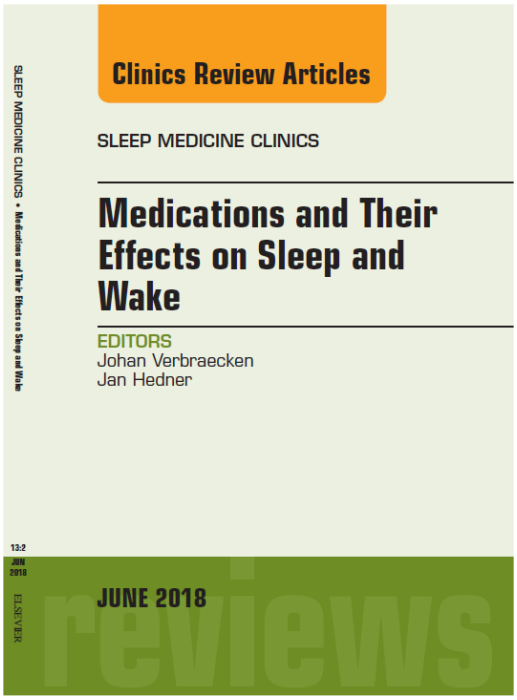

Figure 1. Book Cover

It is hoped that this issue will leave the reader with a better understanding of the usefulness and limitations of drugs for sleep disorders, and its interaction of drugs with normal sleep.

Medication and their effects on sleep and wake, Johan Verbraecken, Jan Hedner, editors, Elsevier publisher, ISSN 1556–407X.

SLEEP-WAKE
Research in the Netherlands

Volume 29, 2018

Abstracts

KETAMINE: DIFFERENTIAL NEUROPHYSIOLOGICAL DYNAMICS IN FUNCTIONAL NETWORKS IN THE RAT BRAIN

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Introduction: Recently, the N-methyl-d-aspartate-receptor (NMDAR) antagonist ketamine has emerged as a fast-onset mechanism to achieve antidepressant activity, whereas its psychotomimetic, dissociative and amnestic effects have been well documented to pharmacologically model schizophrenia features in rodents. Sleep-wake architecture, neuronal oscillations and network connectivity are key mechanisms supporting brain plasticity and cognition, which are disrupted in mood disorders such as depression and schizophrenia.
Methods: In rats, we investigated the dynamic effects of acute and chronic subcutaneous administration of ketamine (2.5, 5 and 10 mg kg-1) on sleep-wake cycle, multichannel network interactions assessed by coherence and phase-amplitude cross-frequency coupling, locomotor activity (LMA), cognitive information processing as reflected by the mismatch negativity-like (MMN) component of event-related brain potentials (ERPs).
Results: Acute ketamine elicited a short, lasting inhibition of rapid eye movement (REM) sleep, increased coherence in higher gamma frequency oscillations independent of LMA, altered theta-gamma phase-amplitude coupling, increased MMN peak-amplitude response and evoked higher gamma oscillations. In contrast, chronic ketamine reduced large-scale communication among cortical regions by decreasing oscillations and coherent activity in the gamma frequency range, shifted networks activity towards slow alpha rhythm, decreased MMN peak response and enhanced aberrant higher gamma neuronal network oscillations.
Discussion: Altogether, our data show that acute and chronic ketamine elicited differential changes in network connectivity, ERPs and event-related oscillations (EROs), supporting possible underlying alterations in NMDAR-GABAergic signaling. The findings underscore the relevance of intermittent dosing of ketamine to accurately maintain the functional integrity of neuronal networks for long-term plastic changes and therapeutic effect.

Ahnaou A, Huysmans H, Biermans R, Manyakov NV, Drinkenburg WHIM. Ketamine: differential neurophysiological dynamics in functional networks in the rat brain. Translational Psychiatry, 2017 7(9): e1237.

DEEP LEARNING FOR SCORING SLEEP BASED ON CARDIORESPIRATORY SIGNALS AS COMPARED TO AUTO AND MULTIPLE MANUAL SLEEP SCORINGS BASED ON NEUROLOGICAL SIGNALS

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Background: Typically, no neurological signals are recorded in home sleep apnea testing (HSAT) and thus standard sleep scoring is not applicable. Previous attempts to estimate sleep based on cardiorespiratory signals achieved Cohen's kappa coefficients up to 0.50.

Aims and objectives: To evaluate if artificial intelligence approaches can improve automatic sleep scoring performance.

Methods: Supervised deep learning for scoring sleep was trained with 472 and tested in 116 PSGs, scored independently by 2 experts and by a consensus scorer. Training was performed separately for neurological and cardiorespiratory features. The resulting recurrent neural networks (RNN) were integrated in the Somnolyzer system and validated in 97 PSGs of OSAS patients scored independently by 4 human experts. Epoch-by-epoch Cohen's kappa agreement for 4 stages (W, L: N1+N2, D: N3, R) was determined as compared to a consensus scoring without the assessed scorer included in the consensus.

Results: Cohen's kappa for the 4 manual expert scorings were 0.80 (W:0.83, L:0.76, D:0.58, R: 0.91), 0.81 (W:0.85, L:0.77, D:0.51, R: 0.91), 0.75 (W:0.85, L:0.70, D:0.43, R: 0.89), and 0.84 (W:0.88, L:0.81, D:0.63, R: 0.91), for neurological autoscoring 0.87 (W:0.93, L:0.84, D:0.66, R: 0.96) and for cardiorespiratory autoscoring 0.68 (W:0.74, L:0.63, D:0.54, R: 0.79).

Conclusions: Autoscoring based on neurological signals outperforms all human expert scorers. With a kappa of 0.68, the cardiorespiratory-based RNN classifier is far above previously published values and reflects a substantial agreement with the manual consensus scoring in patients with sleep-disordered breathing.

Presented at the 28th European Respiratory Society International Congress (ERS) 2018

RECURRENT NEURAL NETWORK FOR CLASSIFICATION OF SNORING AND NON-SNORING SOUND EVENTS

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Introduction: Obstructive sleep apnea (OSA) is a disorder that affects up to 38% of the western population. It is characterized by repetitive episodes of partial or complete collapse of the upper airway during sleep. These episodes are almost always accompanied by loud snoring. Questionnaires such as STOP-BANG exploit snoring to screen for OSA. However, they are not quantitative and thus do not exploit its full potential.

Methods: A method for automatic detection of snoring in whole-night recordings is required to enable its quantitative evaluation. In this study, we propose such a method. The centerpiece of the proposed method is a recurrent neural network for modeling of sequential data with variable length. Mel-frequency cepstral coefficients, which were extracted from snoring and non-snoring sound events, were used as inputs to the proposed network. A total of 20 subjects referred to clinical sleep recording were also recorded by a microphone that was placed 70 cm from the top end of the bed. These recordings were used to assess the performance of the proposed method.

Results: When it comes to the detection of snoring events, our results show that the proposed method has an accuracy of 95%, sensitivity of 92%, and specificity of 98%.

Conclusion: In conclusion, our results suggest that the proposed method may improve the process of snoring detection and with that the process of OSA screening. Follow-up clinical studies are required to confirm this potential.

We would like to acknowledge the support of NVIDIA Corporation with the donation of the Titan X Pascal GPU used for this research. In addition to this, we would like to thank Erik Jansen and Bertram Hoondert for their help with annotations of sound events.

B. Arsenali, J. van Dijk, O. Ouweltjes, B. den Brinker, D. Pevernagie, R. Krijn, M. van Gilst, S. Overeem. Recurrent neural network for classification of snoring and non-snoring sound events.Engineering in Medicine and Biology. 2018. (accepted for publication)

PREVALENCE AND CHARACTERISTICS OF INSOMNIA PHENOTYPE IN MILD SLEEP APNEA PATIENTS FROM THE ESADA STUDY POPULATION

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Introduction: There are limited data concerning symptoms and comorbidities in mild obstructive sleep apnea (OSA) patients. The aim of the study was to explore clinical phenotypes of mild OSA patients and their possible association with comorbidities.

Methods:A prospective follow-up cohort of 3947 adult patients with mild OSA [apnea-hypopnea index (AHI) of 5-15/h] from the ESADA study was divided into four clinical phenotypes based on the presence of excessive daytime sleepiness(EDS) and/or symptoms and signs of insomnia): 1) EDS (daytime+/nighttime-), 2) EDS/insomnia (daytime+/nighttime+), 3) non-EDS/non insomnia (daytime-/nighttime-), 4) and insomnia (daytime-/nighttime+) phenotype.

Results: The distribution of the four phenotypes were 18.9, 26.5, 19.1 and 35.5%, respectively. Sleep apnea severity expressed as AHI or the oxygen desaturation index (ODI) did not differ significantly between groups.
The insomnia phenotype patients were older ($p<0.001$), more frequently female ($p<0.05$) and current smokers. Additionally, cardiovascular comorbidity was more common in the insomnia phenotype compared with the EDS and EDS-insomnia phenotypes (56.8 vs 48.9 and 41.5%, $p=0.022$ and $p=0.01$ respectively). Metabolic, pulmonary and psychiatric comorbidities were more prevalent in the insomnia phenotype ($p<0.05$).

Conclusion: Our findings suggest that a phenotype characterized by symptoms and/or signs of insomnia, accounts for a higher prevalence of cardiometabolic disease among patients with mild OSA.

Eur Respir J 2017;50: Suppl 61:A3434. Abstract presented during the European Respiratory Society International Congress 2017, Milan (Italy), September 9-13, 2017.

UNRAVELLING THE BIOPSYCHOSOCIAL FACTORS OF FATIGUE AND SLEEP PROBLEMS AFTER TRAUMATIC BRAIN INJURY: STUDY PROTOCOL FOR A MULTICENTER LONGITUDINAL COHORT STUDY

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Background: Fatigue and sleep problems are common after traumatic brain injury (TBI) and are experienced as highly distressing symptoms, playing a significant role in the recovery trajectory and can drastically impact the quality of life and societal participation of the patient and their family and friends. However, the etiology and development of these symptoms is still uncertain.
Objective: The aim of this study is to examine the development of fatigue and sleep problems following moderate to severe TBI and explore the changes in underlying biological (pain, brain damage), psychological (emotional state) and social (support family, participation) factors across time.
Methods: Longitudinal multicenter observational cohort study with four measurement points (3, 6, 12 and 18 months post injury) including subjective questionnaires and cognitive tasks, preceded by 7 nights of actigraphy combined with a sleep diary. Recruitment of 137 moderate to severe TBI patients presenting at emergency and neurology departments or rehabilitation centers across the Netherlands is anticipated.
Results: The evolution of fatigue and sleep problems following TBI and their association with possible underlying biological (pain, brain damage), psychological (emotional state) and social (support family, participation) factors will be examined.
Conclusion: To the authors' knowledge this study is the first study that examines the development of both post-TBI fatigue and sleep longitudinally within a biopsychosocial model in moderate to severe TBI using both subjective and objective measures. Identification of modifiable factors such as mood and psychosocial stressors may give direction to the development of interventions for fatigue and sleep problems post-TBI.

The study is funded by Maastricht University.

Bruijel J., Stapert S.Z., Vermeeren A., Ponsford J.L. & van Heugten C.M. (in press). Unravelling the biopsychosocial factors of fatigue and sleep problems after traumatic brain injury: Study protocol for a multicenter longitudinal cohort study. JMIR Research Protocols.

EFFECTS OF THE SHUTI ONLINE CBT PROGRAM FOR INSOMNIA ON OBJECTIVE SLEEP MEASURED NIGHTLY BY SLEEPSCORE BY RESMED TECHNOLOGY IN SUBOPTIMAL SLEEPERS: A PILOT STUDY

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Introduction: SHUTi (Sleep Healthy Using the Internet), provided by BeHealth Solutions, is an online cognitive behavioral therapy for insomnia (CBT-I) program. SHUTi is an interactive, digital therapeutic delivering CBT-I tailored to individual users based on their own sleep patterns and goals. SHUTi consists of 6 themed cores, typically completed in 6-7 weeks. The intervention is time and content based, with users earning access to subsequent cores after completion of previous cores and the passage of time to practice strategies and techniques. SHUTi's effectiveness has been documented previously; however, most of these studies relied on self-report data (e.g., prospective sleep diaries) or single pre-post intervention objective sleep data. Our pilot study used both self-report data and objective data collected nightly using SleepScore by ResMed non-contact sleep monitoring technology.

Methods: 7 adults whose objective sleep data showed suboptimal sleep enrolled in the study. They tracked their sleep at home with the S+ by ResMed monitor before starting SHUTi and every night while following the program. 453 total nights were analyzed: 176 nights prior to program access and 277 nights during which participants actively used the program. Objective sleep data were analyzed in MLwiN using multilevel regression analyses, taking into account the nested structure of the data (nights within participants).

Results: Participants' main sleep concerns improved while using SHUTi: Number of awakenings decreased (p=.027) and duration of wake after sleep onset decreased (p=.046). On average, after finishing SHUTi, participants spent 13 fewer minutes awake at night, as well as a 6-minute average decrease in sleep onset latency (p=.000). There were also increases in 3 types of sleep-related knowledge: environmental, cognitive, and behavioral (all p's<.00). Participants reported new habits, such as maintaining a regular bedtime and going to bed only when sleepy. This resulted in a 28-minute average decrease in objectively-measured time in bed (p=.004) and, in turn, greater sleep efficiency (p=.046). Total sleep time did not increase significantly but, relative to the other sleep stages, participants objectively experienced more deep sleep (p=.003).

Conclusion: Online CBT-I is of use to improve sleep in suboptimal sleepers. Our findings also support the recommendation by the American College of Physicians that CBT-I should be the first-line treatment for insomnia complaints.

52nd Annual Convention of the Association for Behavioral and Cognitive Therapies, 15-18 November 2018, Washington, D.C.

SLEEP HOMEOSTASIS AND THE CIRCADIAN CLOCK: DO THE CIRCADIAN PACEMAKER AND THE SLEEP HOMEOSTAT INFLUENCE EACH OTHER'S FUNCTIONING?

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Sleep is regulated by a homeostatic and a circadian process. Together these two processes determine most aspects of sleep and related variables like sleepiness and alertness. The two processes are known to be able to work independently, but also to both influence sleep and sleep related variables in an additive or more complex manner. The question remains whether the two processes are directly influencing each other. The present review summarizes evidence from behavioural and electroencephalographic determined sleep, electrophysiology, gene knock out mouse models, and mathematical modelling to explore whether sleep homeostasis can influence circadian clock functioning and vice versa. There is a multitude of data available showing parallel action or influence of sleep homeostatic mechanisms and the circadian clock on several objective and subjective variables related to sleep and alertness. However, the evidence of a direct influence of the circadian clock on sleep homeostatic mechanisms is sparse and more research is needed, particularly applying longer sleep deprivations that include a second night. The strongest evidence of an influence of sleep homeostatic mechanisms on clock functioning comes from sleep deprivation experiments, demonstrating an attenuation of phase shifts of the circadian rhythm to light pulses when sleep homeostatic pressure is increased. The data suggest that the circadian clock is less susceptible to light when sleep pressure is high. The available data indicate that a strong central clock will induce periods of deep sleep, which in turn will strengthen clock function. Both are therefore important for health and wellbeing. Weakening of one will also hamper functioning of the other. Shift work and jet lag are situations where one tries to adapt to zeitgebers in a condition where sleep is compromised. Adaptation to zeitgebers may be improved by introducing nap schedules to reduce sleep pressure, and through that increasing clock susceptibility to light.

Neurobiol Sleep Circadian Rhythms 5: 68-77, 2018.

RODENTS AS A MODEL FOR SLEEP AND CIRCADIAN RHYTHM DISTURBANCES: EXPOSURE TO LIGHT AT NIGHT

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Light provides the main input to the master circadian clock in the suprachiasmatic nucleus. Exposure to light at night is associated with insomnia in humans. We developed a rodent model for the effect of light at night on sleep by exposing male Wistar rats to 12 h normal light and 12 h 5 lux dim white light (L:Dim) (Stenvers et al 2016). In the course of L:Dim exposure the amplitude of daily sleep-wake rhythms and daily rhythms found in the NREM sleep EEG power density in the faster frequencies (16-19 Hz) decreased. In addition L:Dim induced internal desynchrony by introducing a free running rhythm with a period of approximately 25 h, next to the light entrained 24-h rhythm. This is the first rodent model of disturbed circadian control of sleep due to light at night. The data show that internal desynchrony is possible in a 24-h L:Dim cycle. The data suggest that chronic sleep disturbances due to light at night in humans may have a similar origin. We recently have extended the data to young and aging mice, showing similar results in young mice. However in older mice the influence of L:Dim on sleep is relatively mild.

Stenvers DJ, van Dorp R, Foppen E, Mendoza J, Opperhuizen AL, Fliers E, Bisschop PH, Meijer JH, Kalsbeek A, Deboer T (2016) Dim light at night disturbs the daily sleep-wake cycle in the rat. Sci Rep 6: 35662.

Presented at the Latin American Symposium on Chronobiology, Valparaiso, Chili, November 2017.

CAFFEINE OR LIGHT AT NIGHT; EFFECTS ON SLEEP AND CIRCADIAN RHYTHMS IN RODENTS

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The presentation will summarize recent data regarding the influence of sleep deprivation, light and caffeine on circadian clock functioning. These can be single influences, but it has also been shown that they can interact.
Light is the most important zeitgeber for the circadian clock. Sleep deprivation was shown to reduce the phase shifting capacity of the circadian clock in response to light. Also neurons in the suprachiasmatic nucleus (SCN) were shown to respond less to light after sleep deprivation. Caffeine has been used for many centuries and in different cultures to alleviate the effects of sleep deprivation and to increase alertness. We showed that the effect of sleep deprivation on the light induced increase in SCN neuronal activity was also normalized after application of caffeine. More recently it was shown that caffeine not only decreases sleep pressure, but also slows down the circadian clock. Both in cell cultures and in intact mice and human it was shown that the clock is delayed or circadian period is increased under influence of caffeine. The effects in vivo were particularly strong when combined with constant light exposure. Thinking of Aschoff's rule it may be that in intact mice caffeine slows down the clock by increasing the effect of light on the clock.
In addition, application of caffeine in the medium of cell cultures or chronically in the drinking water can increase day-night amplitude. We have new data, extending this research, which shows that the amplitude in sleep and waking is also increased under chronic caffeine consumption in mice. Most remarkably, the animals slept deeper in the first hours of the rest phase than animals consuming normal water.
Finally, constant light or dim-light at night disturbs sleep in humans and rodents and was shown to disturb circadian rhythms, resulting in splitting of rhythms or in arrhythmia in rodents. We have now performed additional experiments in older mice and show that the effect of dim light at night is less strong in aged mice.
The data show that a clear difference between day and night in lighting conditions is important for a strong and healthy sleep-wake rhythm. The effects of chronic caffeine in rodents suggest that caffeine may have a supportive role for the central circadian pacemaker by increasing its amplitude, possibly by increasing the influence of light on the circadian clock.

Presented at the Society for Light Treatment and Biological Rhythms meeting, Groningen, The Netherlands, June 2018.

