

SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 24, 2013

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

Ipskamp Drukkers BV, Enschede

ISBN 978-90-73675-21-6

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Founded at Leiden, The Netherlands, June 7, 1990

ISBN 978-90-73675-21-6

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Published by

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CONTENTS

Preface <i>Hans L. Hamburger</i>	10
Editorial Note <i>Tom de Boer</i>	12
In memoriam Hilbert Kamphuisen <i>Al de Weerd</i>	14
PHD THESES	
Light from dawn to dusk: Human entrainment in a changing environment <i>Marina C Gimenez</i>	18
Commentary on the dissertation of Marina C Gimenez <i>Debra Skene</i>	21
Sleep deprivation in rats: Effects on learning and cognitive flexibility <i>Cathalijn Leenaars</i>	23
Commentary on the dissertation of Cathalijn Leenaars <i>Tom Deboer</i>	25
A tailor made approach to obstructive sleep apnea <i>Madeline JL Ravesloot</i>	27
Commentary on the dissertation of Madeline JL Ravesloot <i>Boris A Stuck</i>	30
Mild skin warming, a non-pharmacological way to modulate sleep and vigilance <i>Roy JEM Raymann</i>	32
Commentary on the dissertation of Roy JEM Raymann <i>Tom Deboer</i>	35
Sleep and sleep-wake rhythm in older adults with intellectual disabilities <i>Ellen van de Wouw-van Dijk</i>	37
Commentary on the dissertation of Ellen van de Wouw-van Dijk <i>Michael Echteld</i>	40
MINI REVIEW	
The canon of sleep researchers: The first generation <i>Anton Coenen</i>	44
PIET VISSER POSTERPRICE 2012	
Amplitude of the SCN clock enhanced by the behavioral activity rhythm <i>Floor van Oosterhout, Eliane A Lucassen, Thijs Houben, Henk Tjebbe vanderLeest, Michael C Antle, Johanna H Meijer</i>	58
NSWO 24, 2013	5

RESEARCH PAPERS

- Inhibition of the neurotrophin receptor (p75NTR) alters neurogenesis and sleep wake architecture: Possible relevance to depression 64
A Ahnaou, M Cik, L Andries, T Steckler, WHIM Drinkenburg
- Effects of alzheimer's disease therapeutic drugs on sleep and spectral contents in rats 70
A Ahnaou, WHIM Drinkenburg
- Inactivation of the metabotropic glutamate receptor (MGLUR2) evokes an arousal but not antidepressant-like profile in rodent's sleep-wake EEG 75
A Ahnaou, L Verdonck, WHIM Drinkenburg
- Preoperative screening for obstructive sleep apnea in patients before bariatric surgery 80
CJM van Boheemen, RJ Schimsheimer
- Changes in sleep architecture after an epileptic seizure the day before 84
Th Gutter, AW de Weerd
- Increased prevalence of restless legs syndrome in Crohn's disease 88
PD Hoek, M Smits, NM de Roos, RM Rijsman, BJM Witteman
- Ambulatory automated auditory partial sleep deprivation affects subjective sleepiness without affecting sleep macro structure 94
Melanie Knufinke, Tim RM Leufkens, Roy JEM Raymann
- Recharge yourself; Recharge interventions during festival-induced sleep loss 98
Els IS Møst, Tim RM Leufkens, Melanie Knufinke, Tim EJ Weysen, Roy JEM Raymann
- Comparison of the SPANE and PANAS scales for measuring self-reported affect during total sleep deprivation 102
Samantha M Riedy, Devon A Grant, Hans PA van Dongen
- Restless legs syndrome or Willis-Ekbom disease: What is in a name? 106
Al de Weerd

ABSTRACTS

- Is a questionnaire a useful screening method for sleep apnea in stroke? 110
JA Aaronson, J Nachtegaal, E Groet, T van Bezeij, CAM van Bennekom, JG van den Aardweg, WF Hofman
- Auditory sensory memory and mismatch negative deficits in rats: Assessment of drugs with pro-cognitive potential 111
A Ahnaou, R Biermans, WHIM Drinkenburg
- Mismatch negative (MMN) and P300 correlates in epidural auditory evoked potentials in awake rats: Opportunities for preclinical evaluation of drugs with pro-cognitive potential 112
A Ahnaou, R Biermans, WHIM Drinkenburg
- EEG network oscillations: A target for screening drugs with cognition enhancing and antipsychotic potential 113
A Ahnaou, H Huysman, WHIM Drinkenburg

Pro-cognitive potential of metabotropic receptors (MGLUR5) blockade: Evidence from sleep behavior and cortical network oscillations in rodents <i>A Ahnaou, X Langlois, T Steckler, H Huysmans, P te Riele, L Raeymakers, JM Bartolome, WHIM Drinkenburg</i>	114
Translational validity of EEG oscillations in schizophrenia <i>A Ahnaou, K Tahon, H Huysmans, R Biermans, S Versweyveld, T Jacobs, WHIM Drinkenburg</i>	115
Geographical variation in the prevalence of ADHD: The sunny perspective <i>Martijn Arns, Kristiaan B van der Heijden, L Eugene Arnold, J Leon Kenemans</i>	116
Traveling slow waves in the avian brain <i>G Beckers, J van der Meij, J Lesku, N Rattenborg</i>	117
NMDA receptor blockade: Evidence from AEP mismatch negativity in rats on lack of NR2B-subunit contribution to cognitive disruption <i>R Biermans, A Ahnaou, JB Kelly, JA Kemp, WHIM Drinkenburg</i>	118
Modulation of nicotinic acetylcholinergic receptors may differentially affect auditory event related potentials components in awake rats <i>R Biermans, WHIM Drinkenburg, A Ahnaou</i>	119
CY1A2 polymorphisms in slow melatonin metabolisers: A possible relationship with autism spectrum disorder? <i>W Braam, H Keijzer, HAJ Struijker-Boudier, R Didden, MG Smits, LMG Curfs</i>	120
Internet treatment of adolescents with insomnia <i>EJ de Bruin, FJ Oort, SM Bögels, AM Meijer</i>	121
How sleep, wake and other imposed activity patterns feed back on the clock <i>Tom Deboer</i>	122
The effects of sleep extension on sleep and cognitive performance in adolescents with chronic sleep reduction: An experimental study <i>JF Dewald-Kaufmann, FJ Oort, AM Meijer</i>	123
Sleep deprivation inhibits light responsiveness of the circadian pacemaker <i>Hester C van Diepen, Johanna H Meijer, Tom Deboer</i>	124
Sleep deprivation and caffeine influence light responsiveness of circadian pacemaker neurons <i>Hester C van Diepen, Johanna H Meijer, Tom Deboer</i>	125
Risk of automobile accidents associated with the use of benzodiazepine receptor agonist hypnotics <i>S Eklov, C Drake, J Verster, T Roth</i>	126
Aging of the suprachiasmatic clock <i>Sahar Farjnia, Tom Deboer, Jos HT Rohling, Johanna H Meijer, Stephan Michel</i>	127
On the impact of arousals on the performance of sleep and wake classification using actigraphy <i>Pedro Fonseca, Xi Long, Jérôme Foussier, Ronald M Aarts</i>	128
Association of eveningness with problem behavior in children: A mediating role of impaired sleep <i>Kristiaan B van der Heijden, Leo MJ de Sonnevile, Hanna Swaab</i>	129

Parental education in children with ADHD and sleep onset insomnia <i>JW Hop, RM Brouwer</i>	130
Fractal patterns of neural activity exist within the suprachiasmatic nucleus and require extrinsic network interactions <i>Kun Hu, Johanna H Meijer, Steven A Shea, Henk Tjebbe vanderLeest, Benjamin Pittman-Polletta, Thijs Houben, Floor van Oosterhout, Tom Deboer, Frank AJL Scheer</i>	131
Antagonism versus positive allosteric modulation of metabotropic glutamate (MGLU5) receptors: EEG and sleep-wake behavior indices for potential pro-cognitive drug properties in rodents <i>H Huysmans, A Ahnaou, H Shabab, X Langlois, P te Riele, L Raeymakers, T Steckler, JM Bartolome, WHIM Drinkenburg</i>	132
Guidelines for the recording and evaluation of pharmaco-sleep studies in man: The international pharmaco-EEG society (IPEG) <i>Marc Jobert, Frederick J Wilson, Thomas Roth, Ge SF Ruigt, Peter Anderer, Wilhelmus HIM Drinkenburg, The IPEG Pharmaco-EEG Guidelines Committee</i>	133
Guidelines for the recording and evaluation of pharmaco-EEG data in man: The international pharmaco-EEG society (IPEG) <i>Marc Jobert, Frederick J Wilson, Ge SF Ruigt, Martin Brunowsky, Leslie S Prichep, Wilhelmus HIM Drinkenburg, The IPEG Pharmaco-EEG Guidelines Committee</i>	134
Prevalence and relevance of sleep disturbances in forensic psychiatric patients <i>Jeanine Kamphuis, Marike Lancel</i>	135
Effects of clinically approved, pro-cognitive pharmacological agents on electroencephalography (EEG) in Alzheimer's disease-model mice: potential for translational biomarkers <i>JB Kelley, L Raeymaekers, A Ahnaou, C Babiloni, CC Czech, S Dix, JC Richardson, E Schenker, X Langlois, WHIM Drinkenburg</i>	136
Assessment of human sleep depth is being destandardized by recently advised EEG electrode locations <i>Bob Kemp, Paul van Someren, Marco Roessen, J Gert van Dijk</i>	137
Baseline depression levels do not affect efficacy of cognitive-behavioral self-help treatment for insomnia <i>Jaap Lancee, Jan van den Bout, Annemieke van Straten, Victor I Spoormaker</i>	138
The association between nightmares and daily distress <i>Jaap Lancee, Nadine CML Schrijnemakers</i>	139
Respiration amplitude analysis for REM and NREM sleep classification <i>Xi Long, Jérôme Foussier, Pedro Fonseca, Reinder Haakma, Ronald M Aarts</i>	140
Nocturnal movement in Parkinson's disease patients and subjects at-risk, and controls <i>M Louter, JB Arends, J Prinzen, RC van Lummel, D Berg, J Streffers, M Hobert, B Bloem, S Overeem, I Liepelt</i>	141
Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency <i>Maartje Louter, Ruud JG van Sloun, Dirk AA Pevernagie, Johan BAM Arends, Pierre J Cluitman, Bastiaan R Bloem, Sebastiaan Overeem</i>	142

Measuring sleep deficit through self-report in adolescents: Development and validation of the chronic sleep reduction questionnaire-short form (CSRQ-SF) <i>A van Maanen, JF Dewald-Kaufmann, Frans J Oort, Eduard J de Bruin, Marcel G Smits, Michelle A Short, Michael Gradisar, Gerard A Kerkhof, Anne Marie Meijer</i>	143
Effects of a single night of sleep deprivation on cerebrospinal fluid amyloid-beta dynamics in healthy male volunteers <i>S Ooms, S Overeem, K Besse, MG OldeRikkert, M Verbeek, J Claassen</i>	144
Sleep and circadian rhythmicity in adults ADHD and the effect of stimulants; A review of the current literature <i>Mark A Snitselaar, Marcel G Smits, Kristiaan B van der Heijden, Jan Spijker</i>	145
Effect of laboratory sleep deprivation on self-reported positive and negative affect <i>AM Tucker, GA Kerkhof, H van Dongen</i>	146
The effects of benzodiazepine receptor agonists on driving performance as assessed by standard deviation of lateral position <i>J Verster, S Eklov, C Drake, T Roth</i>	147
The serotonin transporter 5-HTTLPR polymorphism moderates the association between subjective sleep quality and positive affect <i>Jessica A de Wild-Hartmann, Mariëk Wichers, Alex L van Bommel, Catherine Derom, Evert Thiery, Nele Jacobs, Jim van Os, Claudia JP Simons</i>	148
EEG alpha power as an intermediate measure between BDNF Val66Met and depression severity in patients with major depressive disorders <i>HFA Zoon, CPM Veth, M Arns, WHIM Drinkenburg, W Talloen, PJ Peeters, JL Kenemans</i>	149
DUTCH SOCIETY FOR SLEEP-WAKE RESEARCH - MEMBERS	
Honorary Members	152
Regular Members	153

PREFACE

Dear colleagues,

The NSWO proudly presents its 2013 issue of our yearly proceedings.

In the past year we lost our founding member Hilbert Kamphuisen and first president of our society. As professor clinical neurophysiology at Leiden university he was one of the first in the Netherlands to recognize the importance and impact of sleep disordered breathing on health. In this issue you will find an extensive “In Memoriam”. Moreover from this year on we will name our yearly NSWO prize for the best PhD publication the: “Hilbert Kamphuisen prize”.

Sleep in the public domain

This year NSWO was again very successful in promoting awareness for sleep and sleep disorders in the Netherlands .

Our PR committee successfully performed an internet based survey on sleeping problems in children and its impact on sleep in their parents. More than 1,7 thousand responders gave us a reliable view on this important subject. In this issue you will find the details of this very fine study. Again this NSWO survey received widespread media coverage during the weeks and months following the publication of the results.

Moreover, the Dutch National Sleep Week has become a major stimulant for many members to share their knowledge with the general public through activities organised in their sleep centres. Due to this development NSWO is gaining increasing attention from the media concerning broader general subjects on sleep and wake. Public awareness for chronobiological problems due to our “24/7” society and its influences on daytime performance and night shift work is slowly increasing. NSWO contributed also to a survey on Sleepy driving in Europe, an initiative of ANSS and ESRS. A media campaign will be posted in many European countries on the basis of the results this October and November.

Sleep in the professional domain

We are proud to announce that the “Leerboek Slaap en Slaapstoornissen” a Dutch language study book for sleep and sleep disturbances, has recently been published. This book is the result of a cooperative effort of the NSWO together with the Flemish speaking members of the BASS, the Belgian association for sleep research and sleep medicine and the Dutch society for pulmonologists specialized in sleep (WAS). A great number of our members specialized and working in the field of sleep have contributed.

Furthermore NSWO is working on the slow process of integration of all present sleep oriented societies of medical specialists and technicians in The Netherlands to establish one umbrella organization in which all these societies can work together. This is a slow process that will take some years. At present NSWO is happy with its representation in the board of the Taskforce for Sleep and Wake disorders of the Dutch Society for Neurology and the Federation for accreditation of Sleep Medical Centres.

Moreover, NSWO is the only representative of The Netherlands in Europe at the level of ANSS and ESRS, which, amongst others, oversees the European accreditation for sleep specialists, so called “somnologists” and sleep medical centres.

Sleep and teaching

The teaching committee of NSWO has formed a taskforce for the organization of teaching courses. This resulted in well attended courses on all aspects of sleep. We will organize yearly

courses on specific topics in sleep medicine. The upcoming meeting on “Age and Sleep” will be held on May 23 2013, in cooperation with the pulmonologists in sleep (WAS) and the neurologists in sleep (SWS). Furthermore we are happy to announce that NSWO will organize the 7th International Sleep Medicine Course in January 2015. The course will focus on preparation for the ESRS exam for somnologist or certified sleep technologist. Preparations have already been started.

Future goal

The NSWO board will continue to serve as a platform to promote scientific basic research, the spread of knowledge on all subjects concerning sleep and its combination with sleep medicine to promote a healthier society. We also aim to increase the understanding of sleep disorders and to develop better treatment options for patients and to promote the spread of knowledge in the public domain.

NSWO will continue to participate in the process of accreditation of Sleep Medical Centres in all its aspects. Finally, we are working hard on the integration of the many players working in the field of sleep research and sleep medicine by organizing conferences together. It is our future wish to establish one large scientific and clinical sleep and wake society under the umbrella of NSWO.

Hans Hamburger, chairman
Amsterdam November 2013

EDITORIAL NOTE

As last year, in the 24th edition of the proceedings of the Dutch Society for Sleep-Wake Research we reflect on the death of one of the founders of our society. Hilbert Kamphuisen, the first president of the NSWO, passed away this spring.

The scientific part of this edition kicks off with the summary of 5 PhD thesis. They are followed by comments and reflections on the thesis, written by senior researchers –experts in the field- who put the research in a broader perspective. I want to thank all contributors for their efforts. In his mini-review Ton Coenen has put together a Canon of early sleep researchers. He shows us on who's shoulders we, working in the field of sleep research and sleep medicine, all are standing .

The list of mini-papers start with the 2012 winner of the Piet Visser poster price, Floor van Oosterhout. In this issue you will find 11 mini-papers, followed by 40 abstracts. On behalf of the scientific committee I want to thank all NSWO members who contributed to this issue. I also want to thank my co-editors for reviewing the mini-papers, ensuring that we achieve the highest quality possible.

I am very glad that we have been able to stop the downward trend in contributions, we saw in the last 5 years. The present edition has reached a size comparable to the book published in 2008. I hope we can continue this for the next year, when we will celebrate the 25th anniversary of the yearbook.

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

Finally, without the support of Merck Sharp and Dohme the publication of our yearbook would not be possible. Their help is gratefully acknowledged.