DEEPER SLEEP DURING CHRONIC CAFFEINE CONSUMPTION IN MICE

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Caffeine has a well-known impact on sleep and circadian physiology and is one of the most widely consumed psychostimulants. Most laboratory studies available investigated the acute effect of caffeine on sleep. However, in society caffeine is generally consumed chronically on a daily basis. We therefore investigated the acute and chronic effect of caffeinated drinking water on sleep and the electroencephalogram (EEG) in mice.

We recorded the EEG and electromyogram on a control day, on the first day of caffeine consumption (acute), and following two weeks of continuous caffeine consumption (chronic). In the latter condition, a 6-h sleep deprivation was conducted during the light period. For extra comparison, an additional control group of mice provided with normal drinking water was also recorded and sleep deprived.

We found that caffeine induced contrasting effects following acute and chronic consumption. Over 24h, waking increased in the acute condition, at the expense of non-rapid eye-movement (NREM) sleep, whereas no changes over 24-h were found in the chronic condition. In the acute condition EEG slow-wave activity (SWA), a well-known marker for sleep pressure, was significantly reduced. The light-dark amplitude of vigilance states increased in both acute and chronic conditions, with the highest amplitude in the chronic condition, showing an increase in sleep during the light period and an increase in waking during the dark. Furthermore, EEG SWA in NREM sleep was significantly increased during the first half of the light period of the chronic condition, compared to both controls. The sleep deprivation was more challenging and less successful under chronic caffeine.

Together with the increased SWA results, this indicates an increased sleep pressure in the chronic condition. In contrast to the traditional conception of the impact of caffeine consumption on sleep, chronic caffeine intake seems to enhance circadian amplitude, improve daily sleep-wake cycles and increase sleep depth. The results will be discussed in the context of chronic daily caffeine consumption in society.

Presented at the European Sleep Research Society meeting, Basel, Switzerland, September 2018.

THE CONTRIBUTION OF A BODY SCAN MINDFULNESS MEDITATION TO EFFECTIVENESS OF INTERNET-DELIVERED CBT FOR INSOMNIA IN ADOLESCENTS

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Introduction. Insomnia is highly prevalent among adolescents and has severe consequences for daily life, including other mental disorders. Treatment of adolescents with cognitive behavioral therapy for insomnia (CBTI) can be effective in internet-delivered and face-to-face modalities. However, it is yet unclear what the contribution is of mindfulness-based techniques to the effectiveness of traditional CBTI. The present study investigated the relation between the use of a body scan mindfulness meditation, with effectiveness of CBTI for adolescents.

Method. Adolescents who received 6 weeks of internet-CBTI were divided into a group who practiced a body scan meditation (BG; age M = 15.33yr, SD = 1.42, 77% girls) and a group who did not (NBG; N= 28, age M = 15.64yr, SD = 1.80). Differences between the groups were analyzed for subjective and objective sleep outcomes from baseline to post-treatment and to 2 months follow-up.

Results. Results showed moderate to large effect size improvements of sleep parameters from 7-day actigraphy and sleep logs measurements, and large effect size decreases of self-reported symptoms of insomnia and chronic sleep reduction, at post-treatment for both groups, and improvements were maintained at follow-up. However, where the NBG showed no significant change of wake after sleep onset from actigraphy, and self-reported shortness of sleep and irritation, there were medium effect size improvements of these outcomes in the BG group.

Conclusion. These results could indicate that the use of a body scan mindfulness meditation in CBTI may have an additional positive effect on sleep, above and beyond traditional CBTI techniques.

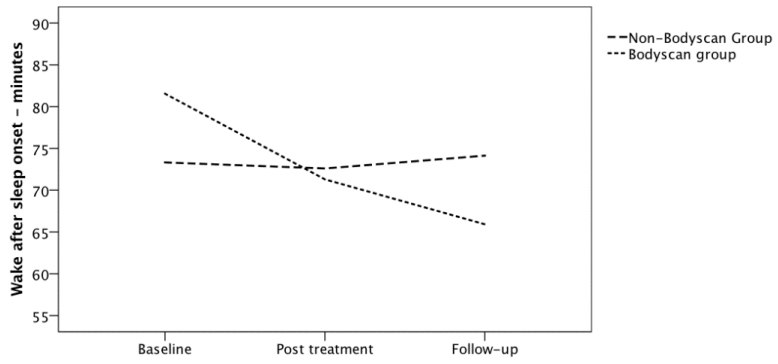

Figure 1. Differential effects of CBTI on wake after sleep onset, for adolescents who did or did not practice a body scan mindfulness meditation.

International Conference on Mindfulness (ICM), Amsterdam, 2018

A PREVENTIVE ADOLESCENT SLEEP INTERVENTION FOR TEACHERS IN SECONDARY EDUCATION: A PILOT STUDY

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Introduction. Sleep problems are common among adolescents and can have severe physical and mental health consequences. However, to date school-based sleep interventions have hardly been investigated. This exploratory pilot study investigated the effects of a preventive sleep intervention aimed at teachers in secondary education.

Method. Fourteen teachers (age = 39.93, SD = 13.58; gender = 9m, 5f) participated in a 3hr. workshop that focused on the education and prevention of sleep problems among students, and that prepared teachers for the application of three lessons on sleep for their students. Through questionnaires and an interview, perceptions and attitudes about adolescents' sleeping behavior, and knowledge about adolescent sleep were measured. Results were compared to a control group (*n*=19; age = 45.26, SD = 14.08; gender = 9 m, 10 f). Transcripts from the interviews were analyzed by two independent researchers using *Interpretative Thematic Analysis*.

Results. From the Interpretative Thematic Analysis of the interviews, seven themes emerged, of which *severity of the problem*, *lack of preventive tools*, and *possible causes* were mentioned most frequent. Principle component analyses yielded three subscales from the questionnaire on perceptions and attitudes about adolescents' sleeping behavior. After participation in the workshop the participants' scores for the subscale *Willingness to act* increased significantly compared to the control group ($F(2,20) = 4.345$, $p = .027$). There were no significant changes in the subscales *Interest* and *Importance of sleep,* which were already relatively high (i.e. 'ceiling-effect'). Furthermore, knowledge about adolescent sleep increased significantly in the participant group compared to the control group ($F(2,20) = 4.072$, $p = .033$).

Conclusion. These preliminary results indicate that a preventive sleep intervention for teachers in secondary education can be effective in providing tools and knowledge to teachers. More research in a randomized controlled design is warranted.

IPSA, Parijs, 2018.

LONG-TERM EFFECTS OF SLEEP DEPRIVATION ON NEURONAL ACTIVITY IN FOUR HYPOTHALAMIC AREAS

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Lack of adequate sleep has become increasingly common in our 24/7 society. Unfortunately diminished sleep has significant health consequences including metabolic and cardiovascular disease and mental disorders including depression. The pathways by which reduced sleep adversely affects physiology and behavior are unknown.
We found that 6h of sleep deprivation in adult male rats induces changes in neuronal activity in the lateral hypothalamus, the paraventricular nucleus, the arcuate nucleus and the mammillary bodies. Surprisingly, these alterations last for up to 48h.
The data show that sleep loss has prolonged effects on the activity of multiple hypothalamic areas. Our data indicate also that measuring electroencephalographic slow wave activity underestimates the amount of time that the hypothalamus requires to recover from episodes of sleep deprivation. We propose that these hypothalamic changes underlie the well-established relationship between sleep loss and several diseases such as metabolic disorders, stress and depression and that sufficient sleep is vital for autonomic functions controlled by the hypothalamus.

The authors would like to thank Drs. D. Swaab and Y.D. van der Werf for comments on previous versions of this manuscript and C.F. Barrett for editing. This work was supported by a post-doc fellowship from Foundation FYSSEN (K.F.), the European Community's Marie Sklodowska-Curie IEF Programme under contract 655135, "The Role of Dopamine in the Regulation of Sleep and Circadian Rhythms(CIRCADOPAMINE)." (K.F.), a grant from the Dutch Technology Foundation (STW, T. D.).

Neurobiol Dis 109: 54-63, 2018.

CIRCADIAN AND HOMEOSTATIC MODULATION OF MULTI-UNIT ACTIVITY IN MIDBRAIN DOPAMINERGIC STRUCTURES

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Although the link between sleep disturbances and dopamine (DA)-related neurological and neuropsychiatric disorders is well established, the impact of sleep alterations on neuronal activity of midbrain DA-ergic structures is currently unknown.
Here, using wildtype C57Bl mice, we investigated the circadian- and sleep-related modulation of electrical neuronal activity in midbrain ventral-tegmental-area (VTA) and substantia nigra (SN).
We found no significant circadian modulation of activity in SN while VTA displayed a low amplitude but significant circadian modulation with increased firing rates during the active phase. Combining neural activity recordings with electroencephalogram (EEG) recordings revealed a strong vigilance state dependent modulation of neuronal activity with increased activity during wakefulness and rapid eye movement sleep relative to non-rapid eye movement sleep in both SN and VTA. Six-hours of sleep deprivation induced a significant depression of neuronal activity in both areas. Surprisingly, these alterations lasted for up to 48 hours and persisted even after the normalization of cortical EEG waves.
Our results show that sleep and sleep disturbances significantly affect neuronal activity in midbrain DA structures. We propose that these changes in neuronal activity underlie the well-known relationship between sleep alterations and several disorders involving dysfunction of the DA circuitry such as addiction and depression.

This work was supported by the European Community's Marie Sklodowska-Curie IEF Programme under contract 655135, "The Role of Dopamine in the Regulation of Sleep and Circadian Rhythms (CIRCADOPAMINE)." (K.F.).

Sci Rep 8: 7765, 2018.

HEART-RATE VARIABILITY-BASED SLEEP STAGING IN HEALTHY SUBJECTS AND PATIENTS WITH SLEEP DISORDERS

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[d] Kempenhaeghe Foundation, Sleep Medicine Centre, the Netherlands

Introduction: The last few years have seen an increase in publications on sleep staging using cardiac and respiratory features. Some of the best recent algorithms achieved Cohen's kappa coefficients up to 0.50 in comparison with polysomnography (PSG). However, most studies have focused on the analysis of healthy participants, and the question of how well these algorithms generalize to sleep disordered patients remains unanswered.

Objectives: To evaluate and compare the 4-class sleep stage classification (Wake, N1+N2, N3 and REM) performance of a long short term memory (LSTM) classifier using heart rate variability (HRV) in healthy subjects as well as sleep disorders patients.

Methods: A total of 136 features describing HRV computed from ECG were used to train an LSTM model for sleep stage classification. The analysis was done in the PSG recordings of the SIESTA dataset, using the manual annotations of 3 experts as ground-truth. The model was trained and evaluated in 4-fold cross-validation with two recordings of each of 195 healthy participants, 51 patients diagnosed with sleep apnea, and 26 with insomnia, all based on the ICD-10 criteria. The performance between different groups and, for the healthy controls, between sexes was compared with a Mann-Whitney U test. Pearson's correlation was used to test correlation with age for the healthy control group.

Results: The overall validation kappa was 0.64. The performance for healthy participants (0.64) was not significantly different than for insomnia (0.66, $p = .18$), but was significantly higher than for sleep apnea (0.60, $p < .001$). Kappa decreased significantly with age (-0.41, $p < .001$) and a significant difference was found between healthy males and females (0.62 vs 0.66, $p < .01$).

Conclusions: With an overall kappa of 0.64 our classifier achieves better performance than recently published algorithms, for healthy and for sleep disordered patients. The slightly lower performance for sleep apnea can be explained by changes in the characteristics of the HRV features which, in the presence of disordered breathing events, fail to completely characterize the differences between sleep stages.

Presented at the 24th Congress of the European Sleep Research Society (ESRS) 2018

A COMPARISON OF PROBABILISTIC CLASSIFIERS FOR SLEEP STAGE CLASSIFICATION

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Objective: To compare conditional random fields (CRF), hidden Markov models (HMMs) and Bayesian linear discriminants (LDs) for cardiorespiratory sleep stage classification on a five-class sleep staging task (wake/N1/N2/N3/REM), to explore the benefits of incorporating time information in the classification and to evaluate the feasibility of sleep staging on obstructive sleep apnea (OSA) patients.

Approach: The classifiers with and without time information were evaluated with 10-fold cross-validation on five-, four- (wake/N1 + N2/N3/REM) and three-class (wake/NREM/REM) classification tasks using a data set comprising 443 night-time polysomnography (PSG) recordings of 231 participants (180 healthy participants, 100 of which had a 'regular' sleep architecture, and 51 participants previously diagnosed with OSA).

Main results: CRF with time information (CRFt) outperforms all other classifiers on all tasks, achieving a median accuracy and Cohen's κ for all participants of 62.8% and 0.44 for five classes, 68.8% and 0.47 for four classes, and 77.6% and 0.55 for three classes. An advantage was found in training classifiers, specifically for 'regular' and 'OSA' participants, achieving an improvement in classification performance for these groups. For 'regular' participants, CRFt achieved a median accuracy and Cohen's κ of 67.0% and 0.51, 70.8% and 0.53 and 81.3% and 0.62 for five-, four- and three-classes respectively, and for 'OSA' patients, of 59.9% and 0.40, 69.7% and 0.45, and 75.8% and 0.51 for five-, four- and three-classes respectively.

Significance: The results suggest that CRFt is not only better at learning and predicting more complex and irregular sleep architectures, but that it also performs reasonably well in five-class classification—the standard for sleep scoring used in clinical PSG. Additionally, and albeit with a decrease in performance when compared with healthy participants, sleep stage classification in OSA patients using cardiorespiratory features and CRFt seems feasible with reasonable accuracy.

Fonseca P, den Teuling N, Long X, Aarts RM. A comparison of probabilistic classifiers for sleep stage classification. Physiol Meas, 39 (055001).

SUSTAINED ATTENTION TO RESPONSE TASK (SART) SHOWS IMPAIRED VIGILANCE VERSATILITY IN NARCOLEPSY TYPE 1 IN AN MRI ENVIRONMENT

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Introduction: Narcolepsy type 1 patients suffer from reduced vigilance levels, severely impairing their daytime performance and quality of life. As hypocretin is known to normally project towards neural attention regulation areas, we assessed the capacity of patients to adapt to changes in vigilance demand using a modified Sustained Attention to Response Task (SART), while simultaneously acquiring EEG-fMRI to identify the functional neural correlates underlying patient's vigilance deficits.

Methods: Twelve drug-naïve ICSD-3-diagnozed narcolepsy type 1 patients and 12 one-on-one age- and gender-matched controls completed the SART while simultaneous EEG-fMRI measurements were recorded. During the SART participants were asked to refrain from pressing keys to one in nine stimuli in two difficulty levels, which differed in stimulus duration. Between-group and repeated-measures analyses (to evaluate the effect of increasing vigilance demand) were performed. Outcome measures were average reaction speed of correct presses, percentage of mistakes and d-prime score as a weighted performance indicator correcting the hit-rate for the false alarm-rate.

Results: By switching from medium to high vigilance demand, patients - but not controls - made significantly more mistakes ($P = 0.018$) and had a lower d-prime score ($P = 0.013$). Patients reacted significantly slower than controls in the more difficult level ($P = 0.048$). No significant differences between groups in test performance and within-group average reaction speed between difficulty levels were found.

Conclusions: We conclude that narcolepsy patients tend to react more slowly than healthy controls, explained by their intrinsically reduced reaction speed and as a coping mechanism to improve precision. When vigilance demand increases, patients are unable to further utilize this speed-accuracy trade-off mechanism, indicating that narcolepsy type 1 patients suffer from impaired regulation of vigilance. The modified SART is a reliable vigilance test in an MRI environment.

J Sleep Res. 2012 Aug;21(4):390-5.

MELATONINEBEHANDELING VOOR SLAAP-WAAKSTOORNISSEN

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Natuurlijk melatonine is een signaal van onze biologische klok. Melatoninebehandeling kan diezelfde klok gelijk zetten; afhankelijk van het tijdstip van toedienen zal de klok verschuiven en daarmee het moment bepalen dat we optimaal slapen. Melatoninebehandeling is geïndiceerd bij inslaapstoornissen als gevolg van verstoringen van de biologische klok: het vertraagde slaapfasesyndroom, bij kinderen met ADHD of met een diagnose in het autismespectrum, bij blinden en bij klachten als gevolg van jetlag. Er zijn enkele aanwijzingen dat het slaap bij dementiepatiënten kan verlengen en bij ouderen het risico op het ontwikkelen van een delier bij opname op de intensivecareafdeling kan verkleinen. Internationale richtlijnen voor de behandeling van primaire insomnie zien geen rol voor melatonine als slaapmiddel.

Psyfar, maart 2018 nummer 1: 9-17

EFFECTIVENESS OF CBTI IN ADOLESCENTS WITH COMORBID DISORDERS: A STUDY IN A SINGLE CASE EXPERIMENTAL DESIGN

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Introduction. Cognitive Behavioral Therapy for Insomnia (CBTI) is an effective treatment for insomnia in adolescents. However, little is still known about effectiveness of CBTI in clinical practice, and with adolescents with comorbid disorders.

Method. In the current study the effectiveness of the CBTI group protocol 'SlimSlapen' was investigated in a Single Case Experimental Design with pre- and post-tests and 2-months follow-up. Five participants with comorbid disorders (M = 14.8yr, SD = 1.1; 3 girls) received CBTI in six weekly group sessions of 1:30hr each. Reliable Change Index (RCI) was used to analyze pre-post data from questionnaires on insomnia (Holland Sleep Disorder Questionnaire) and comorbid complaints (Child Behavior Check List), and Simulation Modeling Analysis (SMA) was used to analyze level- and slope-change of repeated measures over six weeks and follow-up, from sleep diaries. Cross correlations were used to analyze process of change.

Results. After insomnia treatment, insomnia complaints in all participants improved (RCIs between 2.22 and 6.21). In addition, sleep parameters improved significantly for most participants and most improvements were maintained at follow-up (level- and slope change from SMA between r = -.45 and r = -.64 for sleep onset latency, r = -.68 for wake after sleep onset, and r = .47 for total sleep time). Analyses of process of change indicated that these improvements were related to the degree of implementation of the techniques of CBTI, in particular sleep hygiene, and restriction of time in bed. Some comorbid complaints improved significantly after CBTI (RCIs anxiety/depression = -2.76, somatic complaints = -2.99).

Conclusion. This study indicates that CBTI is effective in clinical practice, and improvements appear to be mostly related to the degree of implementation of sleep hygiene, and restriction of time in bed. In addition, some comorbid complaints improved after CBTI.