Leiden, October 2013

Tom de Boer
Chair Scientific Committee
Chief Editor NSWO Proceedings

“Slapen doe je zo ”

IN MEMORIAM HILBERT KAMPHUISEN

Al de Weerd

Slaapcentrum SEIN Zwolle-Groningen

Hilbert Kamphuisen, emeritus professor of Clinical Neurophysiology at the Leiden University Medical Center, passed away on March 24, 2013, at the age of eighty. From his point of view he was in particular the sleep professor and indeed, for many workers in the field of clinical sleep medicine he deserves that title. His scientific production was limited, but he was a great teacher and promotor of sleep medicine in times when this medical subspeciality was taken seriously by only a few persons in The Netherlands. His enthusiastic approach was nearly endless and ranged from fund raising for scientific work to down-to-earth work in the media, either radio, television or the press. Most famous was his trip as the company physician during a Belgian expedition to the North pole. He took that opportunity to have his sleep recorded during this months lasting trip, using small tape recorders and implanted subdermal scalp wire electrodes. The recordings were of good quality, but we never saw the results of the many nights of sleep, possibly due to Hilbert's continuous and restless search for new impressions. At least, many of his friends enjoyed the beautiful film made of that expedition. Just to mention: Hilbert and head of his technical staff in Leiden, Bob Kemp, went even further than our planet and were intensely involved in the Russian Mir space program.

During the sleep conference in Jerusalem in 1988 plans were made by the attending Dutch sleep researchers to found a sleep society in The Netherlands. Although at that moment still an upcoming worker in the field, Hilbert took the initiative and made the first practical steps for founding the NSWO, together with the other clinically oriented sleep researcher in The Netherlands, Guus Declerck. The decision was made on the evening of November 25, 1989; the legal foundation on June 7, the next year. Guus did the formal part, Hilbert used his strong promotional power (and often neglected the rules made by Guus...) in these months and continued to do so up to his retirement as founding chairman in 1994. Together with colleagues with interest in basic aspects of animal or human sleep, both made the NSWO a strong and fruitful society within a short time. At the moment Hilbert's successor, Ton Coenen, took over the chair of the society, the NSWO was already a success.

Hilbert was always optimistic and remained so even in difficult times. The ultimate proof came in 1991 when it became clear that there would be no clinical sleep center in the -at that time- new Leiden University hospital. He called his colleagues in Clinical Neurophysiology, Jonkman and de Weerd, in the Westeinde Hospital in The Hague, and said bluntly that he and Bob Kemp wanted to start a joint venture with The Hague. With the formal help and nearly "unlimited grant" offered by Henk Schippers and Rob Bakker, at that time directors of the hospital in The Hague, a sleep center was founded and within four years grew out to one of the leading sleep facilities in The Netherlands. This was really a nice time for the steadily growing staff in these years and became the base of further clinical and scientific work.

After these initial years Hilbert just copied "old soldiers" and gradually faded away from daily practice. He stopped altogether at the end of 1998 with a big party and a Liber

Amicorum. Both party and book were exactly as he was himself: show what you can and so called limits are there to be crossed.

After his retirement Hilbert sometimes came to see what happened at the center of which he was co-founder. Unfortunately, his wife Ammy started suffering from what proved to be a long lasting illness. Again one of the strong points of Hilbert came about: just like in his working years he spent most of his time with his beloved ones, but now at home. Finally, there were more important things than sleep or neurophysiology, just like it should be.



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

SLEEP-WAKE
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Volume 24, 2013

PhD Theses

LIGHT FROM DAWN TO DUSK: HUMAN ENTRAINMENT IN A CHANGING ENVIRONMENT

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Virtually all places on Earth are exposed to a never-ending sequence of days and nights. This alternation between light and darkness occurs every 24 hours and is accompanied by predictable changes of the environment. The biological clock entrains to this light dark cycle synchronizing our internal biological rhythms with the external 24 h day. Physiological and behavioral functions associated with activity occur during daytime in diurnal organisms, whereas the physiology and behavior associated with rest are in phase with the nighttime. Entrainment largely depends on the quality of the light and darkness we are exposed to. This thesis focuses on investigating how changes in the quality of light (i.e., intensity, spectral composition, and timing) affect humans' rhythms of sleep and of melatonin in the natural environment. To achieve this, no restrictions were imposed upon the behavior of our participants. Visits to the laboratory were limited to the measurements of specific parameters such as the assessment of melatonin profiles. Most of the studied variables described in this thesis were measured in the field under natural conditions. Our observations were not restricted to acute effects of light, but rather focused on long-term effects

In CHAPTER 2 we investigated day-to-day variations in light exposure as well as the patterns of sleep-wake and melatonin rhythms at two different light backgrounds, that is, during the long days of summer versus the short days of winter. At our latitude, both photoperiod and maximal natural light intensities differ throughout the seasons. Humans can however, self-select their light exposure, for instance by the use of curtains and artificial light. Hence, we were curious to know how much of the natural variation in light is perceived by humans and to what extent the rhythms of sleep and melatonin respond to this variation. Our results show that the timing of sleep and of melatonin rhythms was delayed in winter compared to summer. The extent of this delay differed between workdays and days off and this was confounded by the introduction of daylight saving time (daylight saving time, DST). In the Netherlands, we delay our social clock 1 hour in March and we move it back in October imposing an advance in the timing of our activities relative to the day-night cycle. The delay of the rhythms of sleep and of melatonin secretion on days off in winter was larger than the 1-hour expected by DST, whereas the delay on workdays was smaller. This shows how DST impacts the adjustment of the circadian system. In this study melatonin was sampled not only under dim light conditions in the laboratory but also under real life conditions with no restrictions on light exposure. The timing of the melatonin rhythms did not differ between the laboratory and real life conditions, suggesting that light intensities in the laboratory and at home are not sufficiently different to induce an effect at the level of the melatonin signal. The amplitude of the rhythm i.e., the maximum level of melatonin at night, was however lower in the real life environment. We further used information on day-to-day variation in light exposure and tested by means of correlations how this variation, at specific times of the day, may affect (on top of the effects of season and whether it was a work day or a day off) the timing and quality of the sleep-wake and melatonin rhythms. The specific times of the day were chosen to roughly represent phases of the day with advancing (morning), delaying

(evening), suppressing (evening and night) or no (afternoon) expected effects of light on sleep and melatonin parameters. Our results show that depending on the variable (i.e., timing of sleep, quality of sleep, timing of melatonin, amplitude of melatonin, etc.) and on the timing of light exposure, light can have different size and direction effects throughout the whole day. For instance, while increased light exposure during daytime is related to a delay in the onset of sleep, it was related to an advance in the onset of melatonin secretion. This could mean that depending on the daytime light intensity, the day-to-day phase angle between sleep and melatonin rhythms might change. If a causal relationship exists between day-to-day light exposure and phase of entrainment, this could have clear implications for light strategies to improve entrainment.

Waking up during the dark winter months can be challenging. In CHAPTER 3 we tested the potential benefits of reducing sleep inertia (i.e., impaired performance, confusion, and sleepiness after waking up) by an alarm that provides an artificial dawn-type light signal. The study was performed at the subjects' homes to achieve a realistic scenario of the final user. We observed that using the device for a 2-week period had a positive impact on subjective measurements of sleep inertia and well-being. In contrast with our hypothesis, this improvement was not accompanied by a shift in the dim light melatonin onset. Mechanisms other than an advance of circadian rhythms are needed to explain the positive results on sleep inertia of waking up with a dawn signal.

In CHAPTER 4 and 5, we took advantage of cataract surgery to investigate the potential effects on entrainment of a natural reduction of short wavelength transmission through the ocular lenses.

In CHAPTER 4 we describe an objective technique that allows measuring the spectral composition of the light reaching the retina *in vivo*. With a non-invasive procedure that does not take longer than 15 minutes we investigated the improvement factor in lens transmittance after removal of the cataractous lens and replacement by a transparent lens. Our results show that in the short wavelength range, between 420 and 500 nm, lens transmittance is improved by an average factor of 4 whereas in the long wavelengths (505 - 750 nm) the improvement was only a factor of 1.3. It has been hypothesized that age related reduction in the transmission of short wavelength light may underlie sleep-wake rhythm disturbances in the elderly and that by restoring the light transmission of the lens, sleep-wake rhythms may recover.

In CHAPTER 5 we assessed how the changes in lens transmittance affect sleep and nocturnal melatonin rhythms of those elderly people undergoing cataract surgery. We observed a delay of the sleep-wake and melatonin rhythms after surgery. The size of the delay correlated positively with chronotype. The later the chronotype, the larger the delay was after cataract surgery. At first sight, in view of the increase in Zeitgeber strength after cataract surgery, the delay was unexpected. Nonetheless, the recovering of a later phase that we observed after cataract surgery (clear lens) as compared to the earlier phase observed before cataract (yellowish lens), is in agreement with the advances of circadian phase reported with increased aging. We hypothesize that the delay can be attributed to an increase of the level of light transmittance in the evening hours; a time of the day where light exposure in people suffering from cataract might just be below the critical value to exert an effect. A factor 4 increase of short wavelength transmission during the day, when light intensities are already high, is thought to be insignificant for the circadian system.

In CHAPTER 6, we studied the impact of long-term reduced input of short wavelengths to the retina on sleep-wake and melatonin rhythms in a different way. This time, the study was performed in young healthy subjects in order to assess whether the changes we observed in CHAPTER 5 could be reproduced experimentally in young subjects. To achieve

this, subjects wore soft orange contact lenses (SOCL) 24 h/day for two weeks. These lenses lead to a reduction in (blue) light exposure entering the eye. In this study we also assessed the effects of the SOCL on the suppression of melatonin. Melatonin suppression has been widely used as a parameter for describing the sensitivity of the circadian system. The most remarkable result was that suppression of melatonin in response to a light pulse after wearing the SOCL for two weeks was not different from suppression in the control condition, in the absence of lenses. The SOCL were effective in reducing short wavelength input, which was confirmed by showing that wearing them for only 30 minutes leads to less suppression of melatonin in response to a light pulse. An increase in sensitivity seems to have taken place after wearing the SOCL for 2 weeks, which could reflect adaptation of the non-image forming system. Such adaptation may also explain the absence of changes in the timing of sleep and melatonin rhythms between conditions.

Ultimately, the knowledge gathered on non-image forming responses of light could serve to develop light solutions that positively affect human health and performance. The importance of aspects of light quality such as timing, intensity, and spectral composition is emphasized by our observations under natural conditions. Further, our results show that different outputs of the biological clock can be differentially affected by the same stimulus, and that, depending on characteristics of the target population, e.g., young versus old, these effects might, in the long-term, adapt to the new light environment. Developing light solutions is challenging but certainly a stimulating goal towards improving the quality of life of the population that encourages the active cooperation of scientists and companies.

LIGHT FROM DAWN TO DUSK HUMAN ENTRAINMENT IN A CHANGING ENVIRONMENT

Debra J. Skene

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Circadian rhythms are endogenously generated by a pacemaker localised in the hypothalamic suprachiasmatic nuclei (SCN); lesions of these nuclei produce arrhythmicity. Efferent signals from the SCN drive circadian rhythms in numerous physiological and behavioural processes such as melatonin, core body temperature, cortisol, sleep timing, alertness. In normal conditions, the circadian timing system is synchronized (entrained) to the 24 h day primarily by the light-dark cycle. Entrainment to the environmental light-dark cycle allows the timing of daily activities (e.g. sleeping and feeding) to be optimised. In the absence of a light-dark cycle (such as experienced by totally blind individuals), circadian rhythms become desynchronized from the 24 h day and ‘free run’ at their intrinsic period length (τ)¹. In addition to the circadian resetting effect of light, light has a number of other non-visual effects, such as suppression of nocturnal melatonin production, elevation of core body temperature and heart rate, increased alertness and performance, and pupil constriction. These non-visual light responses in humans are primarily blue light (440 - 480 nm) sensitive^{2,3} which is attributed to the photopigment melanopsin that is expressed in a subset of intrinsically photosensitive retinal ganglion cells (ipRGCs)^{4,5}. In addition, rod and cone visual photopigments play a role, their contribution appearing to be primarily routed through the ipRGCs.

Designing light therapy that optimally activates or optimally blocks melanopsin-ipRGC-driven responses is currently an active area of research. Physiological and behavioural responses to light are dependent upon light irradiance, duration, wavelength and time of light administration as well as the photic history of the individual (thus season, latitude and their living environment). In addition, age-related changes in the eye (e.g. reduced lens transmission, reduced pupil size) and the reduced responsiveness of older people to blue light have been described in some, but not all, non-visual light effects⁶⁻⁸. Thus predicting a person’s response to light is not trivial as it depends on these above variables. Monitoring and then modelling how much light a person is exposed to will help to predict their light response.

The studies of Marina Giménez and her supervisors Marijke Gordijn and Domien Beersma add novel data to this body of research⁹. Ambulatory light exposure levels, along with sleep timing and melatonin rhythms, were monitored during winter and summer. A delay in the sleep-wake and melatonin rhythms was observed in winter compared to summer, likely due to a reduction in the zeitgeber strength (day-night difference in light perceived). The findings also emphasised the need to take account of daylight saving time (DST) when interpreting the phase shifting effects of light, as well as distinguishing between workdays and days off.

Gimenez et al.¹⁰ also investigated the effect of artificial dawn (250 lux for 2 weeks) on sleep inertia, sleep timing and melatonin timing. A reduction in sleep inertia complaints was observed, multilevel analysis revealing that this was unrelated to a shift in the timing of

melatonin onset or sleep offset. The findings thus suggest a light-driven mechanism, not mediated by the circadian timing system, which supports accumulating evidence of other brain structures being involved in the effect of light on alertness and cognitive function¹¹.

In a series of experiments the authors manipulated the amount of short wavelength light an individual would be exposed to (before and after ocular lens replacement in older people; wearing of orange soft contact lenses to reduce short wavelength light in young volunteers). These experiments were conducted in a real-world environment with no behavioural restrictions over a relatively long time period. After 2-week exposure to reduced (blue) light (wearing orange soft contact lenses comparable to that of an eye with cataracts), the young participants showed a similar melatonin suppression response as the control condition, implying adaptation over time to the changes in the spectral composition of light. This finding is intriguing. Future studies assessing the temporal characteristics of this adaptation and the relative contribution of the different photoreceptors are warranted. In addition, how light history affects the circadian system in older people requires investigation.

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SLEEP DEPRIVATION IN RATS: EFFECTS ON LEARNING AND COGNITIVE FLEXIBILITY

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A lack of sleep has very clear consequences for cognition; sleep deprivation induces cognitive impairments. However, the mechanism underlying these impairments remains elusive. This dissertation describes a number of experiments that contribute to the understanding of the mechanism(s) responsible for cognitive impairments after sleep disturbance.

The introduction of this thesis starts with a resume of the general knowledge and hypotheses on sleep, and its role in cognitive functioning. It includes a description of the behavioural and electroencephalographic characteristics that we can observe during sleep, which are used to define sleep and distinguish it from wake behaviour. This is followed by the general hypotheses on why we sleep, including sleep's contribution to cognitive functioning, and the specific cognitive domains mostly affected by sleep loss. It provides an overview of common human sleep disorders, which can result in cognitive impairment, and finishes with a description of rodent models for both sleep deprivation and cognitive performance.

Chapter 2 (Leenaars et al., 2011) introduces a new method for inducing sleep deprivation in rats, based on variable forced locomotion. Contrary to some other methods of forced locomotion (e.g. Roman et al., 2006), this method does not induce significant stress, as indicated by the observation that corticosterone levels did not exceed the levels normally seen during the 24-hour day. Moreover, the method did not have the drawback of potential confounding of experimental results by an increase in locomotor activity, as may be the case in some other methods. When our method was applied for 12h of sleep deprivation during the light phase, activity levels did not exceed those normally seen during undisturbed conditions.

When testing behaviour in a sleep-deprived state, other possible confounders have to be addressed as well. Notably, the effects of sleep deprivation on a specific cognitive domain may depend on nonspecific cognitive effects that affect performance on the task of interest. For example, the motivation to "work" for a reward may be decreased, and fatigue may slow motor functioning. These potential problems were investigated using a task on which rats show vast levels of lever pressing to receive food rewards, which makes this task highly sensitive to decreases in motivation and motor impairment. Potential decreases in motivation were limited by imposing a food restriction to 12g/rat/day (Leenaars et al., 2011).

Chapter 3 (Leenaars et al., 2012b) describes the modelling of one sleepless night and one night of disturbed sleep in humans, with 12h of inactive-phase sleep deprivation or sleep disruption in rats. It tests the effect of this sleep disruption on cognitive flexibility and introduces a new switch-task. While 12h of total sleep deprivation during the light (inactive) phase decreases accuracy on switch-task performance, 12h of repetitive sleep disturbance during the inactive phase does not alter task-switching.

Chapter 4 (Leenaars et al., 2013) describes the impairment in instrumental learning; the simple association between lever pressing and food reward, after 3h of active phase nap-prevention. EEG was measured before and between task performance. Learning is accompanied by an increase in REM sleep. Baseline sleep parameters do not predict subsequent individual differences in learning abilities.

In chapter 5 (Leenaars et al., 2012a), both 12h of inactive-phase sleep deprivation (as a model for one sleepless night) and 3h of active-phase nap prevention did not disturb performance on a different cognitive task: spatial reversal learning. Total sleep deprivation for 12h during the

inactive phase does not impair the acquisition of a spatial reversal, and 3h of nap-prevention during the active phase does not impair the consolidation of reversal learning. This indicates that also in rats, sleep-related cognitive deficits are not generalized but limited to certain cognitive domains.

In chapter 6 (Leenaars et al. 2012c), rats were exposed to 5 weeks of non-rotating “shiftwork”, comparable to human night-shifts. They showed no learning deficits on an instrumental learning task (the same task as used in chapter 4) in their 5th week on this protocol, which shows that rats may somehow habituate to regular sleep deprivation for 8h per day on 5 days per week (both in the active and in the inactive phase). Furthermore, the undisturbed control groups in this study demonstrate that instrumental learning is similar during the active and the inactive phase.

CONCLUDING REMARK

Although the effects of sleep deprivation on cognition and weight are regularly overrated in both scientific and popular literature, sleep is important, and further research is essential to find methods that can help people suffering from the consequences of bad sleep.

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SLEEP DEPRIVATION IN RATS: EFFECTS ON LEARNING AND COGNITIVE FLEXIBILITY

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Although the sleep research community does not always agree on how much sleep we need, most sleep researchers do agree that sleep is important for health and well-being. Chronically sleeping less than you need has consequences for the immune system, and may cause cardiovascular problems and is even brought in connection with cancer. Immediate consequences are seen in alertness and cognitive performance.^{1,2}

Therefore, sleep, learning and cognitive flexibility is one of the subjects within the field of sleep and cognition. This is a complex field³. Concerning learning and memory, we must conclude that there is not one type of memory, but there are many. In addition, it is well known that in mammals, there is not one type of sleep, but there are at least two. What is clear is that sleep deprivation and sleep disturbances in humans causes impairment in specific cognitive domains.

In her thesis Cathalijn Leenaars sets out on a journey to investigate learning and cognitive flexibility under influence of sleep deprivation, and sleep disturbances⁴. Not in humans as most researchers do, but in the rat. For some of the tasks tested in humans alternatives exist in rodent research. She wanted to develop an animal model that is comparable to humans in the way it has to perform learning tasks while sleep is manipulated.

And she starts off from scratch.

After introducing the subject, the 2nd chapter describes a new sleep deprivation method, based on variable forced locomotion, with a new device. The device consists of a rotating drum with a fixed central wall in which two rats can be housed simultaneously. The rats are placed in a rotating drum and a computer program drives the timing and speed of rotation. In this chapter it is verified how much the rats still slept when kept awake for 12 hours (astonishingly little) and it is also shown that corticosterone levels were not elevated above baseline levels. The latter indicates that the stress induced by this sleep deprivation method is not very high.

This is already an important result. There are several sleep deprivation methods available for rodents. They all have their advantages and disadvantages and eventually the experimenter should determine which method is best to reach the goal of the experimenter. The device developed at the NIN is very good when sleep deprivation needs to be standard, not stressful and complete (specific sleep stages cannot be determined and the device does not respond to that). It probably works best when animals are not tethered, although the verification study with recordings of EEG and EMG shows that it is possible to record these signals when the animals are in the device.

In chapter 2 and the following chapters the device is used to sleep deprive animals before and between tests. In general the results show that effects of sleep deprivation are subtle and some effects are not that clear. It also turns out that it is difficult to make a distinction between learning deficits and problems with motivation. The animals are rewarded with food and therefore need to be hungry before the tests. However, when animals are sleep deprived the question is which drive (food or sleep) is stronger and deficits in performing the task may not

be the result of deficits in learning and cognitive flexibility, but in deficits in motivation. However, the latter problem, although not often discussed, may also exist in human studies.

Al together, Cathalijn and her colleagues have put a lot of effort and time in developing the sleep deprivation device and subsequently in developing the different tests. Not all the tests worked out as expected, but they gave some good indications in which direction this type of research could go. The sleep deprivation device can also be used for other types of sleep research involving sleep deprivation and would definitely be a nice addition to the sleep deprivation tools existing in the field.

Unfortunately, the research started by Cathalijn Leenaars will not be continued. After Cathalijn finished her work, research on rodent sleep was terminated at the NIN. There may be good reasons for that, but what is a bit alarming is that this seems to be a trend in the Netherlands. The number of laboratories performing (fundamental) sleep research in animals, has decreased considerably in the last years. And that should worry us all, because once you lose it, it is very difficult to get it back.

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A TAILOR MADE APPROACH TO OBSTRUCTIVE SLEEP APNEA

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In chapter 1 the definition, prevalence, pathophysiology, risk factors, diagnostic work-up and consequences of untreated obstructive sleep apnea (OSA) are described. Evidence supporting the various treatment modalities is presented: weight loss, alcohol, tobacco and sedative abstinence, avoidance of worst sleeping position, continuous positive airway pressure (CPAP), mandibular advancement device (MAD) and sleep surgery.

Particular attention is paid to the drug-induced sleep endoscopy (DISE) technique; a unique dynamic technique to evaluate the upper airway. After pharmacological induction of unconscious sedation, it is possible to evaluate endoscopically the structures contributing to upper airway obstruction in sleep disordered breathing. Furthermore the VOTE classification system for reporting DISE findings is reported. The VOTE classification focuses on the primary structures that contribute to upper airway obstruction and represents a common language to describe the patterns of obstruction during DISE. As well as the site of obstruction, the degree and configuration of airway narrowing are evaluated.

The association between DISE findings, polysomnographic (PSG) results and patient characteristics in 100 consecutive patients are studied in a prospective, observational study in chapter 2. Our results suggest that a multilevel collapse, a complete collapse and a tongue-base collapse are statistically significantly associated with higher apnea hypopnea index (AHI) values. A tongue base collapse or epiglottal collapse is associated with positional OSA. A complete concentric collapse is statistically significantly associated with an increased body mass index (BMI). The results of this small-scale study help unravel the pathogenesis of OSA and the various associations between PSG outcomes and DISE results, as well as assisting the sleep surgeon in tailoring surgery for the patient.

In chapter 3, the hypothesis that drug-induced sleep endoscopy variables can predict the outcome of upper airway surgery in OSA patients is tested. Forty-nine OSA patients (41 male; mean AHI of 30.9 ± 18.5 events/hour) underwent propofol-induced sleep endoscopy followed by upper airway surgery (palatal surgery, and/or radiofrequency ablation of the tongue base, and/or hyoid suspension) and subsequently a follow-up PSG to assess surgical outcome. Twenty-three patients (47%) were responders and twenty-nine were non-responders (53%). Non-responders had a higher occurrence of complete or partial circumferential collapse at velum and complete anteroposterior collapse at tongue base or epiglottis level in comparison to responders. Multivariate logistic regression analysis revealed that among baseline clinical and polysomnographic characteristics (e.g. AHI and BMI) and sleep endoscopy findings, the presence of complete a circumferential collapse at velum and complete anteroposterior collapse at tongue base were the only independent predictors of upper airway surgery failure. In conclusion, DISE can be used to predict a higher likelihood of response to upper airway and surgery in OSA.

Chapter 4 presents the results of a prospective observational study measuring the prevalence of OSA amongst 279 consecutive patients on the waiting list for bariatric surgery (BS). All patients were included in the study irrespective of history or clinical findings and underwent a full night PSG. 69.9% of the patients fulfilled the criteria for OSA, of which 40.4% met the criteria for severe OSA. The BMI, neck circumference (NC) and Epworth Sleepiness Scale (ESS) were found to be inadequate predictors of OSA. A mere 13.3% of the patients were diagnosed with OSA prior to being placed on the waiting list for OSA. Both surgeons and anaesthesiologist should be aware that OSA is grossly underdiagnosed in the BS population and that patients with OSA are at an increased risk of major perisurgical adverse outcomes. We advocate mandatory PSG in the pre-operative work-up of patients undergoing BS.

In chapter 5 we report the results of the follow-up study of the previous chapter. 110 patients underwent a 1st postoperative PSG 7.7 months after surgery. The mean AHI significantly decreased from 39.5 to 15.6/hour and the mean BMI from 45.4 to 36.3kg/m². In 58.2% the AHI was reduced to below 10 and in 25.5% to below 5. 50 patients underwent a first PSG 7.1 months and a second PSG 16.9 months after surgery. The mean AHI decreased from 49.1/hour to 22.7/hour to 17.4/hour following BS ($p < .001$, $p < .001$, = .013), the mean BMI from 45.0 kg/m² to 36.7 kg/m² to 35.1 kg/m² ($p < .001$, $p < .001$, = .008). This study clearly objectifies the significant, marked improvement and even remission of OSA following BS in obese patients, as measured by PSG. BS initiates dramatic improvement of clinical and sleep parameters during the first 7 months, which continues at a slower rate over the next 10 months. We recommend a follow-up PSG at 6 and in the case of persistent disease, again at 12 months after surgery to check for residual disease and if necessary, reinitiation of CPAP, which may lead to higher treatment compliance.

In chapter 6 the available literature on positional obstructive sleep apnea (POSA) and therapy (PT) is systematically reviewed. An average of 56% of patients with OSA have POSA commonly defined as a difference of 50% or more in apnea index (AI) between supine and non-supine position. Sixteen studies were identified which examined the effect of various forms of PT on OSA. All studies report a positive effect of PT on the AHI. Evidence is based on small-scale case series and a few randomized trials. When compared to CPAP the compliance of PT is found to be better, but CPAP is a more effective treatment. Nevertheless ineffectiveness, backache, discomfort and no improvement in sleep quality or daytime alertness have been responsible for poor compliance and the subsequent disappointing long-term results of PT. When searching for studies observing combinations of sleep position, PT and other treatment modalities, results yield that MADs are more effective in patients with POSA than in patients without OSA and that most studies suggest that patients being treated with CPAP, need a higher positive pressure in the supine position than in other sleeping positions.

In chapter 7 using mathematical calculations the non-optimal use of optimal therapy (CPAP) is compared to the continuous effect (100%) of often non optimal therapy (surgery). The gold standard treatment for OSA is CPAP. It is however, a clinical reality that the use of CPAP is often cumbersome. The effectiveness of CPAP regarding the reduction of AHI depends both on its impact on airway obstruction and compliance. CPAP treatment is considered compliant when used > 4 hours per night as an average over all nights observed. Surgery, on the other hand is regarded as successful when the AHI drops at least 50% and is reduced below 20/hour postoperative in patients whose preoperative AHI was greater than 20/hour. Due to the fact that different definitions of successful therapy are being used for the different treatment options, surgeons are being forced by the AHI classification to compete on an uneven playing

field. We contend that using a mean AHI in CPAP therapy is more realistic than using arbitrary compliance rates, which, in fact hide insufficient reductions in AHI.

The results of this study indicate that the more severe the AHI, the more percentage of total sleep time CPAP must be used to significantly reduce the AHI. Patients with moderate OSA reduce the AHI by 33.3% to 48.3% when using CPAP 4 hours per night (AHI 0 -5 respectively). The required nightly percentage use rises as one reduces the AHI target to below 5. CPAP must be used 66.67% to 83.33% per night to reduce the AHI below 5 (AHI of 0 while using CPAP).

Evidence is presented in chapter 8, that a positive relation exists between hours of CPAP use and a favourable outcome, therefore supporting the suggestion that treatment effects on the AHI should no longer be reported under conditions of artificial compliance only, but in consideration of the individual compliance to the treatment. This is of particular importance when different treatment options are compared.

In the final chapter, the results obtained in this thesis are discussed in a broader context and general conclusions are drawn.

A TAILOR MADE APPROACH TO OBSTRUCTIVE SLEEP APNEA

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Mrs. Ravesloot has summarised here experiences and scientific contributions to the field of sleep medicine in her thesis “A tailor made approach to obstructive sleep apnea”. The thesis addresses general principles in assessment and definition of sleep apnea and its severity. It analyses novel diagnostic approaches as well as the value of two therapeutical strategies: bariatric surgery and positional therapy.

The thesis starts with an introduction into the field of obstructive sleep apnea (OSA), a disease that affects approx. 4-8% of the population in industrialised countries. OSA leads to a significant reduction in daytime performance and quality of life and it increases cardiovascular morbidity and mortality. The diagnosis is usually based on medical history, sleep medical history, clinical examination and sleep testing, namely polysomnography (PSG). Drug-induced sleep endoscopy (DISE) has been introduced to visualise the anatomical site and the characteristics of airway obstruction. DISE is supposed to enable the sleep physician or surgeon to improve patient selection for specific therapeutic approaches, particularly surgical therapy. However DISE, although routinely performed, is still insufficiently evaluated and its value and impact on treatment outcome is still under debate. Taking this into account Mrs. Ravesloot performed a prospective study with 100 consecutive patients undergoing DISE. She describes the correlation between DISE and PSG results and she was able to demonstrate that more severe OSA is associated with multilevel and more severe airway collapse and a collapse at the level of the tongue base. This multilevel and more severe / total airway collapse is particularly challenging to treat surgically and this reflects the limited surgical success rates in patients with severe OSA. The results of the study underline that the severity of OSA is not only reflected by the frequency of respiratory events but also by the type and degree of airway collapse.

In the second study that is included in the thesis, Mrs. Ravesloot addresses the most crucial aspect of DISE – the value in predicting surgical outcome. In a retrospective analysis of 49 patients who underwent upper airway surgery she correlated surgical outcome with preoperative DISE results. In accordance with the first study of her thesis, non-responders had a higher frequency of complete collapse at different levels of the upper airway. Of particular interest is the fact that two distinct types of airway obstruction were independent predictors of surgical failure. Prospective studies demonstrating that the use of DISE really improves surgical outcome are still missing. The present study however gives first insights into the relationship between the results of DISE and surgical outcome. Both studies regarding DISE were published in „The Laryngoscope“, one of the most respected international journals in the field of Otorhinolaryngology.

As obesity is the most important risk factory for OSA it can be expected that the prevalence of OSA is particularly high in obese patients. Patients in need for bariatric surgery are at risk for

OSA, the prevalence of OSA in this group of patients however has only scarcely been investigated. Mrs. Ravesloot published two papers on OSA and obesity and included both in her thesis. In the first prospective study patients awaiting bariatric surgery were routinely tested with clinical examination and PSG. Approx. 70% of all patients were diagnosed with OSA, 40% with severe OSA. In contrast, only 13.3% were previously diagnosed which demonstrates the lack of awareness of this extremely prevalent comorbidity in severe obesity. With regard to the increased postoperative morbidity and complication rates of patients with OSA the study clearly supports the routine diagnostic testing for OSA in patients scheduled for bariatric surgery.

As obesity is the underlying risk factor for OSA, bariatric surgery should not only lead to weight loss but also to an improvement in OSA. Until now this correlation has mostly been investigated in studies with relatively small patient groups and limited follow-up periods. Mrs. Ravesloot has performed a prospective study on obese patients undergoing bariatric surgery using PSG to assess the impact of surgery and consecutive weight loss on OSA. She could demonstrate a significant decrease in body mass index as well as in the number of respiratory events (reflecting the severity of OSA) 7.7 months (n=110) and 16.9 months (=50) after surgery. A complete remission was detected at least in a subgroup of patients. The study provides insights in the dynamics of weight loss and improvement in OSA and suggests a protocol for postoperative follow-up PSG. Both studies were published in highly respected international journals.

Another therapeutic strategy for the treatment of OSA is positional therapy in those patients that suffer from positional OSA. In her thesis, the data of an extensive systematic review of the literature is provided by Mrs. Ravesloot, giving evidence that positional OSA is more frequent than usually expected and that positional therapy may offer a valid treatment option in these patients.

Ventilation therapy with continuous positive airway pressure (CPAP) is the standard treatment of OSA. It has been demonstrated that CPAP improves daytime function and quality of life and reduces cardiovascular morbidity and mortality. CPAP significantly reduces the frequency of respiratory events during the time of use – compliance however is the major limitation of this approach. Treatment efficacy is usually defined with regard to the reduction of respiratory events during sleep which is assessed with PSG under laboratory conditions. PSG however represents an artificial setting and does not reflect the everyday situation. Mrs. Ravesloot has been the first to systematically address this issue. In the corresponding chapter of the thesis she describes her concept of assessing treatment efficacy with regard to individual compliance. She further provides a formula that calculates treatment efficacy based on the frequency of respiratory events with and without CPAP and the individual hours of use (which are provided by the built in counters of the devices). This formula allows a realistic comparison of the effects of different treatment strategies taking compliance into account. This innovative approach and outstanding underlying publication has started a vivid discussion in the field of OSA research and has been published in the most important international sleep medical journal. The ideas and concepts have further been developed and recently published in one of the most respected journals of Otorhinolaryngology as it is presented in the last chapter of the thesis.