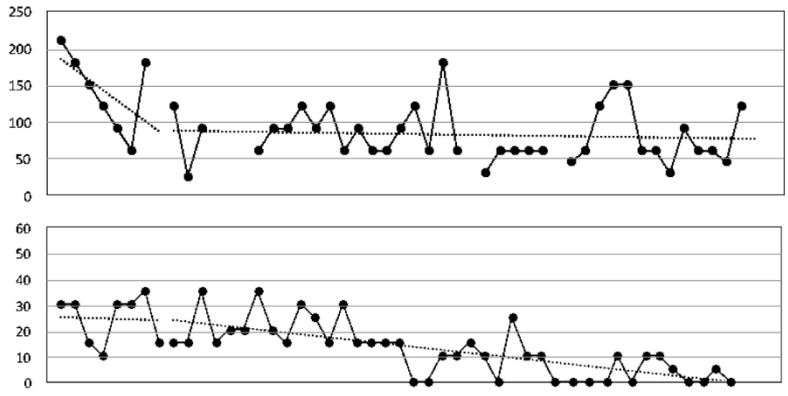

Figure 1. Decrease of SOL (top) and WASO of two participants over six weeks of CBTI.

Submitted

SLEEP ONSET MISPERCEPTION IS ASSOCIATED WITH SLEEP INSTABILITY

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Chronic insomnia is a widespread problem, affecting about ten percent of the adult population. Insomniacs often overestimate their sleep onset latency (SOL). This misperception might be explained by abnormalities in the sleep EEG, for instance increased hyperarousal, reflected by a lower delta/beta spectral power ratio. Other EEG abnormalities playing a role in sleep onset misperception might be impaired sleep protection mechanisms, reflected by an altered sleep spindle index, or sleep fragmentation, such as more wake after sleep onset (WASO) and increased presence of light sleep stages. In this study, we aim to identify which of these mechanisms are involved in misperception of the SOL.

Standard in-lab polysomnographic (PSG) recordings were performed in 20 insomniacs and 21 self-defined good sleepers. The EEG microstructure was analyzed using Philips Somnolyzer software. Sleep stages were scored visually. We assessed differences between the two groups with respect to objective SOL, delta/beta spectral power ratio, microarousals, sleep spindle index, number of awakenings, WASO and number of sleep stage transitions. Additionally, we assessed the correlation between these variables and misperceived sleep onset. Misperceived sleep onset was expressed as the amount of objectively measured Sleep During Subjective Latency (SDSL), according to Saline et al. (2016). The insomniacs and healthy subjects had comparable objective SOL. Both groups showed sleep onset misperception (SDSL 40 ± 54 vs. 15 ± 29 minutes). Insomniacs had a significantly lower delta/beta spectral power ratio in N2 (45.3 ± 19.0 vs. 65.8 ± 29.6) and more arousals/hour during the combined NREM stages (13.6 ± 5.8 vs. 9.9 ± 5.3). Additionally, insomnia patients had a higher sleep spindle index for both low and high frequency spindles (low: 0.73 ± 0.84 vs. 0.36 ± 0.47 and high: 1.24 ± 1.20 vs. 0.71 ± 0.93). No differences in any other variables were found. The amount of SDSL was positively associated with the percentage of N1 ($r=0.40$, $p=0.0095$) and WASO during the first sleep cycle ($r=0.32$, $p=0.04$). Delta/beta spectral power ratio, arousals and sleep spindle index were not associated with SDSL.

In this study, insomnia patients showed high frequency EEG activity and an increased number of arousals, which are signs of hyperarousal, as well as an increased sleep spindle index. Interestingly, these characteristics were not associated with sleep onset misperception. Instead, sleep onset misperception was associated with variables indicating lighter and more fragmented sleep. Based on this results and Bonnet's sleep continuity theory[2], stating that an uninterrupted sleep fragment of at least ten minutes is required for restorative sleep, one could hypothesize that too short sleep fragments are not perceived as sleep. Alternatively, based on the association of SDSL with WASO, it is possible that long fragments of WASO alter the perception of the sleep onset and therefore preceding fragments of sleep could be missed.

2nd International Conference on Sleep Spindles and Related Phenomena, May 24-26, Budapest, Hungary

MODELLING SLEEP STATE MISPERCEPTION AT SLEEP ONSET

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Insomnia patients often overestimate their sleep onset latency (SOL). The mechanism underlying this type of sleep state misperception is not fully understood. We hypothesize that the length of uninterrupted sleep fragments after sleep onset influences the perception of the SOL because too short sleep fragments might be overlooked. We attempt to make a model of the minimum length that a sleep fragment should have in order to be perceived as sleep, and we fit the model to subjective data of insomniacs and healthy controls.

Standard in-lab polysomnographic recordings were performed in 20 elderly, untreated insomniacs and 21 age-matched self-defined good sleepers. Recordings were visually scored according to R&K criteria. In the model sleep onset was defined as the first epoch of the first sleep fragment longer than L minutes, with L varying from 0.5 to 40. We selected the length L that resulted in the smallest Mean Square Error (MSE) of the difference between modelled SOL and SOL perceived by the subject. This was done for both subject groups separately.

For insomniacs, the lowest MSE was found for a length L of 30 minutes (MSE without model: 7195 vs. L=30: 3927). In the healthy subjects, applying the model only resulted in small improvements of the MSE. The lowest MSE was found for L=10 (MSE without model: 1185 vs. L=10: 969), although the results for all model parameters L below 20 were very similar.

The aim of this study was to investigate the mechanisms underlying sleep onset misperception, by modelling the influence of sleep interruption on subjective SOL. The results indicate that in insomnia patients the perception of sleep onset can be influenced if a sleep fragment is interrupted after less than 30 minutes. The different results for the two groups suggest that, for the perception of sleep onset, insomniacs are more sensitive to sleep interruption than healthy subjects. In order to extend our findings to the general population, the analysis should be repeated in different age groups. Additionally, other parameters could be added to the model, for instance sleep depth and the duration of the sleep disruption.

24th *Congress of the European Sleep Research Society, September 25-28, Bazel, Switzerland*

EPIDEMIOLOGY OF SLEEP AND SLEEP DISORDERS IN THE NETHERLANDS

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Introduction: There is a surging public interest in The Netherlands concerning sleep, sleep disorders and associated health. For a proper perspective, it is necessary to have reliable information on the prevalence of sleep characteristics at the national level. This study set out to assess prevalence rates and key characteristics of sleep and sleep disorders in The Netherlands.

Methods: In 2012, a nationally representative sample of 2089 individuals, aged 18 - 70 years, responded to a set of 48 questions, including the Holland Sleep Disorders Questionnaire, a validated questionnaire based on the International Classification of Sleep Disorders.

Results: Prevalence rates were: 32.1% for a general sleep disturbance (GSD), 43.2% for insufficient sleep, 8.2 for insomnia, 5.3% for circadian rhythm sleep disorder, 6.1% for parasomnia, 5.9% for hypersomnolence, 12.5% for restless legs disorder and limb movements during sleep, 7.1% for sleep related breathing disorder, and 12.2% for the presence of comorbidity, i.e. the presence of two or more concurrent sleep disorders. In addition, sleep onset time as well as sleep duration showed U-shaped relationships with GSD prevalence rates, with respectively the 22:00 - 24:00 period and seven to 8 h as optimal associates.

Conclusion: Sleep disorders and insufficient sleep have a high prevalence. As matter of concern, female adolescents reached the highest prevalence rates for most sleep disorders, insufficient sleep and daytime malfunctioning.

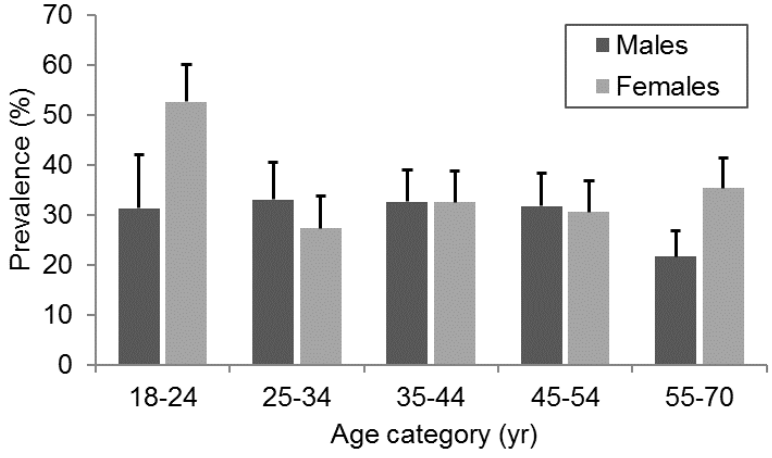

Figure 1. Prevalence ratio's (with upper 95% confidence intervals) of a general sleep disturbance for males and females vs age categories.

Sleep Medicine, 2017, 30: 229-239

SHIFT WORK AND SLEEP DISORDER COMORBIDITY TEND TO GO HAND IN HAND

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Introduction: Taking into consideration that shift work has a wide-ranging impact on circadian and sleep functioning, it is likely that shift work increases the risk of a general sleep disturbance, spread out over a multitude of comorbid sleep disorders. The aim of the present study was to compare shift workers with permanent day workers with respect to the outcomes of a validated sleep disorder questionnaire.

Methods: The sleep disorder data of 250 shift workers and 971 permanent day workers were taken from a nationally representative sample, collected in 2012. Additional data concerning duration, timing and quality of sleep, daytime functioning and social/family variables were added to the analyses.

Results: The results showed that the shift workers experienced significantly more difficulties with the variability of their sleep times, reported more napping and considered themselves more as poor sleepers than the day workers. Most importantly, shift work, in comparison with day work, appeared associated with a significantly higher prevalence of the clinical, International Classification of Sleep Disorders' defined symptoms of nearly all main sleep disorders (including symptoms of shift work disorder). For shift workers, the prevalence of a general sleep disturbance was 39.0 (95%CI 33.2 – 45.2), significantly higher than for day workers (24.6%, 95%CI 22.0 – 27.4). Moreover, shift workers were characterized by high levels of sleep disorder comorbidity. In addition, exclusively for shift workers, the prevalence of disordered sleep systematically decreased across decades of life and was considerably higher for single vs partnered shift workers.

Conclusion: The present study adds to the findings of earlier research by showing that shift work, compared with permanent day work, is associated with a higher prevalence of clinically validated, ICSD-defined symptoms of nearly all main sleep disorders, i.e. insomnia, circadian rhythm sleep-wake disorder, parasomnia, hypersomnolence, and leg movement disorder. Additionally, the prevalence of the symptoms of shift work disorder among shift workers was estimated at 12.4%, slightly above the average prevalence of the six specific sleep disorders (10.2%). Most noteworthy, the present study reveals that sleep disorder comorbidity was more than twice as prevalent among shift workers (18.8%) than among day workers (8.1%), and that the 'degree' of comorbidity correlated significantly with a global sleep disturbance score (rho 0.76). This study adds to the insight into the interacting factors that determine shift work coping and may play a role in occupational health interventions aimed at reducing sleep problems and thus improving the resilience and tolerance of the shift worker.

Chronobiology International, 2018, 35: 219-228

DIM LIGHT, SLEEP TIGHT, AND WAKE UP BRIGHT – SLEEP OPTIMIZATION IN ATHLETES BY MEANS OF LIGHT REGULATION

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Despite sufficient opportunity to sleep, athletes reveal relatively poor sleep estimates. Timing and consolidation of sleep is driven by the circadian system, which requires periodic light-dark exposure for stable entrainment to the 24-hour day. Insufficient morning light exposure and evening light pollution may cause sleep problems. This study sought to determine whether combining fixed sleep-wake schedules with morning light exposure and short-wavelength light restriction in the evening (light regulation), as compared to a fixed sleep-wake schedule only (no light regulation), could optimize sleep in recreational athletes.

The study had a within-subject crossover design. Twenty-six athletes (mean age 24.64 years ± 3.43; 14 female, 12 male) were randomly assigned to start the intervention with either the light-regulation-week or the no light-regulation-week. Sleep was monitored by means of sleep diaries and actigraphy.

Data indicated low protocol adherence regarding the fixed sleep-wake schedules, therefore two datasets were constructed; one including athletes who kept a strict sleep-wake schedule (N = 8), and one that also included athletes who had a more lenient sleep-wake schedule (N = 25). Light regulation improved self-reported sleep onset latency (Δ SOL = 8 minutes; lenient sleep-wake schedule) as compared to no light regulation. This effect was stronger (Δ SOL = 17 minutes) and complemented by enhanced subjective sleep quality in case of a strict sleep-wake schedule. None of the actigraphy-based estimates differed significantly between conditions. Light regulation may be considered an effective sleep optimization strategy for athletes, but less obtrusive methods should be explored to increase protocol compliance.

This research was funded by STW Technology Foundation, The Netherlands under Grant Number [STW 12865].

Knufinke, M., Nieuwenhuys, A., Geurts, S.A.E., Møst, E. I. S., Moen, M. H., Maase, K., Coenen, A. M. L., Gordijn, M.C.M., & Kompier, M. A. J. (under review). Dim light, sleep tight and wake up bright - sleep optimization in athletes by means of light regulation.

THE BI-DIRECTIONAL ASSOCIATION BETWEEN SLEEP PROBLEMS AND AUTISM SPECTRUM DISORDER: A POPULATION-BASED COHORT STUDY

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Background: Sleep difficulties are prevalent in children with Autism Spectrum Disorder (ASD). The temporal nature of the association between sleep problems and ASD is unclear because longitudinal studies are lacking. Our aim is to clarify whether sleep problems precede and worsen autistic traits and ASD or occur as a consequence of the disorder.

Methods: Repeated sleep measures were available at 1.5, 3, 6, and 9 years of age in 5151 children participating in the Generation R Study, a large prospective birth cohort in the Netherlands. Autistic traits were determined with the Pervasive Developmental Problems score (PDP) of the Child Behavior Checklist (CBCL) at 1.5, and 3 years and the Social Responsiveness Scale (SRS) at 6 years. This cohort included 81 children diagnosed with ASD.

Results: Sleep problems in early childhood were prospectively associated with a higher SRS score, but not when correcting for baseline PDP score. By contrast, a higher SRS score and an ASD diagnosis were associated with more sleep problems at later ages, even when adjusting for baseline sleep problems. Likewise, a trajectory of increasing sleep problems was associated with ASD.

Conclusions: Sleep problems and ASD are not bidirectionally associated. Sleep problems do not precede and worsen autistic behaviour, but rather co-occur with autistic traits in early childhood. Over time, children with ASD have an increase in sleep problems, whereas typically developing children have a decrease in sleep problems. Our findings suggest that sleep problems are part of the construct ASD.

We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, ZonMw, the Netherlands Organisation for Scientific Research (NWO), and the Ministry of Health, Welfare and Sport.

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., . . . Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: a population-based cohort study. Mol Autism, 9, 8. doi:10.1186/s13229-018-0194-8194

PRENATAL AND EARLY POSTNATAL MEASURES OF BRAIN DEVELOPMENT AND CHILDHOOD SLEEP PATTERNS

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Background: Brain development underlies maturation of sleep patterns throughout childhood. Intrauterine head growth -marker of early neurodevelopment- has not been associated with childhood sleep characteristics. We explored associations between ultrasonographic measures of prenatal and early postnatal neurodevelopment and childhood sleep.

Methods: Six-thousand-five-hundred-twenty-eight children from a population-based birth cohort (Generation R) were included. Head circumference (HC) and lateral ventricles size were assessed with mid- and late-pregnancy fetal ultrasounds, and with cranial ultrasound 3-20 weeks postnatally. Mothers reported children's sleep duration at 2 and 3 years, and sleep problems at 1.5, 3 and 6 years.

Results: Larger ventricular size, but not HC, was related to longer sleep duration at 3 years (β=0.06hrs, 95%CI:0.02;0.10 in late-pregnancy and β=0.11hrs, 95%CI:0.02;0.20 in early infancy, mid-pregnancy parameters were unrelated to sleep duration). Larger HC in mid-pregnancy was associated with a reduced risk for being a "problematic sleeper" up to age 6 (OR:0.94, 95%CI:0.89;0.99). Consistently, children with larger HC in early infancy were less likely to be "problematic sleepers" at 3 and 6 years.

Conclusions: This study shows that variations in fetal and neonatal brain size may underlie behavioral expression of sleep in childhood. Albeit small effect estimates, these associations provide evidence for neurodevelopmental origins of sleep.

The first phase of the Generation R Study was made possible by financial support from the Erasmus Medical Centre and The Netherlands Organization for Health Research and Development (Zon MW Geestkracht Program 10.000.1003 and VIDI Grant 017.106.370 to HT). ERAWEB scholarship grant financed by the European Commission was granted to DK (grant agreement 2013–2548/001-001-EMA-2).

Pediatr Res. 2018 Apr;83(4):760-766

MELATONIN, BODY TEMPERATURE AND ALERTNESS RESPONSE TO LATE EVENING LIGHT ARE REDUCED BY EARLY EVENING LIGHT EXPOSURE

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Introduction. Evening light can acutely affect melatonin levels, sleepiness and body temperatures. The objective of the current study was to test whether responses to one-hour evening light exposure are reduced when these are preceded by bright light exposure instead of dim light exposure during the beginning of the evening.
Methods. In a randomized crossover study, 12 healthy females participated in three sessions during which melatonin, subjective sleepiness and body temperature were measured. These evening sessions were scheduled to compare the effects of dim light (A), a 1-hour evening light pulse (750 lx, 4000 K starting at 22.30) (B), and the same light pulse (750 lx, 4000 K starting at 22.30) but now preceded by 2.5-hours of bright light (1200 lx, 4000 K starting at 18:30) (C).
Results. As expected, the melatonin levels and subjective sleepiness were reduced, and the change in the (absolute value of the) skin temperature gradients was larger, during the 1-hour evening light exposure (B) as compared to dim light exposure (A). When the 1-hour light exposure was preceded by 2.5-hour exposure to bright light (C), the effects of the 1-hour evening light pulse on melatonin and body temperatures were significantly reduced and the reduction in subjective sleepiness was absent (Figure 1).
Conclusion. The study results demonstrate that 2.5-hour bright light exposure at the beginning of the evening, can reduce the response to a 1-hour light pulse in the late evening. The effects of the light pulse on melatonin, subjective sleepiness and skin temperature gradients were reduced when this was preceded by bright light instead of dim light. By itself, a 2.5-hour bright light exposure in the early evening can already reduce the sleep-disruptive influence of light exposure in the late evening. Future studies are required to test whether prior (daytime) light exposure can also reduce the circadian phase delaying response to evening light.

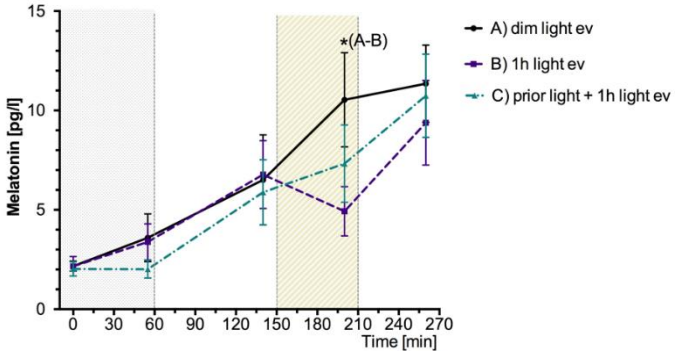

Figure 1. Melatonin concentration during the evening for the different light sessions

This project was funded by the STW–Philips Electronics Nederland B.V. Partnership Program 'Advanced Sustainable Lighting Solutions' (no. 12733).