Taking all this into account, the thesis of Mrs. Ravesloot is in many ways outstanding, as much as the curriculum vitae of this young scientist and it more than justifies the support from the Dutch Sleep-Wake research society.

MILD SKIN WARMING, A NON-PHARMACOLOGICAL WAY TO MODULATE SLEEP AND VIGILANCE

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The thesis entitled “Mild skin warming, a non-pharmacological way to modulate sleep and vigilance” addresses *sleep-permissive* and *wake-promoting* effects of small changes in skin temperature as occur naturally within the thermoneutral zone. Under well-controlled conditions it evaluated the effects of skin temperature manipulations on the onset and maintenance of sleep, and alertness.

In Chapter 1 the skin warming hypothesis (i.e. the skin temperature affects the neuronal activity of sleep-regulating brain regions (Van Someren 2000)) and the relationship between sleep, alertness and thermoregulation are explained. In short: Information about the temperature and control of sleep & wakefulness are processed in the same area of the brains (pre-optic area of the anterior hypothalamus). A cold skin hinders sleep and promote alertness (vigilance) while warm skin sleep to promotes and to decreases vigilance.

Chapter 2 provides an overview of the physiological principles of temperature sensing and temperature regulation, and the alterations within the day (24 hours) and lifetime. In old age, thermoreception, thermogenesis and conservation, heat loss, and central regulation is no longer optimal. This ultimately results in a flattened 24-hour temperature rhythm in the elderly. Given the relationship between sleep and body temperature will affect the sleep of older people.

The skin warming hypothesis (i.e. mild skin warming improves sleep) was tested in various populations. Healthy adolescents were included to understand the physiological and psychological effects of temperature manipulations on sleep and vigilance. Elderly were included to understand the effects of temperature manipulations on sleep in a population where thermoregulation is not optimal. Elderly patients with insomnia and narcolepsy patients finally, were included to understand the effects of temperature manipulation on sleep in populations where both thermoregulation and sleep is not optimal. Research in all four groups was conducted using the same research protocol.

Chapter 3 deals with a rather applied study, testing the effect of simple ways to increase the foot temperature before or during bedtime, such as warm bed socks and a warm foot bath. In adults, sleep onset latency was accelerated by warm and neutral bed socks after lights-off and it correlated to the increase in foot temperature. This increase was attenuated in elderly subjects. We concluded that elderly subjects show an attenuated increase in foot temperature after lights-off and lose the relationship between pre-sleep heat loss activation and sleep latency. The sensitivity of sleep propensity to foot warming changes with age and is attenuated in age-related insomnia.

In order to achieve more subtle skin temperature changes as compared to the ones achieved in Chapter 3, a pajama with woven-in flexible tubes connected to a system that pumped water at a controlled temperature through the tubes was used (Chapters 4-9). The changes in skin temperature were so small (between 0.4°C and 0.7°C) that no thermoregulatory response of

the body occurred (i.e. the body made no attempt to correct for the external temperature change). During this change of skin temperature, both the micro-and macrostructure of sleep was measured in the night. During daytime, sleep propensity and vigilance were measured at different times. Table 1 summarizes the results.

	<i>Hypothesis</i>	Adults	Eldery	Elderly Insomniacs	Narcolepsy patients
Temperature perception	<i>Warmer</i>	+ ⁴	+/ <i>O</i> ⁵	<i>O</i> ⁵	+/ <i>O</i> ⁷
Sleep Onset (MSLT)	<i>Faster</i>	+ ⁴	+ ⁵	+ ⁵	+ ^{*MWT 7}
Sleep Depth	<i>Deeper</i>	+ ⁸	+ ⁸	+ ⁸	+ ⁹
Sleep Maintenance	<i>Increase</i>	<i>O</i> ⁸	+ ⁸	+ ⁸	<i>O</i> ⁹
Vigilance (PVT)	<i>Less alert</i>	+ ⁶	+ ⁶	+ ⁶	<i>O</i> ⁷

Fig 1: Effect of mild skin warming on temperature perception, sleep onset latency, sleep depth, sleep maintenance, and vigilance. Subscripts refer to chapter in the thesis. + = hypothesis confirmed, *O*= no support for hypothesis.

The findings provide support for the notion that skin temperature modulates vigilance regulation, and more than core temperature does. It has been demonstrated in younger and older healthy adults, as well as in patients suffering from either insomnia or narcolepsy, that very mild skin cooling enhances vigilance and the ability to maintain wakefulness (Chapter 6 & 7), while mild skin warming facilitates sleep onset (Chapter 4 & 5) and promotes slow wave sleep and sleep maintenance (Chapter 8 & 9). Skin temperature manipulations may thus even complement available research tools to experimentally affect slow cortical oscillations during sleep. Concertedly, these findings now provide strong support for a causal contribution of skin temperature to vigilance regulation, as was suggested from animal studies.

We conclude that mild skin warming creates both a *sleep-permissive and promoting* condition. Subtle (feedback controlled) skin temperature manipulations could have strong clinical relevance in the management of disturbed sleep especially in the elderly, who have an attenuated behavioural response to suboptimal environmental temperature, which may hamper them from taking appropriate action to optimize their bed temperature.

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MILD SKIN WARMING, A NON-PHARMACOLOGICAL WAY TO MODULATE SLEEP AND VIGILANCE

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From the start of modern sleep research it was recognised that there is a close relationship between sleep and body temperature. Body temperature in humans decreases in the evening at sleep onset and increases in the morning when the sleep episode ends. From research in animals it became clear that core body temperature and brain temperature generally follow the same time course during sleep. This led to the suggestion that the function of NREM sleep was for cooling the brain¹ (and, probably more as a joke, that REM sleep was for heating the brain²).

It was therefore a logical step to try and influence sleep by manipulating body temperature. These experiments, performed in the 1970's and 80's on animals and humans, however, led to mixed results. In some experiments sleep improved significantly, whereas in others, sleep was disturbed, or sometimes even completely eliminated (reviewed in^{3,4}). Confusion all around, and a subfield in sleep research where it was not easy to find your way.

Then, in 1999, Krauchi and co-workers published a landmark paper in *Nature* (one page, one figure!) showing that there was a relationship between distal skin temperature, or the temperature of extremities (hand and feet) and sleep latency⁵. If the distal skin temperature was high relative to proximal skin temperature (skin temperature of the torso), sleep latency was short, if the hands and feet were relatively cool, sleep latency was longer. The authors could show that in the course of the evening, starting at 8 pm, the difference between proximal and distal skin temperature decreased. When this decrease did not occur, or occurred later, sleep latencies were much longer. The data suggested that the single focus on core body temperature as a possible modulator of sleep had been a mistake.

This notion was the basis of the thesis of Roy Raymann⁶. With a special thermo-suit the temperature of different parts of the skin was manipulated separately, and different combinations of proximal and distal skin temperature warming and cooling were applied. The effects of different combinations of skin temperatures were tested on sleep onset latency and vigilance in the course of the day and sleep architecture during the night. This was done at different age groups with good sleep and in elderly insomniacs. In addition, similar experiments were performed in narcolepsy patients.

The most important message from the data gathered by Raymann is that we can influence sleep in a predictable way by manipulating skin temperature. In addition, the thesis may be the starting point to investigate alternative, non-pharmacological, treatments for sleep disturbances. Elderly insomniacs and narcoleptic patients slept better or worse in a predictable way depending on the combination of proximal and distal skin warming and narcoleptic patients were able to remain alert longer during the day when distal skin temperature was cooled.

As always there are questions remaining. More information is needed on the micro-climate in the bed to be able to determine what the optimal skin temperatures for sleep are. This may depend on individual preferences and may even change with season and age. With that information bed warming devices with feedback mechanisms can be developed that change the micro climate temperature within the bed according to individual needs.

More physiological is the question how and why the body uses this rather complicated and inefficient feedback loop within the body. The data seem to indicate that the vasodilating mechanisms, resulting in higher proximal skin temperatures, are not directly connected to the brain centers controlling sleep onset. First proximal skin temperature needs to rise before the brain is willing to go to sleep. This may be related to the ability to feel comfortable and relax. Apparently a sense of comfort and sleep permissiveness needs to be reached before we are willing to relax and make an effort to go to sleep. A promise of thermal comfort in the near future is not enough.

Before incorporating skin temperature as a variable, the literature on sleep and body temperature was full of contradictions. We now understand more of the relationship between sleep and body temperature than we did before 1999, and this is also thanks to the work of Roy Raymann. Some of the work of Raymann (and others) made it already into the major textbooks on sleep⁴ and stands at the basis of the advice to clinicians to assess skin temperature, with objective measures or patient self-reports, in patients with disturbed sleep, to determine the likelihood of dysfunctional thermoregulation and to advise these patients on their thermal discomfort-related complaints as possible part of their sleep disturbance.

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SLEEP AND SLEEP-WAKE RHYTHM IN OLDER ADULTS WITH INTELLECTUAL DISABILITIES

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CHAPTER 1

This thesis investigates aspects of sleep and the sleep-wake rhythm in older adults with intellectual disabilities (ID). Sleep deprivation in older adults in the general population are associated with poorer quality of life, cognitive decline, depression, disability in basic activities of daily living and the necessity of placement in a home for the elderly. Also long sleep time is associated with negative health outcomes in older adults, like poor self-rated health and quality of life, high cholesterol levels and depression and anxiety disorders. Overall, both short and long sleep duration are significant predictors for mortality. All people with ID have some form of brain dysfunction, and in combination with age-related changes to brain structures regulating sleep and wake, older adults with ID might be extra vulnerable to develop sleep-wake disturbances. Both night sleep and the sleep-wake rhythm in older adults with ID were of interest. Until now no epidemiological research had been performed on these topics in this population. Because life expectancy nowadays has increased in people with ID, knowledge about night sleep and the sleep-wake rhythm is of importance for optimal care. Also, for both epidemiological research and individual diagnostics of sleep problems, an objective tool to investigate sleep that is suitable for older adults with ID is needed.

Night sleep and the sleep-wake rhythm were studied in the ‘Healthy Ageing and Intellectual Disabilities’ (HA-ID) study – a large cross-sectional epidemiological study that addressed many aspects of health in older adults (50 years and older) with intellectual disabilities in the Netherlands. Because previous research on sleep in people with ID was mainly based on caregiver interviews, we aimed to investigate night sleep and the sleep-wake rhythm using objective measurements. Polysomnography is too burdensome for the majority of people with ID; therefore we measured sleep using actigraphy (the Actiwatch). The Actiwatch is a watch-like device that measures movement activity, and based on this activity several parameters of the sleep-wake pattern can be calculated.

The main aims of this study were to investigate the validity of actigraphy in older adults with ID, the prevalence of sleep problems in older adults with ID using actigraphy, and which factors are associated with night sleep and the sleep-wake rhythm in this population.

CHAPTER 2

To investigate how sleep problems are defined in research among adults and older people with ID, and to collect information on the prevalence, associated factors and therapy for sleep problems in this population, we performed a systematic literature review. In previous studies on sleep problems in adults with ID, the definitions used to describe a sleep problem are not uniform. The reported estimated prevalence rates of sleep problems ranged from 8.5% to 34.1%. Sleep problems were associated with challenging behaviour, respiratory disease, visual impairment, psychiatric conditions, and using psychotropic, antiepileptic and/or antidepressant medication. Little information was found on older people specifically. Two studies on non-pharmaceutical interventions for sleep problems in a larger study sample suggest that non-pharmaceutical interventions are beneficial. Research on sleep problems in adults and older people with ID has mainly focused on subjectively derived data, and associations were mainly described as correlations.

CHAPTER 3

In Chapter 3, data obtained in the first year of the HA-ID study were studied to explore to what degree Actiwatch measurements were successful in older adults with ID, and to study the influence of the different sensitivity settings of the Actiwatch Sleep Analysis software on sleep parameters. A complete measurement of at least seven days and nights, including at least one weekend day, was considered successful. Of 563 participants who were asked to wear the Actiwatch, 35.5% had a successful measurement. Main causes for an unsuccessful measurement were primarily problems with wearing the device and incomplete information on bedtime and get-up time. Application of different sensitivity settings of the Sleep Analysis software resulted in clear differences of all sleep parameters. Based on this data we concluded that it needs to be investigated which sensitivity setting of the Actiwatch gives most valid results in this specific group.

CHAPTER 4

To study which sensitivity setting of the Actiwatch gives most valid results in older adults with ID, two Actiwatch devices (Actiwatch AW7 and Actiwatch 2) were compared to polysomnography in ten older adults with mild ID, for two consecutive nights in their own living environment. A 1-minute epoch-to-epoch comparison was performed for the Actiwatch and PSG data, for all data collected during nighttime. The high sensitivity setting of the Actiwatch appeared most suitable to detect sleep disturbance in older adults with ID (wake detection percentage of 54.6%, sleep detection percentage of 89.7%). On average, values of sleep parameters calculated using the high sensitivity setting approximate the values of sleep parameters measured with PSG. Outcomes were similar for the two Actiwatch types.

CHAPTER 5

In Chapter 5 we focused on the data that were collected during daytime in the Actiwatch versus polysomnography comparison study. Outcome measures were the percentage of time that was scored as 'sleep' by both the Actiwatch and PSG of all the time that was scored as 'sleep' by the Actiwatch in total, and the percentage of time that was scored as 'wake' by both the Actiwatch and PSG of all the time that was scored as 'wake' by the Actiwatch in total. A large amount of time that was scored as 'sleep' by the Actiwatch during daytime was actually 'wake' according to polysomnography. Based on this pilot, evaluating daytime sleep in older adults with ID using the Actiwatch seems not advisable.

CHAPTER 6

In Chapter 6 we compared the sleep-wake rhythm of older adults with ID to that of older adults in the general population, and investigated which factors are associated with the sleep-wake rhythm in older adults with ID. Outcome measures were stability (interdaily stability), fragmentation (intradaily variability) and amplitude (relative amplitude) of the sleep-wake rhythm.

Compared to older adults in the general population (n=56), the sleep-wake rhythm of older adults with ID (n=501) was significantly less stable, more fragmented, and had a lower relative amplitude. Higher age, dementia, depression, visual impairment, severe hearing impairment, epilepsy and spasticity are independently associated with a more disturbed sleep-wake rhythm in this group. The sleep-wake rhythm is more stable in females and those living at a setting for more intensive care. Higher physical activity levels are strongly associated with both a less fragmented and a more stable sleep-wake rhythm in older adults with ID.

CHAPTER 7

In Chapter 7 we studied sleep and its associated factors in older adults with ID. We investigated the distribution and inter-correlations of objective sleep parameters and which factors are independently associated with these sleep parameters, and estimated the prevalence of sleep problems. Variables of interest were the sleep parameters time in bed, sleep onset latency, total sleep time, wake after sleep onset, sleep efficiency and get-up time latency. To estimate the prevalence of sleep problems, provisional definitions of sleep problems based on sleep parameters were drafted.

Time in bed was very long (mean 630 minutes) in older adults with ID. Longer time in bed was independently associated with female gender, higher age, more severe level of ID, living at a central facility, wheelchair dependence and depressive symptoms. Sleep onset latency was associated with Down syndrome and higher body-mass index. Total sleep time was longer in female, and wake after sleep onset was longer with higher age and in participants with visual impairment. The prevalence of sleep problems was: 23.9% settling problem, 63.1% night waking problem, 20.9% short sleep time, 9.3% early waking problem. 72% of the participants had at least one problem, and 12.3% had three or more sleep problems.

CHAPTER 8

We studied how many sleep problems that were found in the HA-ID study were known by professional caregivers (n=301), and the concordance between objectively measured sleep parameters with client self-report (n=80). Professional caregivers were asked if their client had a sleep problem. Sleep problems were categorized as ‘no sleep problem’, ‘settling problem’, ‘night waking problem’ or ‘unspecified problem’. Participants who were capable of self-report were interviewed using the Inventory of Depressive Symptomatology Self Report (IDS- SR), and their answers were compared to Actiwatch measurements. We found that of all sleep problems that were determined according to the HA-ID definition, the majority (73%) was reported as ‘no sleep problem’ by the professional caregiver. The agreement between client self-report and Actiwatch measurements was poor for time to fall asleep (SOL), night waking (WASO) and early waking (GTL), but for self-reported total sleep time (TST) a significant correlation with Actiwatch measurements was found. It might be useful to develop a tool that enables self-report of individual experience of sleep as an addition to objective sleep measurements.

CHAPTER 9

In this chapter the main results of our study, strengths & limitations, and directions for further research and clinical practice are discussed. A major strength of this study is that objective measurements were performed in a large sample of older adults with ID. A hypothetical model on factors that can influence night sleep and the sleep-wake rhythm in this population is provided, which can be a basis for both further research and clinical practice. Further research should first focus on genetic factors resulting in sleep-wake disturbances. Second, epidemiological research is needed to study causality of relationships, the effects of sleep disturbances on health and wellbeing, and to study which factors are specific for older adults with ID compared to older adults in the general population. Also, further validation of the Actiwatch is recommended. Although further research is needed, actigraphy should become a routine diagnostic instrument. More awareness among professionals regarding sleep and the sleep-wake rhythm is needed, and an individual approach of sleep needs is of importance to improve care for older adults with intellectual disabilities.

SLEEP AND SLEEP-WAKE RHYTHM IN OLDER ADULTS WITH INTELLECTUAL DISABILITIES

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Dr. Van de Wouw – van Dijk investigated sleep parameters and sleep-wake rhythm in older people with intellectual disabilities using actigraphy. She collected data in a near-representative sample of people with all levels of intellectual disability. Aims of the study were to study the validity of actigraphy, describe sleep and sleep-wake rhythm parameters, show the prevalence of sleep problems, and show factors associated with sleep parameters and the sleep-wake rhythm in this population.

Most people with intellectual disabilities are unable to provide subjective data on the quality of their sleep or the extent to which their sleep-wake rhythm is distorted. Yet, these factors play a crucial role in health, especially in old age. With the increasing longevity of people with intellectual disabilities and the many health problems they face, healthy ageing is of central importance in this population—both from a humanitarian and financial point of view. It should therefore be applauded that Van de Wouw, for the first time, provided insight in objective sleep- and sleep-wake parameters in this population.

A first commentary to this dissertation is essential for the understanding of the data this thesis generated: Van de Wouw did not measure sleep or sleep-wake rhythm. She measured movement—wrist-worn actigraphs provide nothing more—from which sleep and wake episodes are derived. Earlier it was not perfectly clear whether the absence of detected movement in older people with intellectual disabilities meant that the individual is asleep, and conversely, whether movement is always detected in individuals who are awake. Perhaps the most elegant substudy in this thesis was a validation study, in which actigraphy data were compared with the gold standard for the detection of sleep and wake episodes: polysomnography. The results show that actigraphy detects sleep in this population well, but wake states are not well identified. Apparently, older people with intellectual disabilities are often in wake states with very low levels of movement. Although actigraphy proved to be valid for the detection of sleep and for identifying sleep parameters (time in bed, sleep efficiency, wake after sleep latency, total sleep time), there is room for improvement. What Van de Wouw did not stress is that we need better actigraphy hardware and more intelligent algorithms for the detection of sleep and wake states in this population.

The studies in this thesis should serve as a wake-up call for caregivers involved in the care for older people with intellectual disabilities. Sleep and sleep-wake problems are serious health problems and are highly prevalent in this population. This demands professional attention, because the identified sleep problems are rarely detected in routine care. Sleep-wake problems are more prevalent in this population than in the general population. The associated factors indicate which individuals may be at risk and may provide caregivers with new directions for diagnostic strategies. Because this thesis showed that actigraphy in this population is feasible, Van de Wouw recommends the wrist-worn actigraph as a diagnostic aid for sleep problems.

Even though these guides are very useful, the contributions to forward research thinking that this thesis provided are at least as important. Van de Wouw presented a number of important

questions and hypotheses for future research in this area. Given that sleep and the sleep-wake rhythm are regulated by various structures and pathways in the brain, how much of the sleep problems and sleep-wake rhythm disturbances are due to brain dysfunction and/or genetic anomalies (problems present in people with intellectual disabilities)? How much do comorbid conditions contribute to these problems? To what extent are sleep and sleep-wake problems predictive of adverse health outcomes? What are the causal pathways involved? How can these problems be prevented and improved and how can evidence-based intervention strategies be implemented in the care for people with intellectual disabilities? These topics, hopefully, will be present on the (international) research agendas in the foreseeable future.

As Van de Wouw pointed out in her discussion that her study, like most studies, has a number of limitations, and should be followed-up. E.g., the subsample of participants in which actigraphy was feasible, was not representative of the population. The actigraphs did not detect sleep perfectly. Data on subjective sleep experiences were not collected. The sample in the polysomnography validation study is small. Nevertheless, the quality of the data presented in this thesis is unique among peers. The bottom line is that collecting high-quality epidemiological data in large samples of people with all levels of intellectual disabilities is very difficult. These people, just like every other citizen, deserve scientific information that may aid in their already complex care, which is so deprived from evidence and high-quality studies. A final comment is not from me, but from one of the members in dr. van de Wouw's PhD committee: "dr. van de Wouw found in her systematic review on sleep problems in adults with intellectual disabilities that the number of available high-quality studies was low. With this thesis, she effectively doubled the amount of high-quality studies". I agree.

SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 23, 2012

Mini review

THE CANON OF SLEEP RESEARCHERS: THE FIRST GENERATION

Anton Coenen

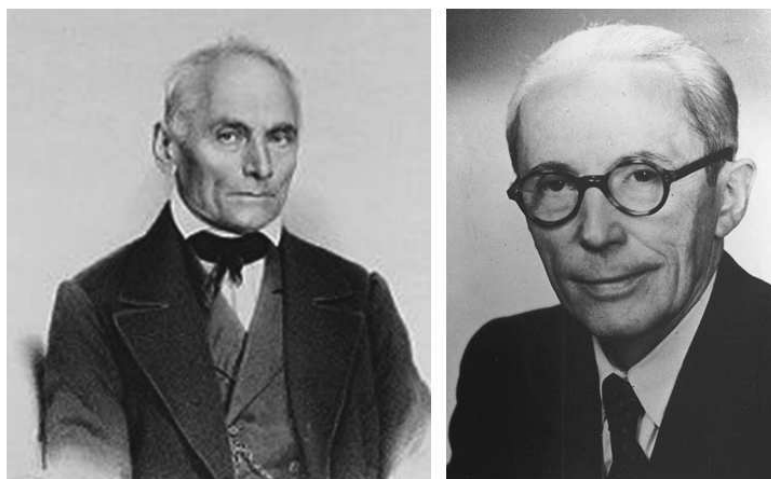
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Throughout ancient times views and opinions on sleep were exclusively based on conjecture and personal experiences. In 1846 the physician Edward Binns published 'The Anatomy of Sleep', still a pool of many opinions and anecdotes, but already with some pieces of experimental knowledge of sleep. Given its experimental flavour this book marks the beginning of the scientific study of sleep.

Since the start of the experimental sleep research in the middle of the nineteenth century, many investigations towards this enigmatic phenomenon have been performed and the nature of sleep, with in its shadow the dream, became more clear. However, many important features of sleep still have to be cleared up. Main lines about the views on sleep with the most important theories and findings are presented here, together with their discoverers and researchers. The time span of this canon is roughly from 1850 until 1975, containing the first generation of sleep researchers.

Initially sleep research and sleep medicine was a European field of research. In later years after the immigration of Europeans to the USA with a strong American influence. It is unfortunate that Dutch researchers are missing. Dutch neuroscientists were more directed to sensory physiology and anatomy, such as Frans C. Donders (1818-1889) ('vision'), Johannes Dusser de Barenne (1885-1940) ('smell'), Hendrik Zwaardemaker (1857-1930) ('olfaction') and Cornelius Ariens Kappers (1877-1946) ('brain development'). The 1924 Nobel Prize laureate Willem Einthoven (1860-1927) is known for his invention of the string galvanometer, a main step forward in the development of electroencephalography, a technique which brought sleep research miles further.

SLEEP REGULATION: THE PASSIVE – DEAFFERENTATION – THEORY



Jan Evangelista Purkyně (1787–1869) was born in Bohemia (then part of the Habsburg monarchy, now Czech Republic). He discovered the Purkinje effect, in which red objects seem to fade faster than other coloured objects as light intensity decreases, as well as the Purkinje cells, large cerebellar neurons with many dendrites. He theorised that wakefulness is

the result of a continuous stream of information to the brain, while sleep results by a blockade of this stream. In sleep research this view is recognised as the ‘passive sleep theory’ or ‘deafferentation hypothesis’, a dominating view for a long time.

Frédéric Bremer (1892–1982), born in Arlon in the Belgian Ardennes, was a pioneer in the field of neurophysiology at the University of Brussels. He was specialised in the neural mechanisms of the sleep-wake cycle. In order to evaluate the ‘deafferentation hypothesis’, Bremer conducted classical brainstem sections in cats. With the ‘cerveau isolé’ and the ‘encéphale isolé’, he could attribute the sleep-wake cycle to the effects of sensory input to the brain. His general conclusion was that sleep is a manifestation of a decrease in cortical input, but later alternative interpretations of Bremer’s outcomes appeared to be more obvious.

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SLEEP REGULATION: THE ACTIVE THEORY



Constantin von Economo (1876–1931) was a Romanian psychiatrist and neurologist of Greek origin. During World War I, he served as a pilot in the Austrian army. In 1916 he went to Vienna to care as a military physician for patients with head injuries. Here, he saw the first cases of the European sleeping sickness ‘Encephalitis lethargica’, a brain inflammation which raged in an epidemic form from 1915 until 1924. Von Economo distinguished two types of this illness: a somnolent type, often leading to coma and death, and a hyperkinetic type, with restlessness and insomnia. Von Economo was inspired by this illness to search for sleep-wake centres in the brain and he postulated specific centres for wakefulness and specific centres for sleep: the active sleep theory was born.

Walter Rudolf Hess (1881–1973) was a Swiss physiologist, connected to the University of Zurich. He won the Nobel Prize in 1949 for mapping areas of the brain, by using the technique of electrical brain stimulation. By stimulating parts of the hypothalamus, he could induce several types of behaviour depending on the region of stimulation. Hess also found that he could induce sleep in cats; a finding that was controversial at that time, though confirming the sleep-wake centre theory postulated by von Economo.

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SLEEP REGULATION: THE RETICULAR THEORY

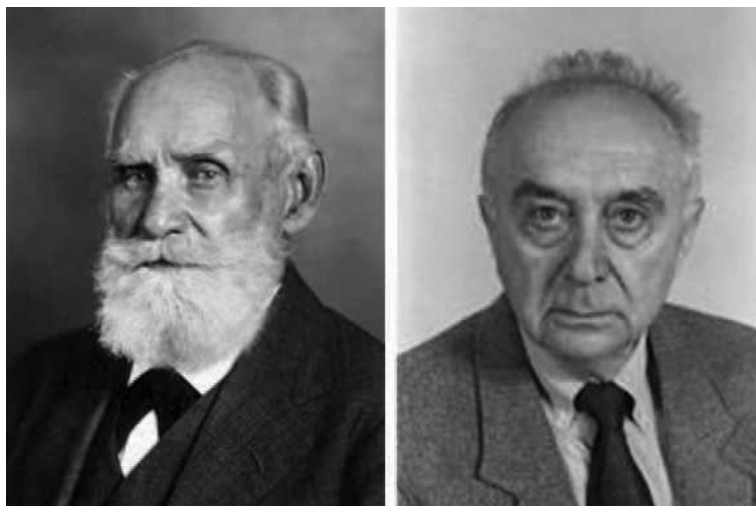


Giuseppe Moruzzi (1910–1986), born in Campagnola, was affiliated to the University of Pisa as a neurophysiologist. In 1948 Moruzzi went to the laboratory of Horace Magoun as a visiting professor and in that year their successful collaboration started.

Horace Winchell Magoun (1907–1991), born in Philadelphia, graduated in medicine and became professor in anatomy at the Northwestern University in the USA. Moruzzi and Magoun identified in cats, with electrical stimulation, brain stem centres responsible for sleeping and waking. They showed that stimulation of a brain stem structure, which they named ‘reticular formation’, caused awakening of the animal, while its destruction made the cat fall into a permanent coma-like sleep. In this way they revealed the role of the reticular formation in the regulation of sleeping and waking. This active sleep theory is often called the ‘reticular sleep theory’. Their seminal paper, published in 1949 describes the activating and deactivating properties of the brain stem reticular formation.

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SLEEP AS AN INHIBITORY BRAIN PROCESS



Ivan Petrovich Pavlov (1849–1936) born in Ryazan in the Central Federal District of Russia was a scientist who is regarded as one of the greatest physiologists of all time. He believed that sleep is due to widespread cortical inhibition and came to this idea when he observed that classical conditioning of dogs to withhold responses in a monotonous environment, is followed by drowsiness and sleep. This long lasting response inhibition leads to exhaustion of large groups of neurons and this neuronal inhibition is spreading over the cerebrum, ultimately resulting in sleep.

Mircea Steriade (1924–2006) born in Bucharest, Romania, immigrated as a physician to Canada in 1968. There he became professor of physiology at the Université Laval in Quebec. His research was on corticothalamic oscillations and he discovered the pacemaker role of thalamic reticular neurons in producing sleep spindles. He also showed that the slow waves of non-REM sleep arise when neurons fire together, then shortly fall silent and then resume their synchronised firing ('burst-pause firing mode'), while they fire regularly during waking ('tonic firing mode'). This is due to increased inhibitory activities in sleep, which is also the reason that sensory stimuli in that situation are blocked at a thalamic level, as shown by Coenen and Vendrik in 1972. 'The brain is blind and deaf during sleep'.

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MEASURING THE DEPTH OF SLEEP



Ernst Kohlschütter (1837–1905) was a German physician born in Dresden. In 1862 he earned his doctorate with an influential dissertation on the measurement of sleep depth. In the beginning of sleep research the determination of the 'auditory awakening threshold' was a relevant topic. Kohlschütter introduced a robust and simple awakening technique: the fall from different heights of a metal ball on a wooden shelf close to the bed of a sleeping person. The minimal height to arouse the subject was the measure for sleep depth. Kohlschütter was affiliated to the Universities of Leipzig and Halle.

Eduard Michelson (1861–1944), was a student of the German psychiatrist Emil Kraepelin. Michelson established a sleep laboratory at the University of Dorpat (Tartu, Estonia), where he was born. Michelson described a 'strange sleep phenomenon': a remarkable periodicity in

the curve of sleep depth. He postulated that this periodicity had to be explained by antagonistic processes in sleep. Unfortunately, his 1891 publication fell into oblivion, although it should be considered as a key study, since the REM–non-REM periodicity was published for the first time, although unknown to Michelson himself.

Kohlschütter, E.: Messungen der Festigkeit des Schlafes. Zeitschrift für rationelle Medizin 17: 210-253, 1862.

Michelson, E.R.: Untersuchungen über die Tiefe des Schlafes. Dorpat: Schnakenburg's Buchdruckerei, 1891.

CHRONOBIOLOGY OF SLEEPING AND WAKING



Jean-Jacques d'Ortous de Mairan (1678–1771) was a French geophysicist and chronobiologist. His observations inspired the beginning of the study of circadian rhythms. De Mairan was intrigued by the daily opening and closing of the leaves of the plant, *Mimosa pudica*, and performed an experiment whereby he exposed these plants to constant darkness in his underground wine cave. De Mairan's key conclusion was that the daily rhythmic opening and closing of the leaves persisted even in the dark. In this way he demonstrated the existence of an internal clock in living organisms.

Jürgen Aschoff (1913–1998), born in Freiburg, was a German behavioural physiologist, who is considered, together with Erwin Bünning and Colin Pittendrigh, as the founder of chronobiology. Aschoff performed experiments on human circadian rhythms in an underground bunker, to isolate human subjects from external environmental cues. After tracking the sleep-wake cycles, body temperature and other outputs, Aschoff and his collaborator Rütger Wever concluded that humans have endogenous circadian oscillators. Aschoff coined the term 'Zeitgeber' to refer to external, environmental cues that synchronise the endogenous oscillators to the environmental cycle.

de Mairan, J.: Observation botanique. In: Histoire de l'Academie Royale des Sciences, pp. 35–36, 1729.

Aschoff, J., Wever, R.: Über Phasenbeziehungen zwischen biologischer Tagesperiodik und Zeitgeberperiodik. Zeitschrift für vergleichende Physiologie 46: 115-128, 1962.

EFFECTS OF SLEEP DEPRIVATION



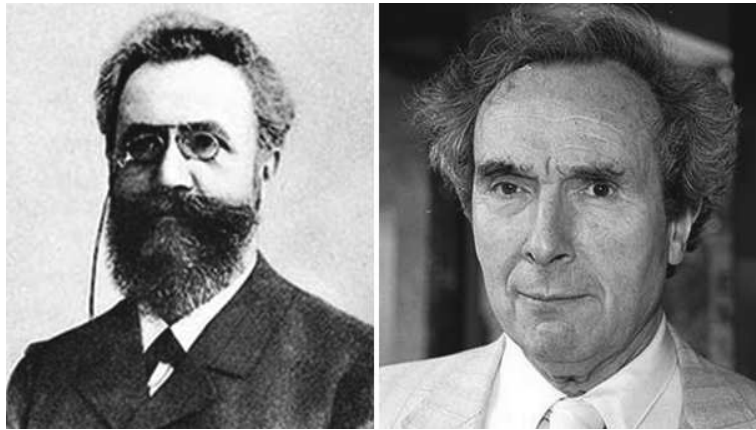
Marie de Manacéine (Maria Mikhaïlovna Manasseina) (1841–1903) was a Russian physician and a pioneer in the study of sleep, working in St. Petersburg. She performed the first experiments on the effects of depriving animals of sleep, and found that puppies died when kept awake for four to nine days, showing that sleep is necessary for life. De Manacéine published a famous textbook about sleep: ‘Sleep: its physiology, pathology, hygiene, and psychology’ in 1897.