Abstract presented at the SLTBR meeting 2018 Groningen; June 21 to June 24 2018.

CONVERGENT AND CONSTRUCT VALIDITY AND TEST–RETEST RELIABILITY OF THE CAEN CHRONOTYPE QUESTIONNAIRE IN SIX LANGUAGES

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Introduction: Chronotype questionnaires provide a simple and time-effective approach to assessing individual differences in circadian variations. Chronotype questionnaires traditionally focused on one dimension of chronotype, namely its orientation along a continuum of morningness and eveningness. The Caen Chronotype Questionnaire (CCQ) was developed to assess an additional dimension of chronotype that captures the extent to which individual functioning varies during the day (amplitude). The aim of this study was to provide a multilanguage validation of the CCQ in six world regions (Arabic, Dutch, German, Italian, Portuguese and Spanish).

Methods: At Time 1, a total of 2788 participants agreed to take part in the study (Arabic, n = 731; Dutch, n = 538; German, n = 329; Italian, n = 473; Portuguese, n = 361; Spanish, n = 356). Participants completed an assessment of the CCQ together with the Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg 1976) as well as questions related to factors theoretically related to chronotype (age, shift work, physical activity, sleep parameters and coffee consumption). One month later, participants again completed the CCQ.

Results: Results showed that the two-factor structure (morningness-eveningness and amplitude) of the CCQ could be replicated in all six languages. However, measurement invariance could not be assumed regarding the factor loadings across languages, meaning that items loaded more on their factors in some translations than in others. Test–retest reliability of the CCQ ranged from unacceptable (German version) to excellent (Dutch, Portuguese). Convergent validity was established through small–medium effect size correlations between the morningness-eveningness dimension of the CCQ and the MEQ.

Conclusion: Taken together, our findings generally support the use of the translated versions of the CCQ. Further validation work on the CCQ is required including convergent validation against physiological markers of sleep, health and well-being.

Chronobiology International, DOI: 10.1080/07420528.2018.1475396

WHITE LIGHT DURING DAYTIME DOES NOT IMPROVE ALERTNESS IN WELL-RESTED INDIVIDUALS

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Introduction: Broad-spectrum light applied during the night has been shown to affect alertness in a dose-dependent manner. The goal of this experiment was to investigate whether a similar relationship could be established for light exposure during daytime.

Methods: Fifty healthy participants were subjected to a paradigm (0730-1730 h) in which they were intermittently exposed to 1.5 h of dim light (<10 lux) and 1 h of experimental light (24-2000 lux). The same intensity of experimental light was used throughout the day, resulting in groups of 10 subjects per intensity. Alertness was assessed with subjective and multiple objective measures.

Results: A significant effect of time of day was found in all parameters of alertness ($p < 0.05$). Significant dose-response relationships between light intensity and alertness during the day could be determined in a few of the parameters of alertness at some times of the day; however, none survived correction for multiple testing.

Conclusion: We conclude that artificial light applied during daytime at intensities up to 2000 lux does not elicit significant improvements in alertness in non-sleep-deprived subjects.

This research was funded by the University of Groningen Campus Fryslân (grant #01110939; cofinanced by Philips Drachten and provincie Fryslân).

Journal of Biological Rhythms in press, https://doi.org/10.1177/0748730418796036

SUBJECTIVE SLEEP QUALITY IS NOT ASSOCIATED WITH INCIDENT DEMENTIA: THE ROTTERDAM STUDY

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Introduction: Poor sleep is related to higher dementia risk, but this association is more equivocal for subjective sleep quality specifically. This study investigates the link between subjective sleep quality and dementia risk in the general population.

Methods: In the prospective population-based Rotterdam Study, 4,835 persons (mean age 72 years, 58% women) underwent a home interview (2002-2006) that included the validated Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality. Participants were followed until 2015 for incident dementia, through in-person screening and continuous monitoring of medical records. We used Cox regression models to associate sleep quality with dementia risk, adjusting for age, sex, education, smoking, employment, coffee consumption, alcohol consumption, activities of daily living, cardiovascular risk factors, anxiety, depressive symptoms, cognition and snoring.

Results: During 41,385 person-years (8.5 years mean), 420 participants developed dementia, of whom 320 Alzheimer's disease (AD). Poorer subjective sleep quality was not associated with the risk of all-cause dementia (hazard ratio [HR] per SD increase in PSQI score: 0.91, 95% CI 0.82-1.02) or AD (HR 0.92, 95% CI 0.81-1.05). Similarly, individual components of the PSQI were also not associated with dementia. Several sensitivity analyses, i.e. excluding last years of the follow-up time duration or restricting to those with best MMSE scores at baseline, did not reveal subgroups with increased risks.

Conclusion: In this study, we found no association of poor subjective sleep quality with higher risk of dementia.

The authors are grateful to both study participants and the staff from the Rotterdam Study, the participating general practitioners and pharmacists and the Erasmus Epidemiology data management team.

J Alzheimers Dis. 2018;64(1):239-247.

ESTIMATED GLOMERULAR FILTRATION RATE (EGFR) CHANGES AFTER OBSTRUCTIVE SLEEP APNEA (OSA) TREATMENT BY POSITIVE AIRWAY PRESSURE: DATA FROM THE EUROPEAN SLEEP APNEA DATABASE (ESADA)

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Introduction: Decreased renal function is associated with OSA in the ESADA cohort (Marrone et al, J Sleep Res 2016). Aim of this study was to evaluate changes in eGFR (ΔeGFR) after different modalities of positive pressure treatment.

Methods: Data from 1,806 OSA patients who were treated by fixed (n=1,177, CPAP) or automatic (n=485, APAP) continuous positive airway pressure were analyzed and compared with data from a group of untreated patients (n=144).

Results: Median follow-up was 541 days (IQR 220-1255). Median baseline eGFR was 91.42 ml/min/1.73m^2. During follow-up, eGFR decreased particularly in the patients with eGFR below the median at baseline ($p<0.0001$ for effect of baseline eGFR); in the CPAP subgroup, eGFR decline was attenuated or reverted ($p<0.0001$ for effect of treatment), but the difference in ΔeGFR between subjects with high and low baseline eGFR was not modified. Follow-up duration above median was associated with eGFR decline in the untreated and APAP groups; eGFR decline was prevented in the CPAP group ($p <0.0001$ by two-way ANOVA for interaction between treatment and follow-up length) (Table 1).

Table 1: Change in estimated glomerular filtration rate (ΔeGFR) during follow-up

Follow-up duration	*ΔeGFR No treatment*	*ΔeGFR APAP*	*ΔeGFR CPAP*
≥median	-5.29 ± 8.64	-3.11 ± 10.84	0.58 ± 11.60
<median	-0.53 ± 8.18	1.33 ± 8.29	0.631 ±10.67

Multiple regression analysis identified advanced age, female gender, cardiac failure, higher baseline eGFR and longer follow-up duration as negatively, and CPAP as positively affecting eGFR (β=3.420 [1.564/5.276], $p<0.0001$).

Conclusion: OSA treatment by fixed CPAP positively affected eGFR, but such an effect could not be demonstrated with APAP treatment.

Eur Respir J 2017;50:Suppl 61:A851. Abstract presented during the ERS Congress 2017, Milan (Italy).

PATIENT SATISFACTION RELATED TO DIAGNOSIS AND TREATMENT OF SLEEP APNEA IN THE NETHERLANDS

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Introduction: Every two years since 2005 the ApneuVereniging has investigated the satisfaction among Dutch apnea patients about their experiences with diagnosis and treatment by healthcare providers & sleep clinics and with apnea treatment (-devices) and their suppliers. Since 2011 we have awarded 'stars' to better performing clinics in patients' opinion. (In the alternating years, we ask sleep clinics about their practices to get a more complete and balanced view).
Method: The 2017 patient satisfaction enquiry was executed by Kantar Public, thru computer assisted web interviewing (CAWI). The performance score was assessed with TRI*M-index. In total n = 5113 patients have responded. Van Mechelen added a trend and outlook assessment.
Results: Most of the respondents were made aware that they might have sleep apnea by a medical specialist or their partner. Many of the patients (57%) stated to think that their complaints were caused by high blood pressure. On average the patients responded that - besides sleep apnea- they have suffered from or are still being treated for almost 4 other diseases.

Table 1: Most common comorbidities of sleep apnea

	High blood pressure	Too high cholesterol	Cardiovascular diseases	Obesity	Diabetes	Stressed Depressed Burn-out	Other Sleep disorders
No complaints	43%	52%	59%	46%	75%	54%	54%
Had some complaints	57%	48%	41%	54%	25%	46%	46%
Consulted physician	51%	41%	35%	34%	22%	29%	24%
Have been treated	45%	34%	28%	19%	18%	20%	11%
Are being treated	38%	28%	22%	14%	16%	8%	7%

Diagnostic sleep examinations are increasingly done at home, usually a pneumonologist and/ or an ENT-specialist of a sleep clinic are involved. Generally, to the patients' satisfaction. A table with appraisal of all (92) sleep clinics in the Netherlands is included in the report.
Usage of the mainly prescribed CPAP apparatus with masks is high. The support of suppliers is appraised positively. The MRA (a dental brace) is prescribed more and more. A large majority of both CPAP and MRA users report to experience a much better health quality! OSAS surgery is much less common and had reportedly an insufficient effect with half of the patients involved.
Conclusion: A main problem remains the timely diagnosis of sleep apnea, as hindsight many patients are treated for symptoms of comorbidities rather than treating the cause sleep apnea directly.

Link: Kantar report "De Keten in Beeld 2017" (55 pages in Dutch language).
https://apneuvereniging.nl/wp-content/uploads/2017/12/Apneu_Kantar_rapport_2017_lr.pdf

AUTONOMIC CARDIAC ACTIVITY IN ADULTS WITH SHORT AND LONG SLEEP ONSET LATENCY

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Sleep problems, in particular the difficulty initiating sleep are becoming more prevalent [1] and worldwide one third of the adults is affected occasionally by sleeplessness symptoms [1], [2]. Difficulties in sleep onset can be measured by polysomnographic (PSG) recordings and changes observed in electroencephalography, electrooculography and electromyography. However, PSG recording is expensive, labor intensive and cannot provide long-term monitoring of sleep. Autonomic cardiac activity during sleep has been widely studied. Research has mostly focused on cardiac activity between different sleep stages and wakefulness as well as between normal and pathological sleep. This work investigates autonomic activity changes during sleep onset in healthy subjects with long and short sleep onset latency (SOL).

PSG and electrocardiography were simultaneously recorded in 186 healthy subjects during a single night. Autonomic activity was assessed based on frequency domain analysis of RR intervals and results show that the analysis of RR intervals differs significantly between the short SOL and the long SOL groups. The mean value of each heart rate variability (HRV) feature during the three examined periods (the first 10 minutes in bed intended to sleep, before and after sleep onset) was compared between the two SOL groups using the non-parametric Mann-Whitney U test.

We found that the spectral power in the low frequency band (LF) was significantly higher in the long SOL group compared to the short SOL group in the first 10 minutes in bed intended to sleep. There was no significant difference for LF and the spectral power in the high frequency band (HF) 10 minutes before and after sleep onset between the two groups. Only in the short SOL group there was a significant increase in HF from the first 10 minutes in bed intended to sleep to 10 minutes before SO, while LF decreased significantly in both groups. The effect of time (5.5-min bin) on the HRV features around sleep onset showed that both LF and HF differed significantly during the period surrounding sleep onset only in the short SOL group.

[1] M. M. Ohayon, “Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders,” Journal of Psychiatric Research, vol. 31, pp. 333–346, June 1997.
[2] M.-M. Nano, P. Fonseca, R. Vullings, and R. M. Aarts, “Measures of cardiovascular autonomic activity in insomnia disorder: A systematic review,” PLOS ONE, vol. 12, p. e0186716, Oct. 2017.

M-M. Nano, P. Fonseca, S. Overeem, R. Vullings, and R. M. Aarts, “Autonomic cardiac activity in adults with short and long sleep onset latency,” 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC),(In press).

CHRONIC SOCIAL DEFEAT STRESS SUPPRESSES LOCOMOTOR ACTIVITY BUT DOES NOT AFFECT THE FREE-RUNNING CIRCADIAN PERIOD OF THE ACTIVITY RHYTHM IN MICE

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In mammals, daily rhythms in behavior and physiology are under control of an endogenous clock or pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN assures an optimal temporal organization of internal physiological process and also synchronizes rhythms in physiology and behavior to the cyclic environment. The SCN receives direct light input from the retina, which is capable of resetting the master clock and thereby synchronizes internally driven rhythms to the external light-dark cycle. In keeping with its function as a clock and pacemaker, the SCN appears to be well buffered against influences by other stimuli and conditions that contain no relevant timing information, such as acute stressors. On the other hand, it has been suggested that chronic forms of stress may have gradually accumulating effects that can disturb normal clock function and thereby contribute to stress-related disorders. Therefore, in the present study we investigated whether chronic intermittent social stress affects the endogenous period and phase of the free-running activity rhythm in mice. Adult male mice were maintained in constant dim red light conditions and exposed to a daily 20 min social defeat stress session for 10 consecutive days, either during the first half of their activity phase or the first half of their resting phase. The overall amount of running wheel activity was strongly suppressed during the 10 days of social defeat, to about 50% of the activity in non-defeated control mice. Activity levels gradually normalized during post-defeat recovery days. Despite the strong suppression of activity in defeated animals, the endogenous free-running circadian period of the activity rhythm and the phase of activity onset were not affected. These findings are thus in agreement with earlier studies suggesting that the circadian pacemaker in the SCN that is driving the rhythmicity in activity is well-protected against stress. Even severe social defeat stress for 10 consecutive days, which has a major effect on the levels of activity, does not affect the pace of the endogenous clock.

Ota SM, Suchecki S, Meerlo P. Chronic social defeat stress suppresses locomotor activity but does not affect the free-running period of the activity rhythm in mice. Neurobiology of Sleep and Circadian Rhythms 5: 1-7, 2018.

CHRONIC HIGH-CALORIC DIET MODIFIES SLEEP HOMEOSTASIS IN MICE

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Obesity prevalence and sleep habit changes are commonplace nowadays, due to modern lifestyle. A bidirectional relationship likely exists between sleep quality and metabolic disruptions, which could impact quality of life.

In our study, we investigated the effects of a chronic high-caloric diet on sleep architecture and sleep regulation in mice. We studied the effect of 3 months high-caloric diet (HCD, 45% fat) on sleep and the sleep electroencephalogram (EEG) in C57BL/6J mice during 24-hr baseline (BL) recordings, and after 6-hr sleep deprivation (SD). We examined the effect of HCD on sleep homeostasis, by performing parameter estimation analysis and simulations of the sleep homeostatic Process S, a measure of sleep pressure, which is reflected in the non-rapid-eye-movement (NREM) sleep slow-wave-activity (SWA, EEG power density between 0.5 and 4.0 Hz).

Compared to controls (n = 11, 30.7 ± 0.8 g), mice fed with HCD (n = 9, 47.6 ± 0.8 g) showed an increased likelihood of consecutive NREM-REM sleep cycles, increased REM sleep and decreased NREM sleep EEG SWA. After SD, these effects were more pronounced. The simulation resulted in a close fit between the time course of SWA and Process S in both groups. HCD fed mice had a slower time constant (T_i = 15.98 hr) for the increase in homeostatic sleep pressure compared with controls (5.95 hr) indicating a reduced effect of waking on the increase in sleep pressure.

Our results suggest that chronic HCD consumption impacts sleep regulation.

This work was supported by a grant from the Dutch Technology Foundation (STW to T. Deboer).

Eur J Neurosci 47: 1339-1352, 2018.

HOW OLD IS YOUR BRAIN? SLOW-WAVE ACTIVITY IN NON-RAPID-EYE-MOVEMENT SLEEP AS A MARKER OF BRAIN REJUVENATION AFTER LONG-TERM EXERCISE IN MICE

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Physical activity is beneficial for health. It has been shown to improve brain functioning and cognition, reduce severity of mood disorders, as well as facilitate healthy sleep and healthy aging. Sleep has been studied in healthy aged mice and absolute slow-wave-activity levels (SWA, electroencephalogram power between 0.75-4.0 Hz) in non-rapid-eye-movement sleep (NREM) were elevated, suggesting changes in brain connectivity. To investigate whether physical activity can diminish this aging-induced effect, mice of three age groups were provided with a running wheel (RW) for 1-3 months (6-months-old, n=9; 18-months-old, n=9; 24-months-old, n=8) and were compared with control sedentary mice (n=11, n=8 and n=9 respectively). Two weeks before the sleep-wake recordings the running wheels were removed. The electroencephalogram (EEG) and electromyogram were continuously recorded during undisturbed 24h baseline (BL) and a sleep-deprivation was conducted during the first 6h of the second day. Increased waking and decreased NREM sleep was found in the young RW mice, compared to young controls. These effects were not evident in the 18 and 24 months old mice. Unlike sleep architecture, we found that SWA was altered throughout the whole age spectrum. Notably, SWA was increased with aging and attenuated with exercise, exhibiting the lowest levels in the young RW mice. To utilize the cross-age revealing features of SWA, we applied machine learning techniques and found that characteristic information regarding age and exercise was enclosed in SWA. In addition, with cluster analysis, we could classify and accurately distinguish the different groups based solely on their SWA. Therefore, our study comprises a three-fold contribution: a) effects of exercise on sleep are sustained following two weeks after removal of the wheel, b) we show that EEG SWA can be used as a physiological marker of brain age in the mouse, c) long-term voluntary regular age-matched exercise leads to a younger phenotype.

Front Aging Neurosci, in press, 2018.

SCALE INVARIANCE ATTENUATION AND ALTERED SLEEP PARAMETERS FOLLOWING INCREASING DIM-LIGHT-AT-NIGHT DURATION PERIODS

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Introduction: Artificial light has a widespread use nowadays. However, light exposure at night has been associated with various health disruptions including metabolic and immunological disturbances, altered circadian timing and sleep disorders. In our study, we investigated the effect of exposure to different dim-light-at-night [DLAN, 12:12 h Light:DLAN (50-100:5 lux)] durations on rest-activity behavior, sleep architecture and sleep electroencephalographic (EEG) parameters in C57BL/6J mice. DLAN can be regarded as a condition mimicking artificial light exposure at night.

Methods: EEG and the electromyogram was recorded in mice during a control light-dark baseline day (n=5), following acute 12-h DLAN exposure (n=5) as well as after one week (n=5), one month (n=5) and three months (n=9) DLAN. For all the different DLAN durations, a second day was recorded at the start of which six hours of sleep-deprivation (SD) were conducted by gentle handling. Additionally, locomotor activity for the control light-dark (LD), the one-month and three-month DLAN conditions was monitored by passive infrared detectors.

Results: Prolonged DLAN exposure led to circadian rhythm disruption and sleep quality degradation. We applied detrended fluctuation analysis (DFA) on the behavioral data and found a significantly lower scaling component α in animals exposed to the 3-month DLAN condition compared to control conditions ($p<0.01$), while following 1-month of DLAN exposure showed intermediate α values between control LD and 3 months DLAN. Additionally vigilance state distribution was altered, showing a gradual delay in the waking peak in the dim light (active) period as a function of DLAN exposure duration (1 day-1 month) compared to control LD. Following 3 months DLAN exposure, mice showed less non-rapid-eye-movement (NREM) sleep during the light period ($p<0.05$), while waking and NREM sleep levels did not differ from control dark period, particularly in the first half of the dim-light period. Interestingly, a diminished response to sleep deprivation as well as a general attenuation of EEG power density across vigilance states was noted in the 3-month DLAN condition ($p<0.05$).

Conclusions: Our data show that prolonged exposure to DLAN induces a diminished integrity of the neurophysiological system, impacting sleep, and sleep regulation as well as the underlying brain network.

Presented at the European Sleep Research Society meeting, Basel, Switzerland, September 2018.

ON THE GENERALIZABILITY OF ECG-BASED OBSTRUCTIVE SLEEP APNEA MONITORING: MERITS AND LIMITATIONS OF THE APNEA-ECG DATABASE

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Introduction: Obstructive sleep apnea syndrome (OSAS) is a sleep disorder that affects a large part of the population. The development of algorithms using cardiovascular features for OSAS monitoring has been an extensively researched topic in the last two decades. Several studies regarding automatic apneic epoch classification using ECG derived features are based on the public Apnea-ECG database available on PhysioNet. Although this database is an excellent starting point for apnea topic investigations, it does not encompass the full complexity of sleep because. For instance, it lacks of other sleep disorders and complex apneic cases. These type of absences can limit the applicability of algorithms exclusively developed on the Apnea-ECG database in real-world situations. This paper reports the effect of testing an apneic epoch classifier trained on the Apnea-ECG database on other databases which include mixed sleep disorders and a broad spectrum of events.

Methods: Two Algorithms for apneic-epoch classification are developed by automatically selecting commonly used cardiac features and classifier parameters using the Apnea-ECG train set. The algorithm is tested on the Apnea-ECG test set and two other databases: the public UCD and the SOMNIA database, collected in the Sleep Center Kempenhaeghe. These databases include more complex apneic cases and the SOMNIA contains a broader spectrum of sleep events and disorders, such as periodic limb movements and insomnia.

Results: Two algorithms are successfully trained on the Apnea-ECG database, but both perform poorly on the other databases (an example in the Table). The reduced performance can be related to the complexity of breathing events, the increased number of non-breathing related sleep events, and the presence of non-OSAS sleep pathologies.

Conclusions: Our research shows that the algorithm is strongly influenced by the choice of the database used to train the classifier. Databases that do not encompass the full complexity of sleep (disorders) are prone to generate solutions which cannot be easily employed in more complex situations. Our work suggests that Apnea-ECG database has to be considered as a starting point for research in this area rather than as the definitive database in the field. Therefore, we want to promote a new effort for larger, more comprehensively annotated and multi-center data collections.

Table 1: Testing results of one of the algorithms for the different databases.

Datasets	*# epochs*	*Sensitivity*	*Specificity*	*Accuracy*	*Cohen's kappa*	*False Detection rate*
Apnea-ECG test set	17254 (37.9%)	87.2%	87.0%	87.1%	0.73	19.6%
UCD	9843 (27.9%)	50.6%	84.0%	74.7%	0.35	45.0%
SOMNIA	29656 (16.2%)	36.6%	87.8%	79.5%	0.24	63.2%

This work is financially supported by STW/IWT in the context of the OSA+ project (No. 14619)

40th International Engineering in Medicine and Biology Conference (EMBC 2018, Honolulu, Hawaii)

CHRONOTYPE AND ENVIRONMENTAL LIGHT EXPOSURE IN A STUDENT POPULATION

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Introduction: In humans and most other species, changes in the intensity and duration of light provide a critical set of signals for the synchronisation of the circadian system to the astronomical day. The timing of activity within the 24 h day defines an individual's chronotype, i.e. morning, intermediate or evening type. The aim of this study was to investigate the associations between environmental light exposure, due to geographical location, on the chronotype of university students.

Methods: Over 6 000 university students from cities in the Northern Hemisphere (Oxford, Munich and Groningen) and Southern Hemisphere (Perth, Melbourne and Auckland) completed the Munich ChronoType Questionnaire. In parallel, light measures (daily irradiance, timing of sunrise and sunset) were compiled from satellite or ground stations at each of these locations.

Results: Our data shows that later mid-sleep point on free days (corrected for oversleep on weekends MFSsc) is associated with (i) residing further from the equator, (ii) a later sunset, (iii) spending more time outside and (iv) waking from sleep significantly after sunrise. However, surprisingly, MSFsc did not correlate with daily light intensity at the different geographical locations.

Discussion: Although these findings appear to contradict earlier studies suggesting that in the wider population increased light exposure is associated with an earlier chronotype, our findings are derived exclusively from a student population aged between 17 and 26 years. We therefore suggest that the age and occupation of our population increase the likelihood that these individuals will experience relatively little light exposure in the morning whilst encountering more light exposure later in the day, when light has a delaying effect upon the circadian system.

This work was supported by the EU 6th Framework Integrated Project [0187241], Wellcome Trust [098461/Z/12/Z,106174/Z/14/Z] and National Institute for Health Research [A90305, A92181].

Chronobiology International, DOI: 10.1080/07420528.2018.1482556

AGE RELATED SLEEP STAGE TRENDS AS MEASURED USING REMOTE SLEEP SENSING HARDWARE

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Objectives / Introduction: With increasing age, an increase in wake after sleep onset (WASO) and a decrease in deep and REM sleep is generally observed and has been confirmed in a meta-analysis published by Oyahon et al in 2004. The Ohayon study provides normative data for sleep in the sleeping environments included in the meta-analysis but is likely not representative of sleeping habits in the home. The rise of consumer sleep trackers enables measurement of sleep as experienced by people in daily life. Using a unique set of sleep recordings collected with the S+ by ResMed (a non-contact bio-motion sensor that enables home sleep staging estimation (Schade et al, 2017)), we improved our sleep estimation model and showed that the S+ technology is capable of capturing the age-related trends in sleep-staging using data collected in real life.

Methods: We analyzed the relationship between age and Time in Bed from a subset of 27098 recordings from the S+ dataset, with the goal of creating a new model that takes into account both sleep stage distribution as reported by Ohayon and Time in Bed in the home environment as measured using S+. This updated set of normative data was then employed to train the S+ algorithm to more accurately capture the age-related trends.

Results: Between the ages of 15 and 75 the Ohayon normative data shows a decrease in Deep (47.9 minutes) and REM (26.4 minutes), accompanied with an increase in Light (13.7 minutes) and WASO (63.3 minutes). The updated S+ algorithm, run on 27098 nights of data showed strong agreement with a decrease in Deep (48.3 min) and REM (26.1 min), accompanied with an increase in Light (11.7 min) and WASO (50.4 min) over the same age range.

Conclusions: Here we show for the first time that non-contact bio-motion sleep sensing technology is capable of capturing the well-known age-related sleep stage trends. As such, its validation goes beyond the traditional sleep stage agreement statistics commonly used to show validation. This work lays the foundations for further improvement in the performance of sleep monitoring technologies and shows their validity for use beyond consumer sleep tracking.

24th Congress of the European Sleep Research Society, 25-28 Sept 2018, Basel, Switzerland

THE ROLE OF SLEEP IN REGULATING STRUCTURAL PLASTICITY AND SYNAPTIC STRENGTH: IMPLICATIONS FOR MEMORY AND COGNITIVE FUNCTION

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Dendritic spines are the major sites of synaptic transmission in the central nervous system. Alterations in the strength of synaptic connections directly affect the neuronal communication, which is crucial for brain function as well as the processing and storage of information. Sleep and sleep loss bidirectionally alter structural plasticity, by affecting spine numbers and morphology, which ultimately can affect the functional output of the brain in terms of alertness, cognition, and mood. Experimental data from studies in rodents suggest that sleep deprivation may impact structural plasticity in different ways. One of the current views, referred to as the synaptic homeostasis hypothesis, suggests that wake promotes synaptic potentiation whereas sleep facilitates synaptic downscaling. On the other hand, several studies have now shown that sleep deprivation can reduce spine density and attenuate synaptic efficacy in the hippocampus. These data are the basis for the view that sleep promotes hippocampal structural plasticity critical for memory formation. Altogether, the impact of sleep and sleep loss may vary between regions of the brain. A better understanding of the role that sleep plays in regulating structural plasticity may ultimately lead to novel therapeutic approaches for brain disorders that are accompanied by sleep disturbances and sleep loss.

Raven F, Van der Zee EA, Meerlo P, Havekes R. The role of sleep in regulating structural plasticity and synaptic strength: implications for memory and cognitive function. Sleep Medicine Reviews 39: 3-11, 2018.

EXAMINING COURSES OF SLEEP QUALITY AND SLEEPINESS IN FULL 2 WEEKS ON/2 WEEKS OFF OFFSHORE DAY SHIFT ROTATIONS

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Introduction: To better understand sleep quality and sleepiness problems offshore, we examined courses of sleep quality and sleepiness in full 2-weeks on/2-weeks off offshore day shift rotations by comparing pre-offshore (1 week), offshore (2 weeks) and post-offshore (1 week) work periods.

Methods: A longitudinal observational study was conducted among N=42 offshore workers. Sleep quality was measured subjectively with two daily questions and objectively with actigraphy, measuring: time in bed (TIB), total sleep time (TST), sleep latency (SL) and sleep efficiency percentage (SE%). Sleepiness was measured twice a day (morning and evening) with the Karolinska Sleepiness Scale.

Results: Changes in sleep and sleepiness parameters during the pre/post and offshore work periods were investigated using (generalized) linear mixed models. In the pre-offshore work period, courses of SE% significantly decreased (p=.038). During offshore work periods, the courses of evening sleepiness scores significantly increased (p<.001) and significantly decreased during post-offshore work periods (p=.004). During offshore work periods, TIB (p<.001) and TST (p<.001) were significantly shorter, SE% was significantly higher (p=.002), perceived sleep quality was significantly lower (p<.001) and level of rest after wake was significantly worse (p<.001) than during the pre and post-offshore work periods. Morning sleepiness was significantly higher during offshore work periods (p=.015) and evening sleepiness was significantly higher in the post-offshore work period (p=.005) compared to the other periods. No significant changes in SL were observed.

Conclusion: Courses of sleep quality and sleepiness parameters significantly changed during full 2-weeks on/2-weeks off offshore day shift rotation periods. These changes should be considered in offshore fatigue risk management programs.

This research was supported and funded by the Nederlandse Aardolie Maatschappij B.V. and Royal Dutch Shell, Assen, Drenthe, The Netherlands.

Chronobiology International 35(6):759-772 (2018).

INVESTIGATING DAILY FATIGUE SCORES DURING TWO-WEEK OFFSHORE DAY SHIFTS

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Objectives: This study examined daily scores of fatigue and circadian rhythm markers over two-week offshore day shift periods.

Methods: A prospective cohort study among N = 60 offshore day-shift workers working two-week offshore shifts was conducted. Offshore day shifts lasted from 07:00 - 19:00 h. Fatigue was measured objectively with pre- and post-shift scores of the 3-minute psychomotor vigilance tasks (PVT-B) parameters (reaction times, number of lapses, errors and false starts) and subjectively with pre- and post-shift Karolinska Sleepiness Scale (KSS) ratings. Evening saliva samples were collected on offshore days 2,7 and 13 to measure circadian rhythm markers such as dim-light melatonin onset times and cortisol. Generalized and linear mixed model analyses were used to examine daily fatigue scores over time.

Results: Complete data from N = 42 offshore day shift workers was analyzed. Daily parameters of objective fatigue, PVT-B scores (reaction times, average number of lapses, errors and false starts), remained stable over the course of the two-week offshore day shifts. Daily subjective post-shift fatigue scores significantly increased over the course of the two-week offshore shifts. Each day offshore was associated with an increased post-shift subjective fatigue score of 0.06 points (95%CI: .03 - .09 $p < .001$). No significant statistical differences in subjective pre-shift fatigue scores were found. Neither a circadian rhythm phase shift of melatonin nor an effect on the pattern and levels of evening cortisol was found.

Conclusion: Daily parameters of objective fatigue scores remained stable over the course of the two-week offshore day shifts. Daily subjective post-shift fatigue scores significantly increased over the course of the two-week offshore shifts. No significant changes in circadian rhythm markers were found. Increased post-shift fatigue scores, especially during the last days of an offshore shift, should be considered and managed in (offshore) fatigue risk management programs and fatigue risk prediction models.

This study was supported by the Nederlandse Aardolie Maatschappij B.V. and Royal Dutch Shell, Assen, Drenthe, The Netherlands.

JERG 71:87-94 (2018)

MATHEMATICAL MODELING OF SLEEP STATE DYNAMICS IN A RODENT MODEL OF SHIFTWORK

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Millions of people worldwide are required to work when their physiology is tuned for sleep. By forcing wake-fulness out of the body's normal schedule, shift workers face numerous adverse health consequences, including gastrointestinal problems, sleep problems, and higher rates of some diseases, including cancers. Recent studies have developed protocols to simulate shift work in rodents with the intention of assessing the effects of night-shift work on subsequent sleep (Grønli et al., 2017). These studies have already provided important contributions to the understanding of the metabolic consequences of shift work (Arble et al., 2015; Marti et al., 2016; Opperhuizen et al., 2015) and sleep-wake-specific impacts of night-shift work (Grønli et al., 2017). However, our understanding of the causal mechanisms underlying night-shift-related sleep disturbances is limited. In order to advance toward a mechanistic understanding of sleep disruption in shift work, we model these data with two different approaches. First, we apply a simple homeostatic model to quantify differences in the rates at which sleep need, as measured by slow wave activity during slow wave sleep (SWS) rises and falls. Second, we develop a simple and novel mathematical model of rodent sleep and use it to investigate the timing of sleep in a simulated shift work protocol (Grønli et al., 2017). This mathematical framework includes the circadian and homeostatic processes of the two-process model, but additionally incorporates a stochastic process to model the polyphasic nature of rodent sleep. By changing only the time at which the rodents are forced to be awake, the model reproduces some key experimental results from the previous study, including correct proportions of time spent in each stage of sleep as a function of circadian time and the differences in total wake time and SWS bout durations in the rodents representing night-shift workers and those representing day-shift workers. Importantly, the model allows for deeper insight into circadian and homeostatic influences on sleep timing, as it demonstrates that the differences in SWS bout duration between rodents in the two shifts is largely a circadian effect. Our study shows the importance of mathematical modeling in uncovering mechanisms behind shift work sleep disturbances and it begins to lay a foundation for future mathematical modeling of sleep in rodents.

Rempe MJ, Grønli J, Pedersen TT, Mrdalj J, Marti A, Meerlo P, Wisor JP. Mathematical modeling of sleep state dynamics in a rodent model of shift work. Neurobiology of Sleep and Circadian Rhythms 5: 37-51, 2018.

EVALUATION OF NIGHT-TO-NIGHT VARIABILITY OF SLEEP APNEA IN HOME POLYSOMNOGRAPHY

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Introduction: Clinical polysomnography (PSG, type 1) is the golden standard for investigating sleep disorders. An alternative for a complete polysomnography investigation is the home polysomnography (H-PSG, type 2). Sleep apnea is diagnosed and graded by conventional thresholds of apneas and hypopneas per hour of sleep, and treatment is usually initiated in the presence of symptoms. This study assessed the night-to-night variability of the apnea hypopnea index (AHI) during two consecutive nights of H-PSG.

Methods: In our tertiary sleep center we were accustomed to perform two consecutive 24 hour H-PSGs. A retrospective study was performed on the data of 262 patients of which 51 patients (72.5 % male, 53.9 ± 12.1 years, BMI: 29.4 ± 6.5 kg/m^2) were diagnosed as having a Sleep Related Breathing Disorder (SRBD) diagnosis based on history and the combined data of first and second night. We compared the apnea hypopnea index (AHI) of the second night to the first night to assess if a second night of PSG affects diagnosis and classification of SRB severity. The sleep apnea was categorized according to conventional thresholds using the AHI (no sleep apnea: <5 per hour; mild: 5 to 14 per hour; moderate: 15 to 30 per hour; and severe: >30 per hour).

Results: Twenty-one percent of the 51 the SRBD patients had a nightly H-PSG AHI variability of greater than 10. Seventeen percent of all patients had a significantly higher AHI on the first night, and 7.8 % had a significantly higher AHI on the second night. The sleep apnea severity category shifts in 35.3 % of the patients. Only four patients (7.8 %) have in the second night such a higher AHI that they shift to a more severe diagnostic group. One patient went from the group no diagnosis to a mild sleep apnea.

Conclusion: Only a slight percentage of the patients shift to a more severe diagnostic category. Therefore, a second H-PSG will not affect the treatment strategy of the majority of the sleep related breathing disorder patients. The Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea of the American Academy of Sleep Medicine (AASM; Kapur et al. 2017) recommends to do a second PSG if the first one is not conclusive. Our data suggest that doing a second night H-PSG hardly alters the treatment strategy.

Financial Disclosure: None.
Conflict of Interest: All authors have no conflict of interest to declare.

24th Congress of the European Sleep Research Society (ESRS) will be presented by an Oral presentation on 26th of September.

SERUM OF NARCOLEPSY TYPE 1 PATIENTS DOES NOT DECREASE HYPOCRETIN RECEPTOR 2 FUNCTION

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Introduction: The loss of hypocretin-producing neurons leading to narcolepsy type 1 is suggested to be caused by an immune response. Even though several studies in narcolepsy type 1 patients found autoantibodies targeting molecules that are moderately specific for hypocretin-producing neurons, such as Tribbles homolog 2, or the hypocretin receptor 2, the functional effect of these antibodies is not clear. Therefore, we assessed the effect of narcolepsy type 1 patient serum on hypocretin receptor 2 functioning.

Materials and methods: Chinese hamster ovary cells transfected with a human hypocretin receptor 2 were incubated with serum from narcolepsy type 1 patients and healthy controls. Hypocretin-1 was subsequently administered to the incubated cells and intracellular Ca^{2+} concentration was measured using flurorescence microscopy and dedicated imaging software. Administration of ATP was used as a positive control. Ratios of Ca^{2+} concentration upon hypocretin-1 and ATP administration was used for standardisation of the results.

Results: 9 narcolepsy type 1 patients and 9 sex- and age-matched healthy controls were included in this study. Mean hypocretin-1/ATP ratios were 1.47±0.76 in experiments with narcolepsy type 1 serum and 1.05±0.56 in those with healthy control serum. Mann-Whitney U-tests showed no significant differences between both groups.

Conclusion: An effect of narcolepsy type 1 patient serum on hypocretin receptor 2 functioning could not be demonstrated. These results do not support the hypothesis that hypocretin receptor 2-specific antibody-mediated auto-reactivity is present in narcolepsy type 1 patients. Future research on the possible role of autoantibodies to hypocretin receptor 2 in the development of narcolepsy type 1 is warranted.