Henri Piéron (1881–1964), born in Paris, was a French psychologist. He was the founder of experimental psychology in France and professor at the Collège de France. He published an eminent monograph on sleep in 1913: ‘Le problème physiologique du sommeil’. With his colleague-physiologist René Legendre, Piéron was interested in potential hypnotoxins emerging during wakefulness. They deprived dogs of sleep by walking hours with them through the streets of Paris. Subsequently, they took from the sleep-deprived dogs some cerebrospinal fluid, possibly containing the hypnotoxin, and injected it into non-sleep deprived dogs. These animals soon fell asleep. Another key-finding was a sharp sleep rebound in the sleep deprived donor animals. Presently the hypnotoxic theory of sleep is greatly abandoned.

de Manacéine, M.: Quelques observations expérimentales sur l’influence de l’insomnie absolue. *Archives Italiennes de Biologie* 21: 322-325, 1894.

Legendre, R., Piéron, H.: De la propriété hypnotoxique des humeurs développée au cours d’une veille prolongée. *Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie* 72: 210-212, 1912.

THE CONSOLIDATION AND RESTORATIVE THEORY OF SLEEP



Hermann Ebbinghaus (1850-1909) born in Barmen, was a German psychologist who pioneered in the cognitive study of memory at the University of Breslau (now Wrocław in Poland). He is known for the discovery of the forgetting curve. In 1885, in his authoritative publication 'Memory: A contribution to experimental psychology', he made the first observation of the benefit of sleep for memory. Renewed interest in this observation emerged in 1924 when John G. Jenkins and Karl M. Dallenbach at Cornell University in the USA compared forgetting over sleep and wake intervals. In doing so, they confirmed Ebbinghaus' finding that sleep is beneficial for memory consolidation.

Ian Oswald (1929-2012) born in London, was a sleep researcher and psychiatrist, who gained extensive knowledge of electroencephalography. Oswald became a lecturer in the Department of Psychological Medicine of the Edinburgh University. He is best recognised for proposing what is known as the 'restoration theory' of sleep. He noted that in normal (non-REM) sleep, there is increased release of growth hormone from the pituitary gland. He observed that people who have had a substantial physical activity during the day spent more time in deep slow wave sleep. Connecting these findings Oswald concluded that non-REM sleep aids the growth and renewal of body tissues.

Ebbinghaus, H.: Über das Gedächtnis: Untersuchungen zur experimentelle Psychologie. Leipzig, 1885.

Jenkins, J.G., Dallenbach, K.M.: Obliviscence during sleep and waking. American Journal of Psychology 35: 605-612, 1924.

Oswald I.: Sleep as a restorative process: human clues. Progress in Brain Research 53: 279-288, 1980.

THE DEVELOPMENT OF THE ELECTROENCEPHALOGRAM TECHNIQUE



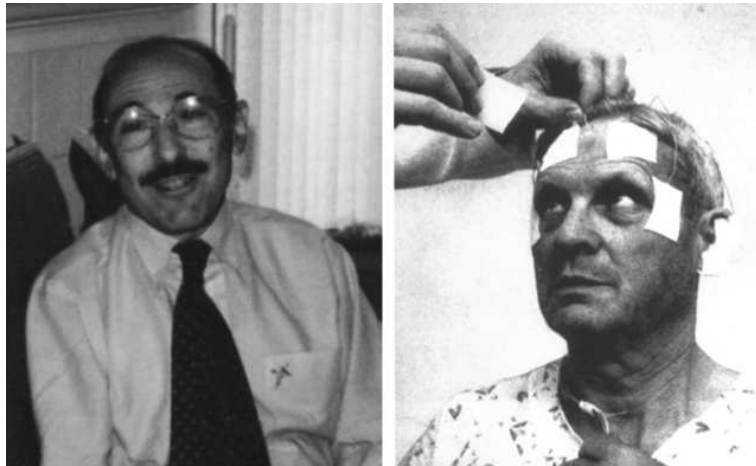
Adolf Beck (1863-1942) born in Kraków was a Polish physician and professor of physiology at the University of Lemberg (now Lviv in the Ukraine). In 1890 he received the degree of MD at the Jagiellonian University in Kraków and in that year he published the results of his extensive research on electrical processes in the brains of animals. His 1890-paper and 1891-thesis on the localisation of functions determined by measuring electrical currents, in collaboration with the famous physiologist Napoleon Cybulski, attracted wide attention and won for him a prominent position among physiologists. He described the electroencephalogram (EEG) desynchronisation when animals increase their alertness.

Hans Berger (1873-1941), born in Neuses near Coburg was a German psychiatrist and neuroscientist. Berger was affiliated to the University Clinic of Jena. He became widely known as the first scientist who recorded the EEG of humans. He also described as the first the beta waves associated with cognitive activities and the alpha-waves in the EEG as the person came into rest. Generally, Berger is regarded as the father of electroencephalography, although Richard Caton (1842-1926) from Liverpool, Vasili Danilevsky (1852-1939) from Charkov (Ukraine) and Adolf Beck, performed earlier experiments with the recording of electrical activity, but they restricted their research to animals.

Beck, A.: Die Bestimmung der Localisation des Gehirn- und Rückenmarksfunctionen vermittelt der electrischen Erscheinungen. *Centralblatt für Physiologie* 4: 473-476, 1890.

Berger, H.: Über das Elektroencephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten* 87: 527-570, 1929.

THE DISCOVERY OF REM-SLEEP



Eugene Aserinsky (1921–1998) born in New York, was an American physiologist who discovered REM-sleep in 1953, while he was a graduate student of Nathaniel Kleitman at the University of Chicago. He made this discovery after spending hours studying the eyelids of sleeping children. Both Aserinsky and his PhD adviser went on to demonstrate that this type of sleep, with a general increase in brain activity, was correlated with dreaming. Aserinsky died when he fell asleep at the wheel and his car hit a tree.

Nathaniel Kleitman (1895-1999) born in Kishinev in Moldavia, was a physiologist and sleep researcher who served as professor in physiology at the University of Chicago. He is recognised as the father of modern sleep research, and is the author of the 1939 book ‘Sleep and Wakefulness’, seen as the bible of sleep research. His graduate student Aserinsky noticed that sleepers went through periods in which their eyes darted wildly back and forth. Kleitman insisted that the experiment should be repeated, also with his daughter Esther. In 1953, he and Aserinsky introduced the world to the ‘rapid eye movement’ or REM-sleep. They demonstrated that REM-sleep was correlated with dreaming. Another graduate student of Kleitman, William Dement, stated: ‘in 1953 the study of sleep became a true scientific field’. Kleitman made countless contributions to the field of sleep research –he conducted sensational sleep studies underground in the Mammoth Cave in Kentucky- and was especially interested in ‘rest-activity’ cycles, leading to many fundamental findings on circadian and ultradian rhythms.

Aserinsky, E., Kleitman, N.: regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 118: 273-274, 1953.

Kleitman, N.: *Sleep and Wakefulness*. Chicago: University of Chicago Press, 1939.

CHARACTERISTICS OF THE PARADOXICAL REM-SLEEP



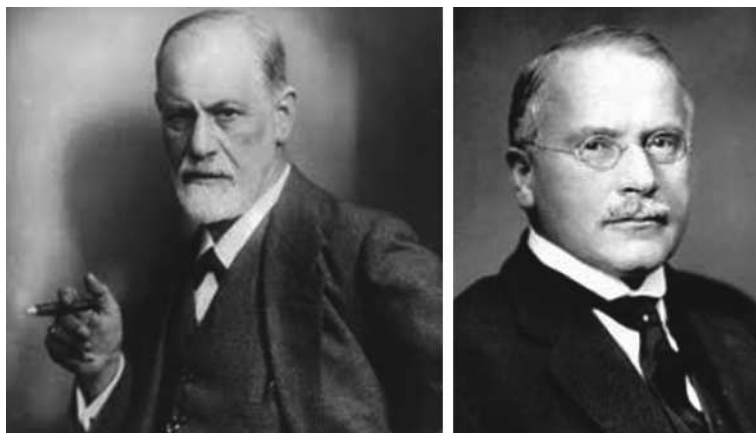
William (Bill) Dement, born in 1928 in the State of Washington, is a pioneering sleep researcher and founder of the Sleep Research Center at Stanford University, the world's first sleep laboratory. He is a leading authority on sleep, sleep deprivation and sleep disorders, such as sleep apnoea and narcolepsy. As a medical student at the University of Chicago, under the supervision of Nathaniel Kleitman, he was the first to study the connection between REM-sleep and dreaming, and numerous aspects of (REM)-sleep and dreaming were studied by Dement.

Michel Jouvet, born in 1925 in the Jura in France, is professor of experimental medicine at the University of Lyon and also affiliated to the Neurological Hospital of Lyon. Jouvet conducted in cats several experiments regarding REM-sleep, which he termed 'paradoxical sleep'. Jouvet was particularly interested in the role of the pons in muscle atonia, as well as in the biochemical regulation of REM-sleep. Jouvet can be regarded as an all-round sleep researcher and a pioneer in animal sleep.

Dement, W., Kleitman, N.: Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *EEG and Clinical Neurophysiology* 9: 673-690, 1957.

Jouvet, M.: Paradoxical sleep – a study of its nature and mechanisms. *Progress in Brain Research* 18: 20-62, 1965.

THE PSYCHOANALYTICAL DREAM THEORY



Sigmund Freud (1856–1939) born in Freiberg in Moravia, was a neurologist-psychiatrist and the founder of psychoanalysis. He worked in Vienna and is recognised as one of the most

influential thinkers of the 20th century. His book 'Die Traumdeutung' about the unconscious and the content of dreaming, is regarded as the foundation of psychoanalysis. He proposed that dreams contain hidden messages from the unconscious. In dreams unsocial, often sexually coloured, wishes could be fulfilled. By analysing dreams these wishes could be revealed, giving insight in the person's nature.

Carl Gustav Jung (1875–1961) born in Kesswil, was a Swiss psychiatrist and psychotherapist, and a pupil of Freud. Jung developed the concepts of the personality, with archetypes and the collective unconscious. In later years, Jung denied the importance of Freud's sexual coloured wishes and focused on the collective unconscious, containing memories and ideas inherited from our ancestors. Jung regarded dreams as a way of communicating with the unconscious, implying that dreams could offer solutions to problems faced in waking life.

- Freud, S.: Die Traumdeutung. Leipzig und Wien: Franz Deuticke, 1900.

- Jung, C.G.: Erinnerungen, Träume, Gedanken. Pantheon Books, 1963.

THE ACTIVATION-SYNTHESIS HYPOTHESIS OF DREAMING



J. Allan Hobson, born in 1933 in Connecticut, is an American psychiatrist and dream researcher. He is professor of psychiatry at the Harvard Medical School and known for his research on REM-sleep. Together with McCarley he is the founder of the activation-synthesis hypothesis, which suggests that dreams have no meaning. Hobson's 'The dreaming brain: how the brain creates both the sense and nonsense of the dreams', is a bestseller. Although Hobson originally dismissed the idea that there are deep, hidden meanings in dreams, presently he supports the notion that dreams might contain useful information.

Robert (Bob) McCarley, born in 1937 in Kentucky, is professor of psychiatry at the Harvard Medical School. McCarley is a prominent researcher in the field of sleeping and dreaming, as well as schizophrenia. McCarley developed with Hobson the activation-synthesis theory of dreaming, saying that dreams do not have meanings and are the result of the brain attempting to make sense of random neuronal firing during REM-sleep. Moreover, McCarley has extensively studied the brainstem mechanisms that control REM-sleep.

- 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: 1335-1348, 1977.

THE DESCRIPTION OF NARCOLEPSY

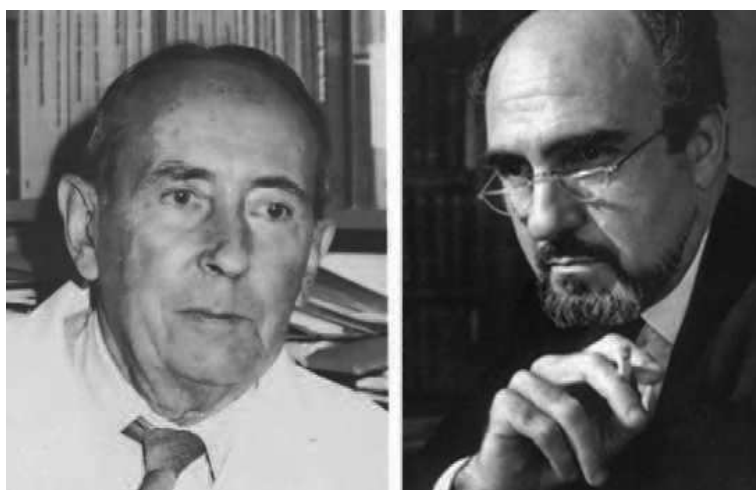


Carl Friedrich Otto Westphal (1833–1890) was a German neurologist and psychiatrist from Berlin. After receiving his doctorate, he worked at Berlin Charité and attained in 1874 the title of full professor of psychiatry. He was the first physician to provide a clinical description of narcolepsy and cataplexy.

Jean-Baptiste-Édouard Gélineau (1828–1906) was a French physician, born in the Gironde, who coined the term ‘narcolepsy’. He noticed the intrinsically symptoms of narcolepsy, such as excessive daytime somnolence, cataplexy and hypnagogic hallucinations, and incorporated them into a single clinical syndrome. Gelineau was working at the school of medicine of the Université de Montpellier, and after his retirement he switched back to his hobby: the production of wines.

- Westphal, C.: Zwei Krankheitsfälle. Archiv für Psychiatrie und Nervenkrankheiten 7: 631-635, 1877.
- Gélineau, J.: De la narcolepsie. Gazette des Hôpitaux Civils et Militaires 53: 626-628, 1880.

FIRST STUDIES ON SLEEP APNOEA



Richard Jung (1911–1986) was a German neurologist and neurophysiologist born in Frankenthal. Jung built, on the remnants of what was left of the Neurology Department in Freiburg of destroyed, post-war Germany, a neurological clinic with basic research and main

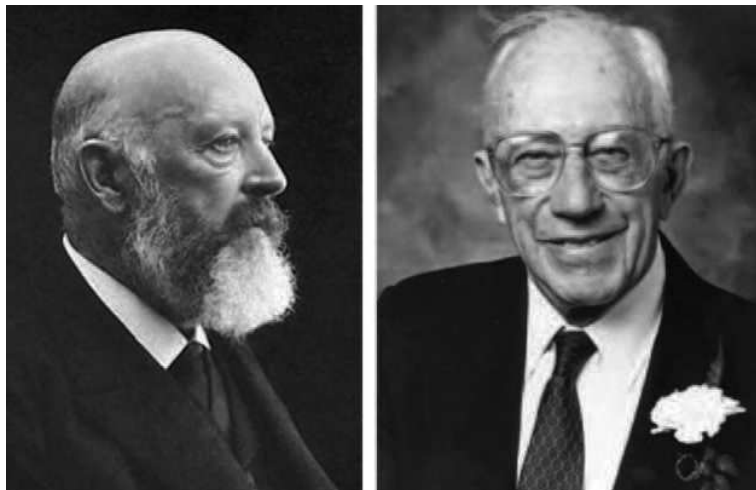
attention for sleep medicine. Together with his colleague Wolfgang Kuhlo, he presented at the European Society of Neurology in 1964 pioneering studies of sleep apnoea, performed with physiological techniques.

Henri Gastaut (1915–1995), born in Monaco and affiliated to the Neurological Institute of Marseille, had major interest in the study of electroencephalography. He was a recognised epileptologist ('Lennox-Gastaut syndrome'), with special attention for the relationship between seizures and sleep disorders. Obstructive sleep apnoea was first brought into prominence by Gastaut in 1965, when he published the first polygraphic studies of the Pickwick syndrome.

- Jung, R., Kuhlo, W.: Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome. *Progress in Brain Research* 18: 140-159, 1965.

- Gastaut, H., Tassinari, C.A., Duron, B.: Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. *Brain Research* 1: 167-186, 1966.

SLEEP MEDICATION: BARBITURATES AND BENZODIAZPINES



Adolf von Baeyer (1835–1917) born in Berlin, was a German chemist who synthesised, among many other drugs, barbituric acid. He was the 1905 recipient of the Nobel Prize in Chemistry. He worked on several universities, at Ghent, Strasbourg, Munich and Berlin. Barbituric acid is the parent compound of the barbiturates. Based on this compound, von Baeyer's pupils Emil Fischer and Joseph von Mering synthesised the first barbiturates, such as barbital (Veronal). Barbiturates are powerful sleeping pills, as well as anaesthetics. Given their toxicity and the development of the benzodiazepines, they are not longer in use as sleep medication.