This abstract will be presented as a poster at the ESRS 2018 Congress in Basel, September 2018

MASS CYTOMETRY-BASED ANALYSIS OF THE COMPOSITION OF THE IMMUNE SYSTEM IN PERIPHERAL BLOOD IN NARCOLEPSY TYPE 1

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Introduction: The presence of an auto-immune process as possible explanation for the loss of hypocretin-producing neurons in narcolepsy has long been suspected. Even though the increased incidence of narcolepsy in several European countries following the 2009 H1N1 pandemic and subsequent vaccination campaign rejuvenated research on this process, the immune cells driving the destruction of the neurons have not yet been found.
To identify these immune cells, we used mass cytometry as unbiased method to search for immune cell populations that are enriched in narcolepsy type 1 patients as compared with healthy controls.

Methods: Peripheral blood mononuclear cells from narcolepsy type 1 patients and HLA-, age- and sex-matched healthy controls were collected from outpatient clinics of Sleep Centres in the Netherlands and Germany. These cells were stained with antibodies targeting 36 immune cell surface molecules for mass cytometry data acquisition. Resulting data was visualised by t-SNE, a dimensionality reduction technique. Phenotypically distinct subsets are identified and compared between narcolepsy type 1 patient and healthy control samples.

Results: High-dimensional differences were readily found both between different samples from narcolepsy type 1 patients and between samples from narcolepsy type 1 patients and those from healthy controls. The identification of phenotypically distinct subsets is being performed with these samples now and the outcomes will be presented at the symposium.

Conclusion: Mass cytometry is a technique that allows for unbiased in-depth examination of immune cell composition and provides new opportunities for assessing the mechanisms that lead to the destruction of hypocretin-producing neurons in narcolepsy.

This abstract will be presented as a poster at the 7th International Narcolepsy Symposium in Boston, September 2018

SLEEP-STATE AND DREAM PERCEPTION IN SLEEP DISORDERS

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Introduction: Sleep-state misperception is a common phenomenon among primary insomnia patients with a prevalence ranging between 9.2 and 50%. In obstructive sleep apnea, inverse sleep-state misperception has been reported. These studies depend on polysomnography measures for the identification of sleep-state misperception and predicting patient-related factors. We assessed factors influencing sleep-state perception during the 20-minute naps of a multiple sleep latency test.

Materials and methods: In this prospective observational study, 247 consecutive patients undergoing a routine multiple sleep latency test between March 2014 and October 2017 in SEIN Heemstede, a tertiary sleep-wake centre in the Netherlands, were included. Sleep and dream perception was assessed by questionnaires after each nap. Mixed models were applied to assess the influence of patients' clinical data on sleep-state and dream perception.

Results: Patients fell asleep in 82.3% of nap opportunities. Patients reported to have slept in 72.8%. A lower age (β = -0.042/year ± 0.017; $p = 0.014$), the occurrence of N2 stage sleep (β = 2.106 ± 0.842; $p = 0.012$) and a shorter sleep onset latency (β = -0.225/minute ± 0.052; $p < 0.001$) were significant predictors for correct sleep-state perception. Sleep diagnosis did not predict correct sleep-state perception ($p = 0.575$). In 28.0% of naps in which patients did not reach REM sleep, patients reported to have dreamed. On the contrary, patients reported not to have dreamed in 26.4% of naps in which REM sleep did occur. Dream perception percentage was not significantly different between diagnosis categories.

Conclusion: Sleep-state perception is better in younger patients with shorter sleep onset latencies during a nap in which N2 sleep occurred. Sleep-state perception does not differ between sleep diagnosis categories during the short naps of the multiple sleep latency test. Notably, the perception of dreaming is influenced by, but definitely not limited to the occurrence of REM sleep.

This abstract will be presented as a poster at the ESRS 2018 Congress in Basel, September 2018

RED EARS WHILE SLEEPY: RELATION BETWEEN EAR SKIN TEMPERATURE AND SLEEPINESS

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Introduction: Red ears in sleepy children is a commonly described phenomenon. This ear discolouration could represent increased blood flow in the skin of the ear, consistent with an increased distal skin temperature observed before sleep onset in adults. We hypothesise that ear skin temperature is associated with objective and subjective sleepiness in subjects without sleeping disorders.

Materials and methods: Distal, proximal and ear skin temperature were measured in two groups of patients undergoing diagnostic EEG examination for suspected epilepsy: one group was sleep-deprived (n=7), one group was not (n=20). Prior to, during and after the EEG examination, ear skin temperature was measured using different methods: thermographic imaging, ear surface and wireless skin temperature measurement. Objective and subjective sleepiness were assessed by sleep-onset latency during the EEG examination and the Stanford Sleepiness Scale, respectively.

Results: We found no association between pre- and post-EEG ear skin temperature and either objective (Spearman's ρ = 0.036; p = 0.885) or subjective sleepiness (Spearman's ρ = 0.218; p = 0.285). However, the sleep-deprived group showed a trend of a stronger increase in ear skin temperature during the EEG examination compared with the group that was not sleep-deprived (1.89 ± 0.84°C vs. 0.48 ± 0.33°C; p = 0.067). Higher objective (1.93 ± 0.71°C vs. 0.39 ± 0.34°C; p=0.035) and subjective (1.27 ± 0.39°C vs. -0.16 ± 0.55°C; p=0.051) sleepiness were both associated with an increase in ear skin temperature during EEG examination.

Conclusion: Objective and subjective sleepiness are associated with an increase in ear skin temperature during EEG examination in patients without sleeping disorders. This may reflect ear skin temperature changes preceding sleep onset. Intervention studies are needed to elucidate the relationship between sleepiness and ear skin temperature and explain the physiological mechanism behind sleepy children's red ears.

This abstract will be presented as a poster at the ESRS 2018 Congress in Basel, September 2018

HETEROGENEITY IN THE CIRCADIAN AND HOMEOSTATIC MODULATION OF MULTIUNIT ACTIVITY IN THE LATERAL HYPOTHALAMUS

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The lateral hypothalamus (LH) is a relatively large hypothalamic structure containing several neurochemically different, but spatially intermingled, neuronal populations. While the role of these neurons in the homeostatic regulation of diverse physiological and behavioral functions such as sleep/wake cycle has been studied extensively, the impact of sleep history on the electrophysiology of the LH and whether this effect is homogenous across LH is unknown.
By combining multiunit activity (MUA) recordings in different regions of LH with electroencephalogram recordings in freely moving rats, we unraveled a heterogeneity of neural-activity patterns within different sub regions of LH. This heterogeneity was evident in both the circadian and the vigilance state-dependent modulation of MUA. Interestingly, and consistent with this heterogeneity under baseline conditions, the magnitude of MUA suppression following 6 hr of sleep deprivation (SD) was also different within different locations of LH. Unlike the cortex and in contrast to the predictions of the synaptic homeostatic hypothesis, no correlation was found between the magnitude of activity increase during SD and the percentage of suppression of MUA during recovery sleep.
These data provide in vivo evidence of a functional heterogeneity in the circadian and homeostatic modulation of neuronal activity in LH.

This work was supported by a postdoc grant from Foundation FYSSEN (KF), the European Community's Marie Sklodowska-Curie IEF Programme under contract 655135, "The Role of Dopamine in the regulation of Sleep and Circadian Rhythms (CIRCADOPAMINE)" (KF), a grant from the Dutch Technology Foundation (STW, TD).

Sleep 41, in press, 2018

RE-ENTRAINMENT OF SLEEP-WAKE STATES AND SPIKE-WAVE DISCHARGES AFTER A PHASE DELAY IN WAG/RIJ RATS

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Rapid changes in photoperiod lead to desynchronization of circadian rhythms, its consequences require a considerable amount of time to recover. Timed administration of melatonin or melatonin agonists was found beneficial in accelerating re-synchronization. The aim of the present study was to investigate the re-adaptation of the various sleep-wake states and absence seizures to an 8-hour phase delay and whether the melatonin agonist agomelatine affects the speed of re-entrainment of the different sleep-wake states.

Two experiments were conducted: an acute pharmacological study towards the effects of various doses of agomelatine on sleep-wake states and absence seizures. Next, chronic administration was investigated following the 8-hour phase delay. Both experiments were done in symptomatic male WAG/Rij rats, a strain endowed with hundreds of spontaneous spike-wave discharges (SWDs) daily, group size was always 8 animals per group. Simultaneous electroencephalographic (EEG) and electromyographic (EMG) recordings were made continuously during 3 days in the acute and 11 days in the chronic study. The experimental design of the acute study was as follow: saline, agomelatine and sham injection on the first, second and third day, respectively. In the chronic study saline injection was made on the first day then the phase shift took place followed by agomelatine injections during subsequent 10 post-shift days.

Agomelatine showed neither an effect on sleep-wake parameters in the acute study, nor affected SWDs and re-entrainment processes in the chronic study. Sleep-wake and SWDs rhythms were advanced immediately as a result of the 8 hour delay of the light phase. The magnitude of the advance and the speed of subsequent re-entrainment were different for various rhythms. Coupling between active wakefulness and deep slow-wave sleep, as well as SWDs and light slow-wave sleep was observed. A post-shift increase in passive wakefulness and a reduction in deep slow-wave sleep resulted in an aggravation of epileptic activity during the light phase. Opposite changes in these states in the dark phase resulted in a decrease in the number of SWDs.

Different speed of re-entrainment and coupling between various rhythms suggests that SWDs and light slow-wave sleep are controlled by a common circadian mechanism distinct from that of active wakefulness and deep slow-wave sleep. The increase in the number of seizures after the phase shift may be highly important for people with epilepsy planning a long trans-meridian flight.

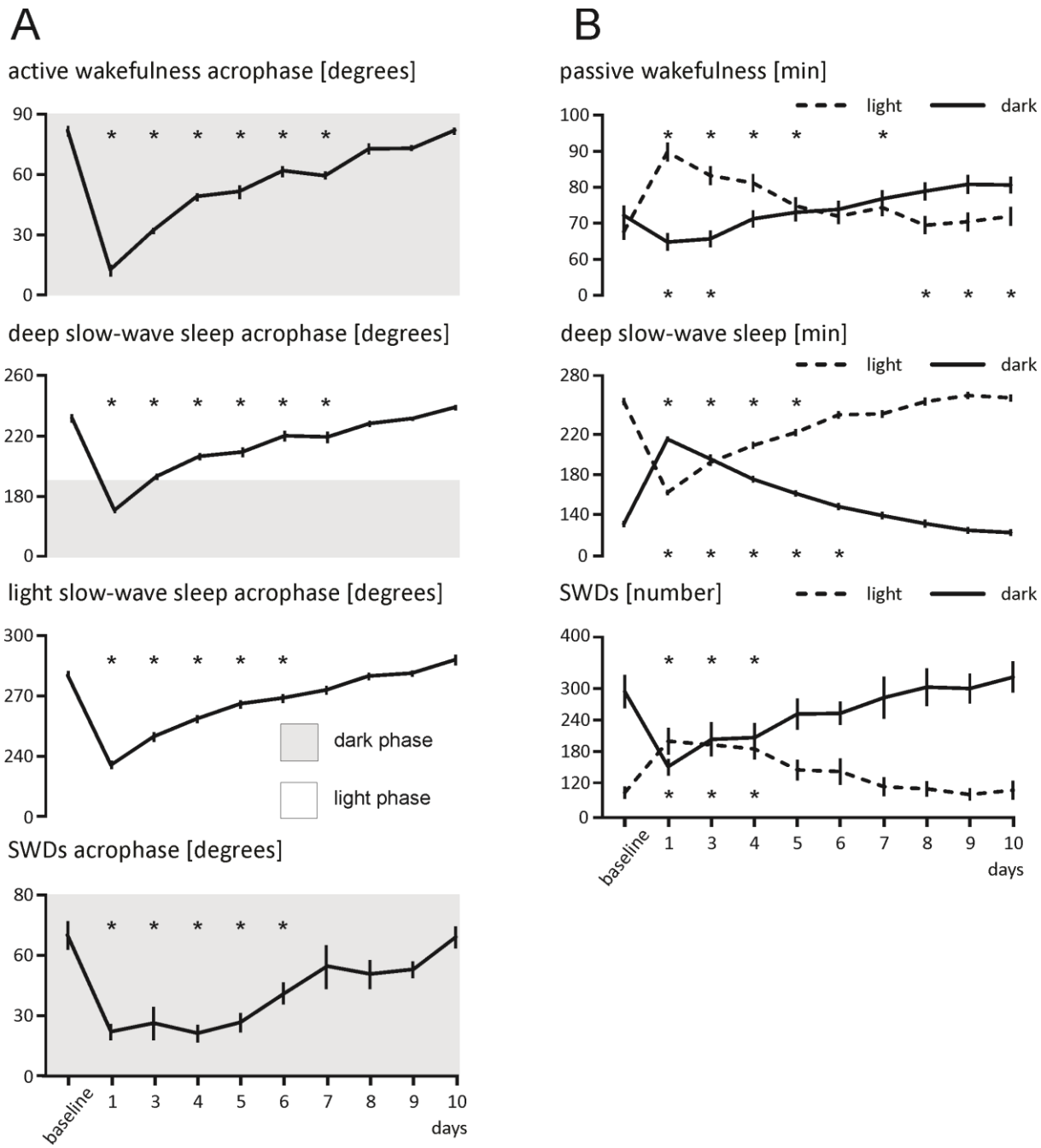

Figure 1. Results of the chronic study. A) Mean and SEM (n = 8) of the acrophase calculated in degrees (360 degrees = 24 hours) of the coupled rhythms during the baseline and after the light phase delay. B) Mean and SEM (n = 8) of the total duration of sleep-wake states in minutes and the number of SWDs in the light and the dark phase of the 12:12 light-dark cycle during the baseline and after the light phase delay. * $p < 0.05$, baseline vs. post-shift days, ANOVA for repeated measures design, Bonferroni post-hoc test.

The authors would like to thank Dirk Nuyts for his excellent technical assistance and Dr. Abdallah Ahnaou for fruitful scientific discussion. The authors would like to express the gratitude to Janssen Research and Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium for supplying facilities to perform the study.

Presented data are a part of doctoral thesis "Chronobiology of Absence Epilepsy" by M.K. Smyk, Donders Graduate School for Cognitive Neuroscience Series, ISBN 978-94-6284-031-7.

THE EFFECT OF CHRONIC SLEEP DEPRIVATION ON COGNITION IN HEALTHY MIDDLE-AGED MARITIME PILOTS

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Introduction: Recent evidence indicates a bi-directional relation between poor sleep and the development of Alzheimer's disease (AD). Poor sleep may play a causal role in the pathology of AD by influencing the clearance and/or production of the amyloid beta (Aβ) protein. Previous studies have shown that one night of total sleep deprivation increases Aβ concentrations. This led to the hypothesis that extended periods (>10 years) of disturbed sleep could lead to Aβ accumulation with subsequent cognitive decline in the context of AD. The present study was conducted to study the relationship between chronic sleep disturbances (due to an extrinsic cause, shift work) and cognitive function among healthy middle aged men to investigate the hypothesis that prolonged abnormal sleep behavior increases the risk of AD-related cognitive decline.

Methods: Our study population consisted of male volunteers (n=19), aged 50 to 60 years, who show fragmented sleeping patterns due to irregular work schedules. This chronic sleep deprivation group was compared to a group of healthy volunteers (n=19) with normal sleep, matched in gender, education and age. All participants underwent one night of standard polysomnography (PSG), preceded by approximately 10 days of actigraphy (Actiwatch 2, Philips Respironics) and maintenance of a sleep-wake diary. Cognitive function (including memory consolidation) was assessed with a neuropsychological test battery.

Results: The chronic sleep deprivation group showed more slow wave sleep (N3=16,4 % (±7.39)) compared to the healthy controls (N3=12 % (±5.61)), but no difference in cognitive test scores were found. The chronic sleep deprivation group performed only significantly (p=0.007) better on a memory consolidation test (short delay) (A'=0.92 (±0.03); hits=27.4 (±1.5)) than the controls (A'=0.88 (±0.05); hits= 25.8 (±2.11)).

Conclusions: Identifying poor sleep as one of the preventable risk factors for the development of AD could create more awareness about individual sleeping behavior. However, we found no negative effects of poor sleep on cognitive function in the chronic sleep deprivation group. This could be related to the finding of enhanced slow wave sleep in this group, which might serve as a compensatory mechanism for years of sleep disturbances. In the near future we will perform amyloid PET-CT scans in order to explore the effects of long-term exposure to partial sleep deprivation on biomarkers of AD.

Abstract partly presented as poster at SLAAP 2017 (Ermelo, The Netherlands) and fully presented as poster at SLTBR 2018 (Groningen, The Netherlands)

CHRONOTYPE AND DEPRESSIVE SYMPTOMS IN STUDENTS: AN INVESTIGATION OF POSSIBLE MECHANISMS

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Introduction: Individuals with an evening chronotype are at increased risk of experiencing emotional problems, including depressive symptoms. However, the mechanisms underlying these associations remain unclear. The present study aimed to determine whether poor sleep quality, substance use and cognitive emotion regulation difficulties – which have been implicated in the etiology of depression – mediate the relationship between chronotype and depressive symptoms in a student sample, which was assessed cross-sectionally and after 1 year.

Methods: A total of 742 Dutch students (75% women, mean age 21.4 ± 2.9 years) completed the Quick Inventory of Depressive Symptomatology, the Morningness-Eveningness Questionnaire, the Pittsburgh Sleep Quality Index, a questionnaire assessing alcohol, caffeine, tobacco and cannabis use, the Cognitive Emotion Regulation Questionnaire and the Behavioral Inhibition/Activation Scale. A subsample (n = 115) was assessed 1 year later with the same questionnaires.

Results: Cross-sectional analyses showed that evening chronotype was associated with more depressive symptoms, adjusted for age and gender (β = −0.082, p = 0.028). The relationship between eveningness and depressive symptoms was mediated by sleep quality, alcohol consumption and the cognitive emotion regulation strategies of self-blame and positive reappraisal. In longitudinal analyses, eveningness at baseline predicted more depressive symptoms at follow-up, adjusted for age and gender (β = −0.29, p = 0.002); after additional adjustment for baseline depressive symptoms, chronotype remained a significant predictor of depressive symptoms at T2 (β = −0.16, t = −2.01, p = 0.047). Only poor sleep quality at follow-up was a significant mediator of this relationship.

Conclusion: Even though the effect is small in terms of explained variance, eveningness is related to depressive symptoms and this relationship is mediated by poor sleep quality, also in a prospective design. Self-blame and reduced positive reappraisal are correlated with eveningness. Further research is needed to assess the efficacy of chronotherapeutic interventions for the prevention of depression, in addition to sleep education and cognitive approaches.

Julia F. Van den Berg, Liia Kivelä & Niki Antypa (2018) Chronotype and depressive symptoms in students: An investigation of possible mechanisms, Chronobiology International, DOI: 10.1080/07420528.2018.1470531

CHRONIC SLEEP REDUCTION IS ASSOCIATED WITH ACADEMIC ACHIEVEMENT AND STUDY CONCENTRATION IN HIGHER EDUCATION STUDENTS

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Introduction: Inadequate sleep impairs cognitive function and has been associated with worse academic achievement in higher education students; however, studies that control for relevant background factors and include knowledge on sleep hygiene are scarce.

Methods: This study examined the association of chronic sleep reduction (i.e. symptoms of chronic sleep reduction such as shortness of sleep, sleepiness and irritation), subjective sleep quality and sleep hygiene knowledge with academic achievement (grades and study credits) and study concentration among 1378 higher education students (71% female, mean age 21.73 years, SD = 3.22) in the Netherlands. Demographic, health, lifestyle and study behaviour characteristics were included as covariates in hierarchical regression analyses.

Results: After controlling for significant covariates, only chronic sleep reduction remained a significant predictor of lower grades (last exam, average in current academic year). Better sleep quality and sleep hygiene knowledge were associated with better academic achievement, but significance was lost after controlling for covariates, except for a remaining positive association between sleep hygiene beliefs and grades in the current academic year. Moreover, better sleep quality and lower scores on chronic sleep reduction were associated with better study concentration after controlling for significant covariates.

Conclusion: To conclude, chronic sleep reduction is associated with academic achievement and study concentration in higher education students. Inadequate sleep hygiene knowledge is moderately associated with worse academic achievement. Future research should investigate whether sleep hygiene interventions improve academic achievement in students of higher education.

This study was supported by a grant (GH20 I 5-4-02) from the Netherlands Brain Foundation (Hersenstichting).

Sleep Res. 27 (2): 165-174 (2018).

EXOME-WIDE META-ANALYSIS IDENTIFIES RARE 3'-UTR VARIANT IN ERCC1/CD3EAP ASSOCIATED WITH SYMPTOMS OF SLEEP APNEA.

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Introduction: Obstructive sleep apnea (OSA) is a common sleep breathing disorder associated with an increased risk of cardiovascular and cerebrovascular diseases and mortality. Although OSA is fairly heritable (~40%), there have been only few studies looking into the genetics of OSA.

Methods: In the present study, we aimed to identify genetic variants associated with symptoms of sleep apnea by performing a whole-exome sequence meta-analysis of symptoms of sleep apnea in 1,475 individuals of European descent.

Results: We identified 17 rare genetic variants with at least suggestive evidence of significance. Replication in an independent dataset confirmed the association of a rare genetic variant (rs2229918; minor allele frequency = 0.3%) with symptoms of sleep apnea ($p\text{-value}_{meta} = 6.98 \times 10{-}9$, $\beta_{meta} = 0.99$). Rs2229918 overlaps with the 3' untranslated regions of ERCC1 and CD3EAP genes on chromosome 19q13. Both genes are expressed in tissues in the neck area, such as the tongue, muscles, cartilage and the trachea. Further, CD3EAP is localized in the nucleus and mitochondria and involved in the tumor necrosis factor-alpha/nuclear factor kappa B signaling pathway.

Conclusion: Our results and biological functions of CD3EAP/ERCC1 genes suggest that the 19q13 locus is interesting for further OSA research.

Funding: The ERF study as a part of EUROSPAN (European Special Populations Research Network) was supported by European Commission FP6 STRP grant number 018947 (LSHG-CT-2006-01947) and also received funding from the European Community's Seventh Framework Programme (FP7/2007-2013)/grant agreement HEALTH-F4-2007-201413 by the European Commission under the programme "Quality of Life and Management of the Living Resources" of 5th Framework Programme (no. QLG2-CT-2002-01254). High-throughput analysis of the ERF data was supported by joint grant from Netherlands Organization for Scientific Research and the Russian Foundation for Basic Research (NWO-RFBR 047.017.043). Exome sequencing analysis in ERF was supported by the ZonMw grant (project 91111025).
The generation and management of the exome sequencing data for the RS was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, EMC, The Netherlands. The Exome Sequencing data set was funded by the Netherlands Genomics Initiative (NGI)/Netherlands Organization for Scientific Research (NWO) sponsored Netherlands Consortium for Healthy Aging (NCHA; project nr. 050-060-810), by the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, and by a Complementation Project of the Biobanking and Biomolecular Research Infrastructure Netherlands (BBMRI-NL; www.bbmri.nl; project number CP2010-41). The RS is funded by EMC and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam.
The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with Boston University (Contract No. N01-HC-25195 and HHSN268201500001I). SHARe Illumina genotyping was provided under an agreement between Illumina and Boston University. A portion of this research was conducted using the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center.
Funding support for the Framingham Sleep Heart Health Study was provided by NIH/NHLBI grant U01 HL 53941.

Van der Spek A, Luik AI, Kocevska D, Liu C, Brouwer R, Van Rooij JGJ, Van den Hout MCGN, Kraaij R, Hofman A, Uitterlinden AG, Van Ijcken WFJ, Gottlieb DJ, Tiemeier H, Van Duijn CM, Amin N. Exome-wide meta-analysis identifies rare 3'-UTR variant in ERCC1/CD3EAP associated with symptoms of sleep apnea. Frontiers Genetics 2017, 8:151.

DOES ONLINE INSOMNIA TREATMENT REDUCE DEPRESSIVE SYMPTOMS? A RANDOMIZED CONTROLLED TRIAL IN INDIVIDUALS WITH BOTH INSOMNIA AND DEPRESSIVE SYMPTOMS

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Introduction: Insomnia is effectively treated with online Cognitive Behavioral Therapy for Insomnia (CBT-I). Previous research has suggested the effects might not be limited to sleep and insomnia severity, but also apply to depressive symptoms. Results, however, are mixed.

Methods: In this randomized controlled trial we investigated the effects of guided online CBT-I on depression and insomnia in people suffering from symptoms of both. Participants (n = 104) with clinical insomnia and at least subclinical depression levels were randomized to (1) guided online CBT-I and sleep diary monitoring (i-Sleep) or (2) control group (sleep diary monitoring only). The primary outcome was the severity of depressive symptoms (Patient Health Questionnaire-9 without sleep item; PHQ-WS). Secondary outcomes were insomnia severity, sleep diary parameters, fatigue, daytime consequences of insomnia, anxiety, and perseverative thinking.

Results: At post-test, participants in the i-Sleep condition reported significantly less depressive symptoms (PHQ-WS) compared with participants in the sleep-diary condition (d = 0.76). Large significant effects were also observed for insomnia severity (d = 2.36), most sleep diary parameters, daytime consequences of insomnia, anxiety, and perseverative thinking. Effects were maintained at 3 and 6 month follow-up. We did not find significant post-test effects on fatigue or total sleep time.

Conclusion: Findings indicate that guided online CBT-I is not only effective for insomnia complaints but also for depressive symptoms. The effects are large and comparable with those of depression therapy. Clinical trial registration number: NTR6049 (Netherlands Trial Register).

Van der Zweerde, T., Van Straten, A., Effting, M., Kyle, S., & Lancee, J. (2018). Does online insomnia treatment reduce depressive symptoms? A randomized controlled trial in individuals with both insomnia and depressive symptoms. Psychological Medicine, 1-9. doi:10.1017/S0033291718001149

SLEEP IN ATR-X SYNDROME

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Introduction: X-linked alpha thalassemia mental retardation (ATR-X) syndrome is characterized by four main symptoms: severe mental retardation, alpha thalassaemia, facial dysmorphisms and genital abnormalities, occurring exclusively in males. Sleep disorders are commonly reported in clinic, but their frequency and nature have not been studied. In this cross-sectional study we explored sleep rhythm, and the prevalence and treatment of sleep disorders in ATR-X syndrome.

Methods: All members of the Dutch and international ATR-X foundation were asked to participate in this study. If they were willing, parents received the sleep questionnaire of Simonds and Parraga and kept a graphical sleep diary for two weeks.

Results: Thirty-seven participants joined the study with mean age of 12.9 year (range 1.8-43.5 years). Twenty six out of 37 (70%) reported sleep problems (62% current, 8% in the past). The most frequent occurring sleep problems were difficulty falling asleep (41%) and maintaining sleep (51%). The sleep diary (N=17) showed a total sleep time of 10.4 hours, total bed time of 12.3 hours (daytime naps included), sleep efficiency 85% and sleep onset of 0.96 hours. There was no decrease in sleep time or total bed time with increasing age. Individuals with sleep problems went to bed earlier ($p=0.03$) and had a lower sleep efficiency ($p<0.01$) than individuals without self-reported sleep problems. Parents mentioned gastro-intestinal problems, jerky movements and hyperactivity as possible sleep disturbers. Sixteen out of 37 participants (43%) used medication (predominantly melatonin N=10) to improve sleep which gave improvement in only two (melatonin together with temazepam; alimemazine).

Conclusions: Seventy per cent of individuals with ATR-X syndrome experienced sleep problems, although total sleep time was normal in most patients. Physical discomfort and hyperactivity were mentioned by parents as a possible cause of sleep problems. However, long bedtimes might also have a negative influence on sleep efficiency. Sleep medication is usually not effective, urging the need for new treatment programs in these patients.

This research was funded with an unrestricted grant from the Dutch ATR-X syndrome Foundation.

Presented at the 24th congress of the ERSR, Basel, Switzerland, September 2018

VALIDATION OF THE DUTCH TRANSLATION OF THE PARIS AROUSAL DISORDER SEVERETY SCALE IN A ONE YEAR AND ONE MONTH VERSION

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Introduction: The Paris Arousal Disorders Severity Scale (PADSS) was developed to evaluate clinical symptoms and severity of sleep walking and sleep terrors. The original PADSS is used as a screening tool to assess nighttime behavior, its frequency and consequences over the past year. However, to monitor treatment effects, evaluation over a shorter time frame would be preferable. The aim of this study was to test the psychometric properties of the Dutch version of the PADSS and to develop and validate a one month version.

Methods: The Dutch PADSS was obtained by forward-backward translation of the original French questionnaire. A second version was created evaluating symptoms over the past month, instead of the past year. Both versions were completed by patients with sleep walking and/or sleep terrors; and healthy control subjects.

Results: The PADSS was completed by 46 consecutive patients (age 27.0±6.0 years) with sleep walking/sleep terrors and 34 healthy controls (age 27.7±5.6 years). The PADSS showed a good internal consistency in both the one-year version (Cronbach's alpha = 0.727) and the one-month version (Cronbach's alpha = 0.790). Factor analysis using a 2-factor model, yielded factors representing wandering and violence, comparable to the French version. Patients had higher scores than healthy controls on both the one-year version (16.4±4.6 vs. 1.6±3.4, $p<0.001$ and the one-month version (14.5±5.1 vs. 1.0±2.9, $p<0.001$). Dutch patients had lower (total) scores on the PADSS one-year version than the previously published French cohort (16.4±4.6 vs. 19.4±6.3, $t=2.797$, $p<0.01$). A lower cutoff score to discriminate between patients and healthy controls yielded better results The best Dutch cutoff score was 11.5 (sensitivity 81.8%, specificity 97.1%, ROC-AUC 0.988), whereas the optimal cutoff in the French cohort was 13.5.

Conclusions: Both versions of the Dutch-PADSS are scales with good internal consistency. Although a lower cutoff score was preferred, the PADSS one-year version can be used as a screening tool for non-REM parasomnias. The PADSS one-month version could be used to evaluate current symptoms and potentially to monitor treatment effects. Therefore, its responsiveness to changes should be validated next.

Presented at the 24th congress of the ERSR, Basel, Switzerland, September 2018

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOM SEVERITY AND SLEEP PROBLEMS IN ADULT PARTICIPANTS OF THE NETHERLANDS SLEEP REGISTRY

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Background: We examined whether current overall attention deficit hyperactivity disorder (ADHD), inattention, or hyperactivity symptom severities are associated with the current presence and persistent history of sleep problems.

Methods: N = 942 participants of the Netherlands Sleep Registry filled out online several validated questionnaires. Regression analyses were performed to assess the association between (1) current overall ADHD symptom severity and the current presence of sleep problems, (2) current ADHD symptom-severity groups and the persistent history of sleep problems, and (3) current inattention or hyperactivity symptom severities and the current presence of sleep problems.

Results: (1) Current overall ADHD symptom severity was associated with the odds of suffering from probable obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS), periodic limb movement disorder (PLMD), insomnia disorder (ID) with predominant difficulties initiating sleep (DIS) and maintaining sleep (DMS), but not with the odds of suffering from narcolepsy or ID with predominant early-morning awakening (EMA). Current overall ADHD symptom severity was also associated with an extreme evening chronotype but not with short sleep. (2) The group with the most severe current ADHD symptoms was more likely to have a history of persistent OSAS, RLS, and ID. (3) The severity of symptoms of hyperactivity, but not of inattention, was specifically associated with probable RLS, PLMD, ID with DIS or DMS, and short sleep. Inattention symptom severity was only related to the probability of being an extreme evening chronotype.

Conclusion: ADHD severity, especially the severity of hyperactivity, is associated with the current presence and persistent history of sleep problems.

Vogel SWN, Bijlenga D, Benjamins JS, Beekman ATF, Kooij JJS, Van Someren EJW. Attention deficit hyperactivity disorder symptom severity and sleep problems in adult participants of the Netherlands sleep registry. Sleep Med. 2017 Dec;40:94-102. doi: 10.1016/j.sleep.2017.09.027.

STRONGER RESPONSE TO METHYLPHENIDATE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WHEN SOLAR IRRADIANCE DECREASES

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Background: Individuals with ADHD often show a circadian phase delay, which can be counteracted by exposure to intense natural light. The prevalence of ADHD is lower in geographical areas with extreme sunlight intensity. Sensitivity to light could be increased by caffeine intake in mice. This study examines whether 1) solar irradiance (SI) relates to variation in inattention within ADHD, and 2) the response to methylphenidate (MPH) is dependent on sunlight exposure.

Methods: 336 individuals with ADHD (mean age 11.9 yrs; 245 males) were treated with MPH in a multi-center, international, prospective open-label trial (iSPOT-A). ADHD symptoms severity was assessed by the clinician rated ADHD-Rating Scale-IV at baseline and endpoint (6 weeks). SI was calculated by the global radiation amount (Gh kWh/m2) summed per month for the areas of interest. The amount of false negative errors on a Continuous Performance Task was used as a second, uncorrelated measure of inattention.

Results: 185 participants from the Northern hemisphere were included in the main analyses. SI significantly explained 3.2% of the inattention severity at baseline with 86.52% certainty. 7.8% of the change on inattention symptoms and 5.8% of false negative errors was explained by seasonal variation. Response to MPH was stronger when started during decreasing SI compared to increasing (SI change X inattention: $F(1,183)=9.978$, $p=.002$, $d=-0.464$. SI change X false negative errors: $F(1,98)=7.097$, $p=.009$, $d=-0.540$).

Conclusions: The previously reported relationship between SI and ADHD was extended, and demonstrated to interact with MPH response opening new avenues to unravel the neurobiology of ADHD and optimize its treatment.

Presented at the Society of Biological Psychiatry Annual meeting, New York, USA, May, 2018.

TWO MILLION NIGHTS TO CHARACTERIZE SLEEP HETEROGENEITY: WHAT OBJECTIVE AND SELF REPORT BIG DATA TELL US

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Introduction: Demographic, health, and lifestyle factors all affect sleep. However, little is known about how heterogeneity among such factors relates to sleep outcomes, and most studies use a single self-report sleep measure. We used big data -- both objective and self-report -- to identify distinct sleep profiles.

Methods: We analyzed 1,920,457 nights of objective sleep data collected between 7-13-14 and 1-8-18 via S+ by ResMed sleep tracking technology, complemented with self-report data. We performed Multiple Correspondence Analysis and hierarchical profiling on 20 self-report categorical variables reflecting demographic, health, and lifestyle factors (e.g., age, BMI, smoking, exercise, blood pressure, stress) to reveal distinct clusters of sleepers. We set the number of clusters to 8 based on the inertia gain criterion and visual inspection of the dendrogram. Each cluster was then profiled using objective sleep data, including TST, SOL, Number of Awakenings, and Sleep Stage durations (Wake, Light, Deep, and REM).

Results: Analysis of the self-report data revealed 8 clusters. Profiling those clusters with objective sleep data revealed between-cluster heterogeneity: (1) Active and healthy (n=2,679); (2) Older, with healthy lifestyle (n=1,857); (3) Stressed, tired but active patients without sleep issues (n=1,379); (4) Active and healthy but with restless sleep and sleep breathing issues (n=1,955); (5) Otherwise healthy with sleep disorders (n=1,420); (6) Stressed smokers (n=640); (7) Overweight and older with health issues and restless sleep (n=1,811); and (8) Overweight older patients with health issues and sleep disorders (n=1,120). Interestingly, the two clusters with the poorest sleep included the most smokers and the most people whose BMI indicated obesity, showing an important association between sleep and lifestyle factors.

Conclusion: This study is the first to identify sleep profiles using both self-report and objective big data collected in the home environment. Uncovering heterogeneity among sleep profiles can help us better understand relations between sleep and demographic, health, and lifestyle factors. Findings can inform the development of behavior change guidelines that might aid in achieving better sleep and new interventions to improve sleep.

24th Congress of the European Sleep Research Society, 25-28 Sept 2018, Basel, Switzerland

SLEEP-WAKE PATTERNS AND COGNITION OF OLDER ADULTS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT (AMCI): A COMPARISON WITH COGNITIVELY HEALTHY ADULTS AND MODERATE ALZHEIMER'S DISEASE PATIENTS.

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Objective: Age-related cognitive impairment and the prevalence of neurodegenerative disease contribute to decreasing quality of life in affected individuals and their families as well as demand considerable societal responsibility. Sleep supports overall brain activity and contributes to both physical and mental health. As a result, sleep is an attractive target for exploring ways to promote health in accelerated cognitive aging. The aims of this study were to characterize cognitive performance and sleep wake behavior in older adults with different degrees of cognitive impairment.

Methods: Cognitive ability in a variety of domains of amnestic mild cognitive impairment (aMCI) individuals, moderate AD patients and cognitively healthy adults was assessed with the Mini-Mental-State- Examination and five computerized tests (CANTABeclipse™). It was imperative to exclude mixed diagnosis, comorbidities (psychiatric, neurological, sleep disorders), anti-dementia medication, institutionalized subjects, and to study participants within their home to minimize confounders. Sleep profiles were assessed with the Jupiter Sleep Questionnaire and Pittsburgh Sleep Quality Index completed by participants and carers. Participants' sleep-wake activity was monitored for three weeks using a wrist-worn actigraph and a semi-standardized diary. Groups were compared according to their diagnostic category and then pooled to correlate sleep data with cognitive performance.

Results: Mild cognitive impairment in aMCI individuals was reflected in domains of verbal and visuospatial memory but not attentional capacity or episodic memory. All self-reported and objective measures of sleep quality and sleep quantity of the aMCIs were within the normal range and comparable to those of cognitively healthy controls. Moderate AD patients scored significantly lower on all cognitive tests and had lower rest-activity amplitudes and distinctively longer nightly sleep periods that were not associated with sleep disorders, sleep medication or poor sleep efficiency. Self-rated and actigraphic quality of sleep was equally good (i.e. 90% sleep efficiency) in all groups.