Leo Henryk Sternbach (1908–2005) was a Croatian born Polish-American chemist who is credited with the discovering of the benzodiazepines, a main class of tranquillizers and hypnotics. He synthesised chlordiazepoxide (Librium) in 1957, followed by the golden drug diazepam (Valium) in 1960. These drugs are more specific as the barbiturates, since they affect only those brain cells which are sensitive for the inhibitory neurotransmitter GABA. Benzodiazepines are the most popular psychoactive drugs in the world, used for anxiety, stress, epilepsy and insomnia.

- von Baeyer, A.: Untersuchungen über die Harnsauregruppe. *Annalen* 130: 129, 1864.

- Sternbach, L.H.: The benzodiazepine story. *Progress in Drug Research* 22: 229-266, 1978.

- Fischer, E., von Mering, J.: Über ein neue Klasse von Schlafmitteln. *Therapie Gegenwart* 44: 97–101, 1903.

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**Annual Proceedings of the NSWO
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Winner Piet Visser Posterprice 2012



**Floor van Oosterhout with the Piet Visser Poster price 2012
(picture by F van Oosterhout)**

AMPLITUDE OF THE SCN CLOCK ENHANCED BY THE BEHAVIORAL ACTIVITY RHYTHM

Floor van Oosterhout^{a,b}, Eliane A. Lucassen^a, Thijs Houben^a, Henk Tjebbe vanderLeest^a, Michael C. Antle^{a,c}, Johanna H. Meijer^a

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^b current address: Centre for Sleep and Wake Disorders, Slotervaart Medical Centre, Amsterdam

^c Department of Psychology, Department of Physiology and Pharmacology, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

INTRODUCTION

Twenty-four hour rhythms in behavioral activity and sleep are driven by the circadian clock of the SCN. Synchronization of the clock to the environmental day and night primarily relies on external light information. However, the phase of the clock is also affected by behavioral activity^{1,2}. Arousal or increased voluntary behavioral activity, brought on by a variety of stimuli, exert changes in the circadian clock that are evidenced by period changes or phase shifts in the overt functions^{3,4}. For instance, wheel running activity is known to affect the period of the clock in a dose-dependent manner⁵ and novelty-induced wheel running elicits phase shifts of the circadian activity rhythm⁴. Also in humans, behavioral activity during the day accelerates phase resetting to new time zones⁶ and physical exercise may have beneficial effects for circadian rhythm disorders related to dementia and aging⁷. Thus, a reciprocal interaction exists between the behavior and the SCN clock. By use of *in vivo* SCN electrical activity recordings in combination with video-tracked behavioral activity, we investigated the acute effects of various identified spontaneous behaviors on SCN neuronal activity in the mouse, and we examined the impact of behavioral activity on the SCN rhythm amplitude.

METHODS

In vivo recordings of multiunit electrical activity from SCN neurons were performed in C57BL/6 mice (n = 14) following micro-electrode implantation under anesthesia with analgetics⁸. Animals were kept on LD12:12 and after several cycles the animals were released into constant darkness (DD). Recording chambers were equipped with a Passive Infra-Red (PIR) movement detector. Behavioral activity profiles were recorded simultaneously with electrical activity in similar time bins (2 s). Activity measurements were verified and inspected at more detailed levels by video-records provided by an infrared-sensitive camera that was placed in front of the cage. The cage was illuminated with infrared LEDs to provide a clear image for the infrared-sensitive camera in the dark. Type and intensity of spontaneous behavioral activity were analyzed off-line.

RESULTS AND DISCUSSION

SCN electrical activity recordings showed high levels during the subjective day (rest phase) and low levels during the subjective night (active phase). These rhythms were in anti-phase with the animal's behavioral activity rhythm in all recordings. Episodes of behavioural activity were associated with acute suppression of SCN neuronal activity. Suppressions were superimposed on the SCN circadian rhythm (Fig. 1).

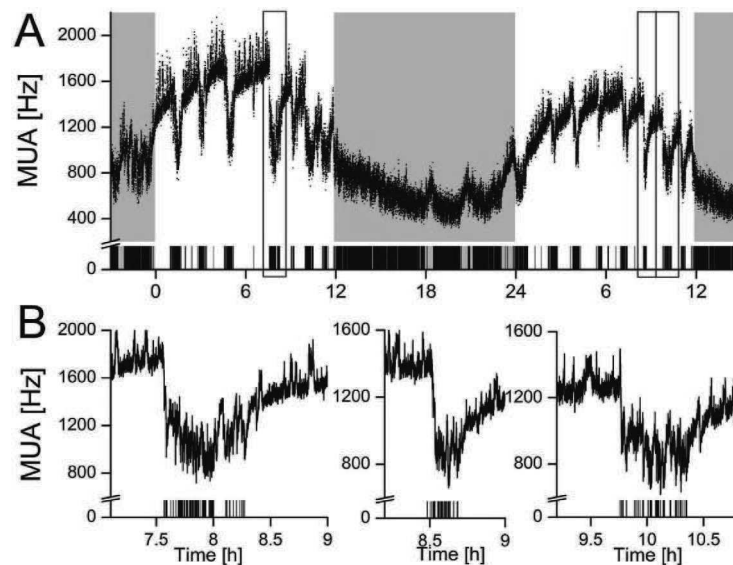


Figure 1. **A)** 48h recording of SCN activity. **B)** Expanded plots of SCN activity during episodes of behavioral activity. Grey background: lights off. Lower bars: behavioral activity.

Typically, at the start of behavioral activity, an abrupt drop in firing rate was observed. Firing frequencies remained suppressed for the duration of behavioral activity, and the electrical activity level gradually returned to baseline level after the animal had ceased its activity. Suppression of SCN activity was typically sustained, irrespective of the duration of behavioral activity (Fig. 2A-C). Even ultra-short, or non-intense types of behavior are capable of inducing substantial suppression of the SCN activity. More vigorous types of behavior led to larger suppression (Fig. 2D-E). The suppression was moderate (32%) for low-intensity behaviour and considerable (59%) for locomotor activity.

When we distinguished between active and inactive episodes, we found that both in the absence and in the presence of behavioral activity, clear circadian rhythms exist in SCN neuronal activity. When the animal was active, the level of the neuronal activity rhythm was lowered (Fig. 3).

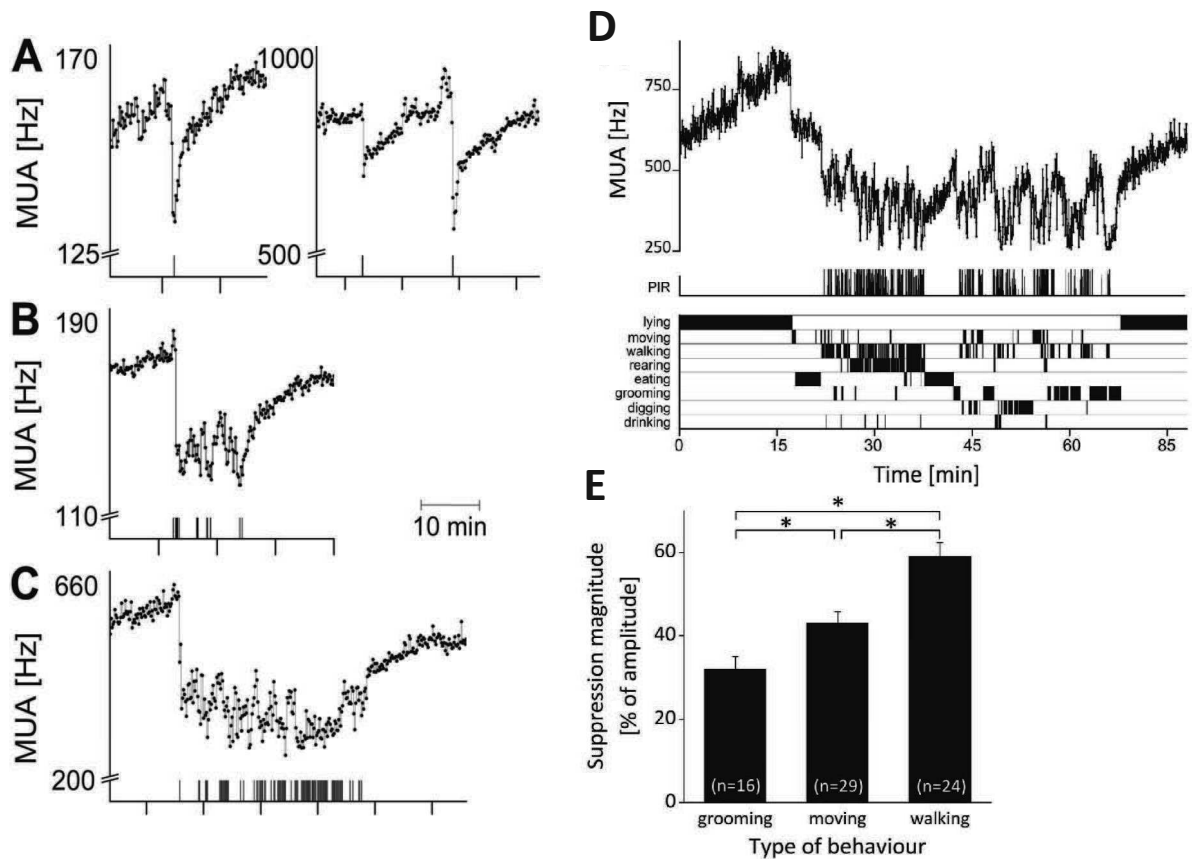


Figure 2. A-C) SCN response to different durations of behavioral activity. Lower bars: behavioral activity as measured by the passive infrared detector. D-E) Relationship between type and intensity of behavioral activity and SCN activity. Fig. D shows the SCN response to a full episode of behavioral activity (~45min). In this example, the initial behavior leading to a suppression of SCN activity is associated with moving, and is followed by eating which does not induce further suppression but keeps the SCN electrical activity at a reduced level. A further decrease of spike rate is induced when the animal starts locomotor behavior. While the suppression lasts for the full duration of the behavioral activity bout, gradual changes are associated with different types or intensities of behavior, and electrical activity gradually returns to baseline when the animal has ceased its behavioral activity; Fig. E shows the magnitude of suppression as a function of type of behavior.

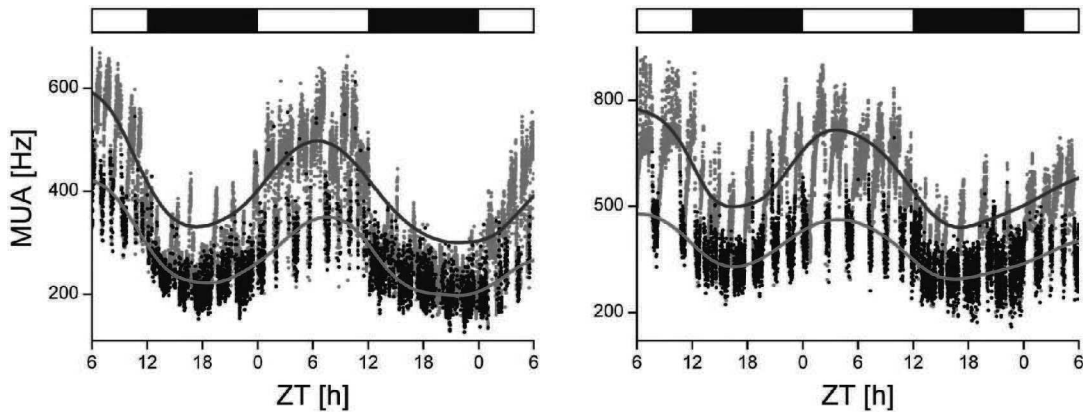
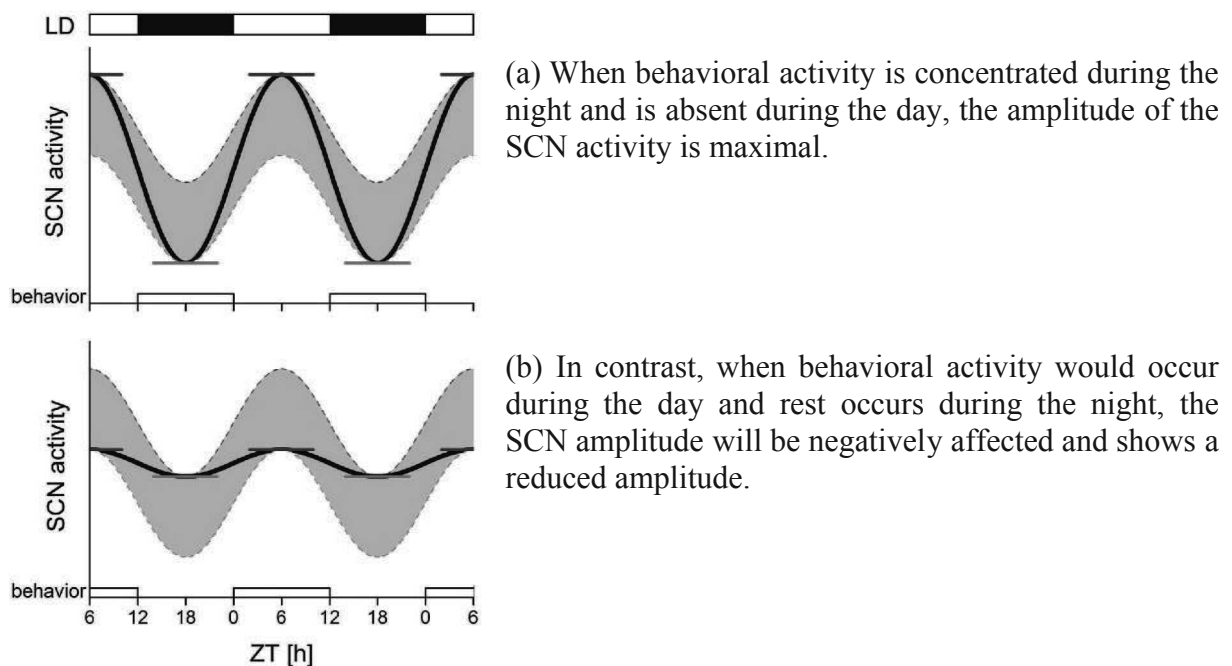


Figure 3. Circadian profile of the SCN neuronal activity in the absence of behavioral activity (grey dots; dark grey curve) and in the presence of behavioral activity (black dots; light grey curve). The figure shows two representative examples.

Based on Fig. 3, consequences of night- versus day-time activity on SCN rhythm amplitude in nocturnal animals can be modelled:



While the results are obtained from nocturnal animals, similar mechanisms (though with opposite sign) are likely to be present in humans. Indeed, in humans, behavioral activity during the day has a synchronizing effect on the clock². Shift workers may end up with a reduced rhythm amplitude. A reduced rhythm amplitude is associated with aging and with a number of diseases, such as metabolic syndrome, depression, sleeping disorders and cardiovascular problems⁹⁻¹¹. Exercise at the proper time of the cycle can boost the amplitude of the rhythm of the SCN clock and may therefore have beneficial chronotherapeutic effects on health^{7,12}.

CONCLUSIONS

By use of micro-electrodes we measured the acute effects of behavior on the SCN and showed that behavioral activity itself acts as a potent stimulus that modulates SCN pacemaker activity. The SCN electrical activity was strongly affected by the animal's spontaneous behavioural activity level in an intensity- and duration dependent manner. The results indicate that exercise at the proper time of the cycle can enhance the amplitude of the rhythm of the SCN clock. This occurs by modulation of the central pacemaker activity itself, rather than through downstream mechanisms, and has potentially beneficial effects for other rhythmic functions that are under the control of the SCN.

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- ⁴ Reeb SG, Mrosovsky N. Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. *J Biol Rhythms* 1989; 4:39-48.
- ⁵ Deboer T, Tobler I. Running wheel size influences circadian rhythm period and its phase shift in mice. *J Comp Physiol A* 2000; 186:969-973.
- ⁶ Miyazaki T, Hashimoto S, Masubuchi S, Honma S, Honma KI. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. *Am J Physiol Regul Integr Comp Physiol* 2001; 281:R197-205.
- ⁷ Van Someren EJ, Lijzenga C, Mirmiran M, Swaab DF. Long-term fitness training improves the circadian rest-activity rhythm in healthy elderly males. *J Biol Rhythms* 1997; 12:146-156.
- ⁸ Van Oosterhout F, Lucassen EA, Houben T, vanderLeest HT, Antle MC, Meijer JH. Amplitude of the SCN clock enhanced by the behavioral activity rhythm. *PLoS One* 2012; 7:e39693.
- ⁹ Farajnia S, Michel S, Deboer T, vanderLeest HT, Houben T, Rohling JH, Ramkisoensing A, Yasenkov R, Meijer JH. Evidence for neuronal desynchrony in the aged suprachiasmatic nucleus clock. *Neurosci* 2012; 32:5891-5899.
- ¹⁰ Souète E, Salvati E, Belugou JL, Pringuey D, Candito M, Krebs B, Ardisson JL, Darcourt G. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res* 1989; 28:263-78.
- ¹¹ Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 2010; 11:589-599.
- ¹² Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, Kukull WA, LaCroix AZ, McCormick W, Larson EB. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA* 2003; 290:2015-2022.