Conclusion: This investigation is of clinical importance, because major confounding variables were excluded. The lack of comorbidities might be responsible for the absence of sundown syndrome and sleep disturbances commonly reported in AD patients. Whether there is interdependence between progressive decline in cognition and long sleep duration remains elusive. Future studies should address whether prolonged sleep at night and decreased day-time activity can be altered to delay the progression of cognitive decline.

Curr Alzheimer Res. 2017;14(10):1030-1041

MELANOPSIN- AND L-CONE–INDUCED PUPIL CONSTRICTION IS INHIBITED BY S- AND M-CONES IN HUMANS

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Introduction: The human retina contains five photoreceptor types: rods; short (S)-, mid (M)-, and long (L)-wavelength–sensitive cones; and melanopsin expressing ganglion cells. Recently, it has been shown that selective increments in M-cone activation are paradoxically perceived as brightness decrements, as opposed to L-cone increments.

Results: Here we show that similar effects are also observed in the pupillary light response, whereby M-cone or S-cone increments lead to pupil dilation whereas L-cone or melanopic illuminance increments resulted in pupil constriction. Additionally, intermittent photoreceptor activation increased pupil constriction over a 30-min interval. Modulation of L-cone or melanopic illuminance within the 0.25–4-Hz frequency range resulted in more sustained pupillary constriction than light of constant intensity. Opposite results were found for S-cone and M-cone modulations (2 Hz), mirroring the dichotomy observed in the transient responses.

Conclusion: The transient and sustained pupillary light responses therefore suggest that S- and M-cones provide inhibitory input to the pupillary control system when selectively activated, whereas L-cones and melanopsin response fulfill an excitatory role. These findings provide insight into functional networks in the human retina and the effect of color-coding in nonvisual responses to light, and imply that nonvisual and visual brightness discrimination may share a common pathway that starts in the retina.

This work was funded by Nederlandse Organisatie voor Wetenschappelijk onderzoek/ Stichting voor de Technische Wetenschappen OnTime Program Grant 10.13039/ 501100003958 (project 12187).

PNAS 115(4):792-797 (2018).

ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND INSOMNIA: AN UPDATE OF THE LITERATURE

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Purpose of review: Insomnia is diagnosed when there is dissatisfaction with sleep quantity or quality. It has a prevalence in the general population ranging from 31 to 56%. Insomnia has previously been associated with adult attention-deficit/hyperactivity disorder (ADHD). In this review, we address three topics: (1) the cross-sectional relationship between ADHD and insomnia in adulthood, (2) the longitudinal relationship between ADHD and insomnia, and (3) insomnia as a side effect of pharmacological treatments for adult ADHD.

Recent findings: Three cross-sectional, clinical, and population studies report a prevalence of insomnia in ADHD adults ranging from 43 to 80%. Longitudinal evidence for a link between childhood-onset ADHD and insomnia at later age is mixed, with one study confirming and another study not supporting such a longitudinal association. In randomized, placebo-controlled trials, insomnia is reported significantly more often in the treatment arm than in the placebo arm. In varying percentages of trial participants, insomnia is a treatment-emergent adverse effect in triple-bead mixed amphetamine salts (40-45%), dasotraline (35-45%), lisdexamfetamine (10-19%), and extended-release methylphenidate (11%). Ten to seventeen percent of subjects in placebo-controlled trials of atomoxetine report insomnia, possibly related to poor metabolizer status. The mechanisms explaining the relationship between ADHD and sleep problems are incompletely understood, but both genetic and non-shared environmental influences may be involved. Adults with ADHD should be assessed for insomnia, which is frequently comorbid, and both conditions should be treated.

Wynchank D, Bijlenga D, Beekman AT, Kooij JJS, Penninx BW. Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Insomnia: an Update of the Literature. Curr Psychiatry Rep. 2017 Oct 30;19(12):98. doi: 10.1007/s11920-017-0860-0.

THE ASSOCIATION BETWEEN INSOMNIA AND SLEEP DURATION IN ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM A GENERAL POPULATION STUDY

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Study objectives: Insomnia and short or long sleep duration are important comorbid conditions in adults with attention-deficit hyperactivity disorder (ADHD), but reports of the association vary. In a general population study, we evaluated the relationship between ADHD symptom severity, insomnia symptoms, and sleep duration in adults.

Methods: Data were from the third wave of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2; n = 4,618). ADHD symptom severity and symptom dimensions (hyperactivity and inattention) were assessed using the Adult ADHD Self-Report Scale screener. Self-reported insomnia symptoms (Insomnia Rating Scale; IRS) were defined as clinically relevant if IRS ≥ 9. Self-reported short sleep duration was defined as ≤ 6 hours, and long sleep duration as ≥ 10 hours.

Results: Within the group with clinically relevant ADHD symptoms, 43% reported significant insomnia symptoms (odds ratio [OR] = 2.66, 95% confidence interval [CI] 1.74-4.07); 41% short sleep duration (relative risk ratio [RRR] = 1.94, 95% CI 1.31-2.85) and 6% long sleep (RRR = 5.87, 95% CI 1.97-17.45). Increased inattention symptoms were associated with IRS ≥ 9, short and long sleep duration in fully adjusted models (OR = 1.10, 95% CI 1.06-1.14; RRR = 1.06, 95% CI 1.02-1.09; RRR = 1.16, 95% CI 1.05-1.28, respectively). Increased hyperactivity symptoms were associated with IRS ≥ 9 (OR = 1.17, 95% CI 1.11-1.23) and short sleep duration (RRR = 1.12, 95% CI 1.05-1.19).

Conclusions: Both clinically significant ADHD symptoms and inattention and hyperactivity symptom dimensions were consistently associated with insomnia symptoms and altered sleep duration. These associations confirm that sleep disturbances should be assessed and given appropriate clinical attention in adults with ADHD.

Wynchank D, Ten Have M, Bijlenga D, Penninx BW, Beekman AT, Lamers F, de Graaf R, Kooij JJS. The Association Between Insomnia and Sleep Duration in Adults With Attention-Deficit Hyperactivity Disorder: Results From a General Population Study. J Clin Sleep Med. 2018 Mar 15;14(3):349-357. doi: 10.5664/jcsm.6976

BEING ASLEEP WHILE WALKING AROUND? MODULATION OF THALAMOCORTICAL OSCILLATIONS BY TRIP8B, AN AUXILIARY SUBUNIT FOR HCN CHANNELS.

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Introduction: The neurophysiological basis of delta waves characterizing slow-wave sleep is bursting activity in thalamocortical cells. Bursting occurs via interplay between classical low-voltage activated T-type calcium channels and hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channels. More general, HCN channels have important functions in controlling neuronal excitability and generating rhythmic oscillatory activity. The role of tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b), a brain specific auxiliary subunit for HCN channels in regulation of hyperpolarization-activated inward current (I_h) in the thalamocortical system and its functional relevance for the physiological thalamocortical oscillations were investigated.

Methods: Trip8b-deficient mice (TRIP8b$^{-/-}$) were used in our study and always compared with C57BL/6J mice. Immunofluorescence, gene and protein expression for different HCN channel subunits, and patch-clamp recordings regarding I_h and transient outward K^+ current (I_A) were done in cortical and thalamic slices, thalamic cAMP levels were determined, and in vivo LFP recordings were made in freely moving mice.

Results: A significant reduction in HCN channels protein expression in thalamus and cortex of TRIP8b$^{-/-}$ mice was found by western blot analyses of the brain and confirmed immunohistochemically. TRIP8b$^{-/-}$ mice showed a significant decrease in I_h current density, in both thalamocortical relay (TC) and cortical pyramidal neurons. In addition, basal cAMP levels in the brain were found to be decreased while the availability of the fast transient A-type K^+ current, I_A, in TC neurons was increased. These changes were associated with alterations in intrinsic properties and firing patterns of TC neurons, as well as intrathalamic and thalamocortical network oscillations, revealing a significant increase in slow oscillations in the delta frequency range (0.5–4 Hz) during episodes of active-wakefulness in cortex and thalamus. The **Figure** contains the raw data and the outcomes of spectral analyses of ten sec epochs of slow-wave sleep and active- wakefulness. In addition, the absence of TRIP8b suppressed the normal desynchronization response of the LFP during the switch from slow-wave sleep to wakefulness.

Conclusion: TRIP8b$^{-/-}$ mice show a sleep-like pattern on LFP during active-wakefulness. It seem that this protein is necessary for the modulation and better desynchronization of normal physiological thalamocortical oscillations due to its direct effect on HCN channels expression in the thalamus and cortex and that mechanisms related to reduced cAMP signaling may contribute to the present findings. The functional consequences of this aberrant electrophysiological pattern deserve to be studied.

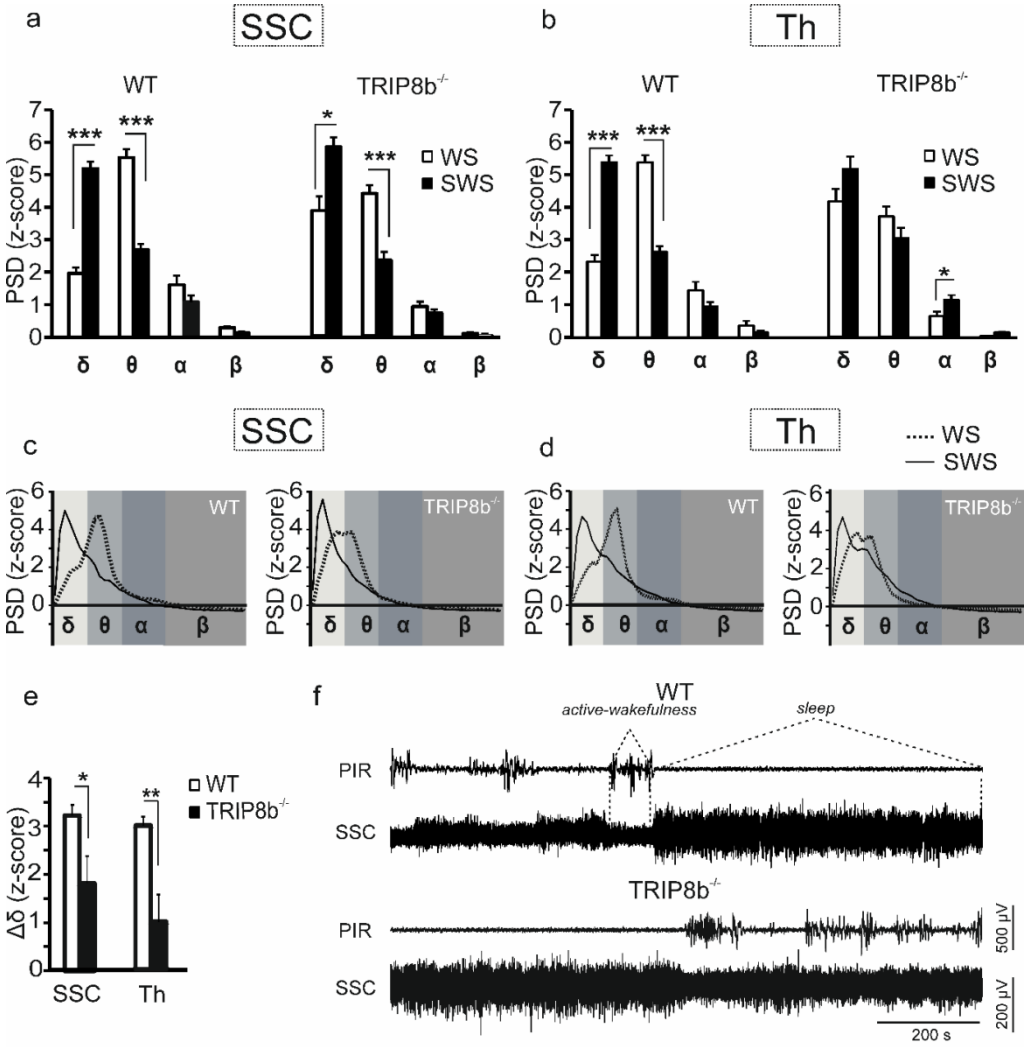

Figure. **Modulation of cortical and thalamic slow-frequency oscillations by TRIP8b during episodes of slow-wave sleep and active-wakefulness. a** and **b** Bar graphs comparing the normalized peak frequency PSD (z-score) of four frequency bands (δ–β) in somatosensory cortex (SSC) and VPM (Th) of WT and TRIP8b$^{-/-}$ mice between episodes of active-wakefulness (WS) and slow-wave sleep (SWS). (mixed repeated measures ANOVAs followed by Student's t tests, n = 7/7, *, **, *** indicate $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively). **c** and **d** Representative spectrograms indicating the difference between the PSD during WS and SWS. **e** Bar graph comparing the changes in delta frequency oscillations (Δδ) between the deep non-REM sleep (SWS) and active-wakefulness in WT and TRIP8b$^{-/-}$ mice. As illustrated, TRIP8b$^{-/-}$ mice (n = 7) show less (Student's t tests, $p < 0.05$ for SSC and $p < 0.01$ for thalamus) changes in Δδ compared to WT (n = 7) mice. **f** Sample LFP recordings from the SSC of WT (upper panel) and TRIP8b$^{-/-}$ (lower panel) mice, showing the LFP signal during non-REM sleep and active-wakefulness in combination with the signal recorded from infrared movement detector (PIR). Note the smaller difference in the amplitude of the LFP between deep non-REM sleep and active-wakefulness in TRIP8b$^{-/-}$ compared to WT mice. Dashed lines indicate episodes of sleep and active-wakefulness detected with the aid of both PIR and LFP signal.

Zobeiri, M., Chaudhary, R., Datunashvili, M. et al. Brain Struct Funct (2018) 223: 1537. https://doi.org/10.1007/s00429-017-1559-z

CHANGE IN WEIGHT AND CENTRAL OBESITY BY POSITIVE AIRWAY PRESSURE TREATMENT IN OBSTRUCTIVE SLEEP APNEA PATIENTS: LONGITUDINAL DATA FROM THE EUROPEAN SLEEP APNEA DATABASE (ESADA).

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Introduction: The effect of continuous positive airway pressure (CPAP) treatment on body weight and central obesity in obstructive sleep apnea (OSA) patients is still unclear. We aimed to study body composition change during CPAP treatment in the European Sleep Apnea Database (ESADA).

Methods: OSA patients with a CPAP treatment follow-up time of more than 30 days in the ESADA registry were selected (n=2015). Body mass index (BMI), body weight, waist-, hip- and neck-circumferences were assessed at baseline and follow-up (median [interquartile range], 242 [380] days). Predictors for body composition changes with CPAP were analyzed adjusting for confounders.

Results: Overall, there were no systematic changes in weight and central obesity measures from baseline to follow-up in patients treated with CPAP. Independent predictors of individual weight gain included higher CPAP compliance, lower BMI, shortened sleep time (≤5 hours), use of antidepressive medication and coexisting metabolic disease (diabetes and hyperlipidemia). A gain in body weight was associated with an attenuation of the CPAP induced reduction in sleepiness (Epworth Sleepiness Scale score in patients with 2% weight loss -5±5 versus patients with 2% weight gain -4±5, p=0.003).

Conclusion: Standard CPAP treatment was not associated with a systematic, unidirectional body weight change in OSA patients. Active weight reduction therapy should therefore be considered in overweight and obese OSA patients receiving CPAP. Future studies to identify clinical OSA phenotypes predisposed to weight change after CPAP are warranted.

Eur Respir J 2017;50: Suppl 61:A5070. Abstract presented during the European Respiratory Society International Congress 2017, Milan (Italy), September 9-13, 2017.

LONG-TERM MELATONIN THERAPY FOR ADOLESCENTS AND YOUNG ADULTS WITH CHRONIC SLEEP ONSET INSOMNIA AND LATE MELATONIN ONSET: EVALUATION OF SLEEP QUALITY, CHRONOTYPE, AND LIFESTYLE FACTORS COMPARED TO AGE-RELATED RANDOMLY SELECTED POPULATION COHORTS

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Abstract: The extent of continuance of melatonin therapy initiated in pre-pubertal children with chronic sleep onset insomnia (CSOI) was investigated in young adult life. Sleep timing, sleep quality, adverse events, reasons for cessation of therapy, and patient characteristics with regard to therapy regimen, chronotype and lifestyle factors possibly influencing sleeping behavior were assessed. With an online survey using questionnaires (Pittsburgh Sleep Quality Index, Insomnia Severity Index, Morningness-Eveningness Questionnaire, and Munich Chronotype Questionnaire), outcomes were measured and compared with age-related controls. These controls were extracted from published epidemiological research programs applying the same questionnaires. At the moment of the survey, melatonin was still continued by 27.3% of the patients, with a mean treatment duration of 10.8 years. The overall average treatment duration was 7.1 years. Sleep quality of both discontinued and persistent melatonin users did not deviate from controls. Sleep timing and chronotype scores indicated evening type preference in all responders. Adverse events were scarce but the perceived timing of pubertal development suggested a tendency towards delayed puberty in former and current users of melatonin. This study may underestimate the number of children that are able to stop using melatonin due to the response rate (47.8%) and appeal for continuing users. Sleep timing parameters were based on self-reported estimates. Control populations were predominantly students and were of varying nationalities. The statistical power of this study is low due to the limited sample size. Melatonin therapy sustained for 7.1 years does not result in substantial deviations of sleep quality as compared to controls and appears to be safe. The evening type preference suggests a causal relation with CSOI. This study shows that ten years after initiation of treatment with melatonin for CSOI, approximately 75% of the patients will have normal sleep quality without medication.

The melatonin treatment continuation over the years of the 33 participants of the current study is schematically depicted in Figure 1.

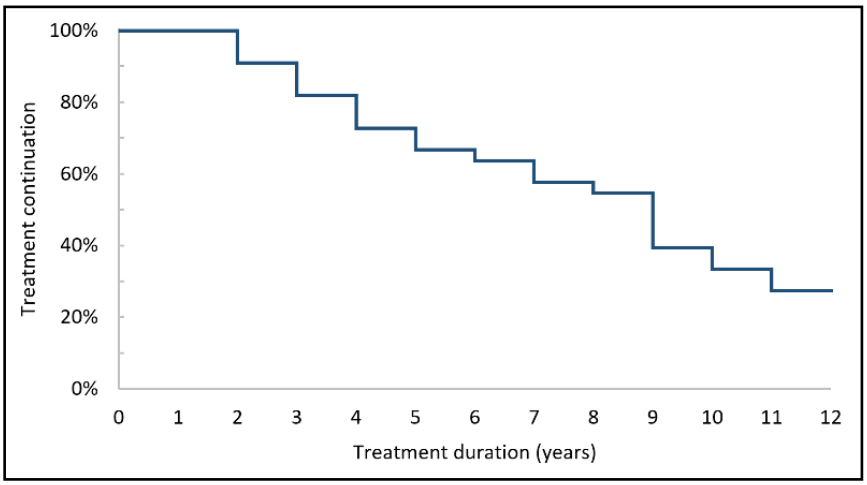

Figure 1. Melatonin treatment continuation of the 33 participants over the years.

Healthcare 2018, 6, 23.

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Volume 29, 2018

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