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Volume 24, 2013

Research papers

INHIBITION OF THE NEUROTROPHIN RECEPTOR (p75NTR) ALTERS NEUROGENESIS AND SLEEP WAKE ARCHITECTURE: POSSIBLE RELEVANCE TO DEPRESSION

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INTRODUCTION

Over the last 10 years, converging lines of evidence have established a relationship between depression and neurodegenerative processes that lead to loss of synaptic connectivity in hippocampal and cortical brain structures¹. The fact that current symptomatic antidepressant agents require several weeks before clinical efficacy imply that long-term adaptation in downstream synaptic networks and organization of neurotrophic pathways are necessary for therapeutic effects to be seen². Therefore, direct targeting of neurotrophic pathways is thought to be a novel approach to achieve antidepressant efficacy.

Two types of cell surface receptors mediate the responsiveness of neurons to neurotrophins. On one hand the high affinity tropomyosin-related kinase receptor (e.g. TrKA or TrkB) modulates survival, differentiation and growth of brain cells, and the other hand the low-affinity p75 neurotrophin receptor (p75NTR), which contains a sufficient and necessary cytoplasmic death domain “chopper” regulates apoptosis^{3,4}. Both receptors are often co-expressed on the same cell, in which p75NTR provide a positive modulatory influence on NGF and BDNF signalling through TrkA and TrkB, and increases NGF/BDNF survival signalling. The distribution pattern of p75NTR in cortical and hippocampal neurons is consistent with clinical evidence showing an association of the receptor with depression and antidepressant response^{5,6}.

Sleep and depression are intimately related as sleep disturbance are prevalent symptoms in depression, whereas improvement of sleep has often been considered as one of the first signs of impending recovery^{7,8}. Therefore, measuring sleep response may provide biomarkers for treatment response to antidepressant.

Based on the neurogenetic hypothesis of depression, we hypothesized that inhibition of p75NTR signalling would increase neurogenesis and potentially accelerates the onset of antidepressant action while limits unwanted side effects. In the present study, we used a specific antagonist of the p75NTR (JNJ-17024865) to investigate in rats whether inhibition of the chopper death domain signalling could provide neuroprotection and/or enhance neurogenesis in certain brain regions. Specifically, we studied 1) Signs of apoptosis in cerebral tissues using TUNEL-staining on paraffin sections, 2) Cell proliferation in hippocampal tissue using chromogenic immunostaining for proliferating cell nuclear antigen (PCNA) on paraffin sections, 3) The effects of acute and chronic administration of JNJ-17024865 (1, 10, 30 mg/kg i.p.) on sleep-wake behavior in rats.

METHODS

The receptor binding profile carried out by CEREP evaluated the affinity of JNJ-17024865 for different receptors and channels in competitive radioligand binding assays and demonstrated

that this compound exhibits less affinity to all the receptors tested. The p75NTR antagonist was also found to potently inhibit full length and chopper p75NTR domain induced cell death in different p75NTR constructs transiently expressed in human embryonic kidney (HEK 293T) cells, and consistently increased survival rate of chicken DRG cells.

Immunohistochemistry

Following chronic treatment with JNJ-17024865, animals were perfused and fixed with 4% paraformaldehyde in Millonig buffer. The frontal part of the brain was frozen and the hippocampal part was embedded in paraffin. For detection of apoptosis, a TUNEL-staining was used on paraffin sections while a chromogenic immunostaining for proliferating cell nuclear antigen (PCNA) on paraffin sections was used for cell proliferation detection. For each staining, 2 sections (distance 200 μ m) were investigated. For quantification of TUNEL, stained cells were counted in the cerebrum of both hemispheres and expressed as number of cells per investigated area (external capsule and alveus, cortex, hippocampus or total cerebrum). For quantification of PCNA-labeling, stained cells were counted in the granular cell layer and in the hilus of the dentate gyrus, in the external capsule and alveus, and in the cortex along one side of the brain.

Animals and surgery procedure

All experimental protocols were carried out in strict accordance with the European Communities Council Directive of 24th November 1986 (86/609/EEC) and were approved by Janssen pharmaceutica local ethical committee.

Under Isoflurane anaesthesia, male adult Wistar rats were chronically instrumented with epidural frontal and parietal cortical EEG (AP + 2 mm, L - 2 mm, and AP - 6 mm, L +3 mm from Bregma) and EOG (peri-ocular muscle) and EMG (nuchal muscle). After recovery and adaptation to the recording conditions, online polygraphic recordings of EEG/EOG/EMG and body activity were performed for 16 hours, starting 15 days after the surgery.

Pharmacological treatments and recording procedure

Acute study: two EEG/EMG recordings were performed in 32 operated animals. A baseline recording was obtained after administration of saline to all rats. A treatment recording was performed for the same duration following saline and different doses of JNJ-17024865 (1, 10 and 30 mg/kg i.p.; n=8 rats per conditions).

Chronic study: EEG/EMG recordings were weekly performed after once daily administration of JNJ-17024865 at 10 mg/kg i.p for 3 weeks. The drug was dissolved in vehicle and administered in a volume of 10 ml/kg body weight. An equivalent volume of vehicle was administered in control conditions.

Off-line, vigilance states in control and treated groups were determined over 16 hours recording sessions. Four vigilances stages were classified as being indicative of wake, light sleep, deep sleep and rapid eye movement (REMS) sleep. Different sleep-wake parameters were calculated and the amount of time spent in each state during the first 4 hrs is presented here.

Data analysis

In sleep wake organization studies, statistical significance was evaluated by using non-parametric Wilcoxon Mann Whitney Signed Rank test for paired samples in consecutive hours. In immunohistochemical studies, differences between groups were evaluated by a Wilcoxon/Kruskal-Wallis and Student's t test. All data are presented as mean value \pm S.E.M., and a value of $p < 0.05$ was considered to be significant.

RESULTS

Apoptosis

Most apoptotic cells were found in the area between the hippocampus and the cortex, both of which brain structures are relevant to potential antidepressant applications. However, the number of apoptotic cells was low in both cortical and hippocampal structures after chronic administration of JNJ-17024865. No consistent differences in total number of TUNEL positive cells were observed in different brain regions between sham and treated animals (Figure 1A).

Neurogenesis

Most proliferation-associated (PCNA-stained cells) were observed in the area between hippocampus and cortex (external capsule and alveus). P75NTR blockade consistently reduced proliferating cells in the granular cell layer of the hippocampus and in the subventricular zone (alveus and external capsule) of the lateral ventricles (Figure 1B). However, no changes in cell proliferation were observed in the hilus and the cortex (data not shown).

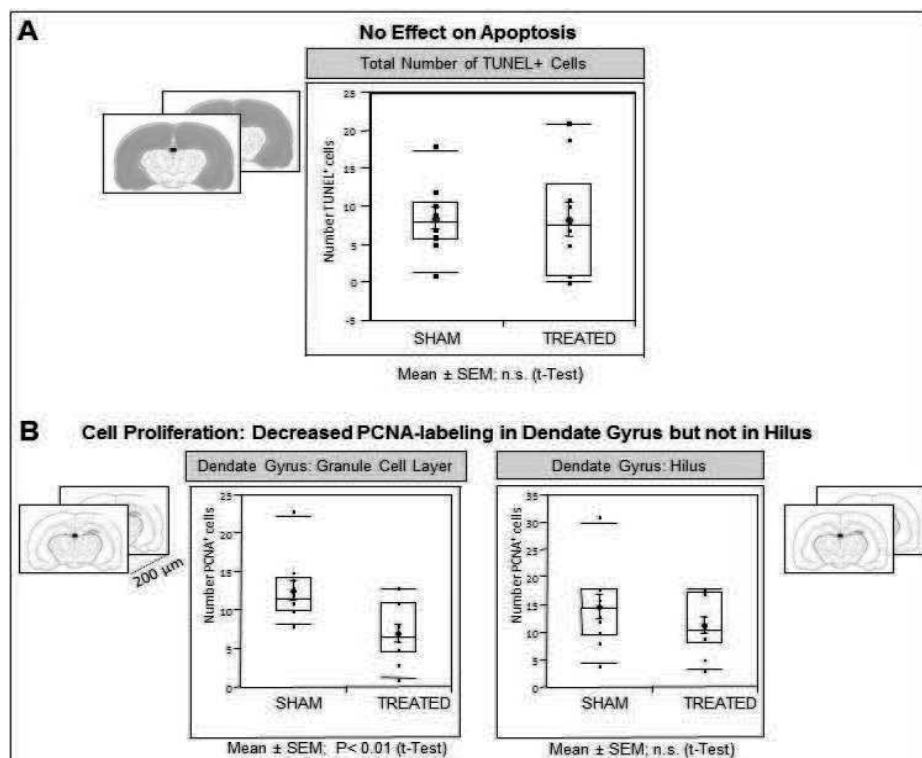


Figure 1: A. No effect of chronic administration of JNJ-17024865 on apoptosis. B. Decreased PCNA-labelling in the dentate gyrus but not in the hilus.

Vigilance states

The major finding observed in sleep-wake distribution following acute inhibition of the apoptosis pathway was a decrease in time spent in rapid eye movement (REM) sleep during the second and third hours post-administration of JNJ-17024865 (10 mg/kg).

However, no clear effects were observed in sleep-wake behaviour following chronic administration of JNJ-17024865 at 10 mg/kg during 3 recording sessions across the study (Figure 3).

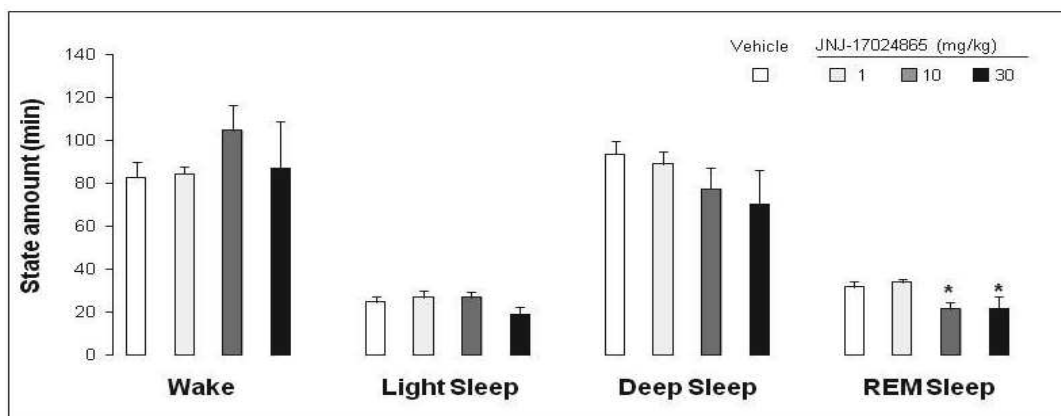


Figure 3: Effects of acute intraperitoneal administration of JNJ-17024865 at 1, 10, 30 mg/kg and of vehicle on vigilance states in rats during the first 4 hours of the recording session. Mean values of 8 rats, expressed as percentages of the recording time for the states wake, light sleep, deep sleep and rapid eye movement sleep. $p < 0.05$ vs. control.

DISCUSSION

Neurotrophic factors are promising new therapeutic candidates in neurodegenerative and psychiatric disorders, in which exogenous application of neurotrophins can restore neuronal phenotypic characteristics and connectivity following physical injury in the brain. It is believed that drugs that would enhance neurogenesis, through direct inhibition of the apoptosis pathway may represent a potential novel class of antidepressant agents. Here, we investigated in rats whether repeated inhibition of the p75NTR chopper death domain could provide neuroprotection for specific neuronal populations and/or enhance neurogenesis in certain brain regions. Our morphological findings suggest that chronic inhibition of the p75NTR did not alter immunoreactive elements of the cell death in both hippocampal and cortical areas. However, p75NTR blockade consistently decreased the cell proliferation in neurogenic zones of the hippocampus and in the subventricular zone (alveus and external capsule) of the lateral ventricles. This observation suggests that neurons are minimally responsive to endogenous neurotrophins after selective inhibition of the cell death pathway making the interaction between p75NTR and TrKs receptor the most likely mechanism for the increased neurogenesis. The results point to an involvement of the chopper domain signalling in the proliferation of neuronal cells in the hippocampus and suggest that p75NTR acts as an important negative regulator for triggering cell proliferation in the adult rat brain. Further analysis of neurotrophins and TrKA and TrKB receptor expression in the hippocampus following the inhibition of the cell death signalling pathway will provide an insight into the relationship between p75NTR and neurogenesis.

We subsequently studied the effects of acute and chronic inhibition of p75NTR signalling on sleep-wake architecture in rats to examine whether these central structural changes affect the brain functional activity. The major finding observed in sleep-wake distribution was a decrease in time spent in rapid eye movement (REM) sleep during the first four hours following acute administration of the p75NTR antagonist (10 mg/kg), whereas no such effect was found after chronic administration.

Sleep disturbances are commonly found in depressed patients and considered core symptoms of the disorder. REM density and REM latency are often used as fundamental diagnostic criteria in major depressive disorders⁷. Clinical and preclinical evidence consistently demonstrated a suppressive effect on REM sleep following acute and chronic treatment with most clinically effective antidepressants^{9,10}. Brainstem glutamatergic, GABAergic,

cholinergic and monoaminergic networks play a key role in the genesis of REM sleep. Earlier experiments demonstrated a role of Trk receptors and p75NTR in the action of neurotrophins on neurotransmitters release and synaptic plasticity^{11,12,13}. Therefore, the acute blockade of p75NTR might partly mediate the suppression effects of REM sleep through modulation of these networks. Additional experiments are needed to delineate the mechanism underlying the REM sleep disinhibition following chronic treatment. Further, the contribution of sleep to hippocampal neurogenesis is supported by sleep restriction or fragmentation studies in rodents, which consistently demonstrated a suppression of cell proliferation in the hippocampal dentate gyrus likely through the glucocorticoid pathways¹⁴. Here, chronic inhibition of p75NTR had no major effect on vigilance states, while the effect on the integrity of the hippocampus in term of proliferation and survival of neurons needs to be further investigated.

Collectively, the findings suggest that p75NTR is crucial for triggering neuronal proliferation in the hippocampus, and indicate that chronic blockade of p75NTR signalling was not associated with profound changes in vigilance states. Outcomes are of interest to further unravel the intricate relationship between depression and neurogenesis.

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EFFECTS OF ALZHEIMER'S DISEASE THERAPEUTIC DRUGS ON SLEEP AND SPECTRAL CONTENTS IN RATS

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INTRODUCTION

Cognitive decline is prevalent in mild cognitive impairment (MCI) and dementia due to the neurodegenerative process, of which Alzheimer's disease (AD) is the most common. Cholinergic neurotransmission contributes significantly to the mechanism of sleep and associated sleep-dependent cognitive processes¹, while hypofunction of this system is heavily involved in progressive deterioration of cognitive abilities of patients². Sleep and circadian rhythms disturbances with increased incidence of seizures are frequently reported in MCI and AD patients. Consequently, the behavioral, functional, and cognitive capacities of patients are affected to the point of becoming a major determinant of caregiver burden, and considered the main reasons to institutionalize patients³. Decreases in sleep time and sleep efficiency, reduction of deep and REM sleep, sleep fragmentation, sleepiness and nocturnal agitation are the cardinal sleep abnormalities that closely parallel the level of severity of dementia.

The 'second-generation' cholinesterase inhibitors (ChEIs), donepezil, galantamine and rivastigmine and the N-methyl-d-aspartate (NMDA) receptor antagonist memantine are the mainstay medication with proven efficacy in improving cognition, behaviour, activities of daily living, and global functioning in mild-to-moderate AD. These therapeutics are generally safe and well tolerated; however, existing literature today indicates mixed clinical results as to their side effects on sleep architecture. For instance, sleep disturbances such as poor subjective sleep quality associated with increased rates of insomnia and abnormal dreams have been identified in some reports, which may exacerbate the burden to caregivers⁴, whereas other clinical trials demonstrated negative effects on subjective and objective sleep⁵. The current studies aimed to investigate sleep-wake architecture and spectral EEG effects of these symptomatic treatments of AD in rats, of which a case study with donepezil is reported here.

METHODS

Animals and EEG recording

32 Male Sprague Dawley rats (Charles River, France) weighing 250–300 g at the time of surgery were used in this polygraphic recording experiments. Animals were maintained under controlled environmental conditions throughout the study: 22 °C ± 2 °C ambient temperature, relative humidity 60%, standard 12:12 light cycle regime (illumination intensity: ~ 100 lx). All experimental protocols were carried out in strict accordance with the European Communities Council Directive of 24th November 1986 (86/609/EEC). Electrodes were chronically implanted for recording the frontal and parietal EEG (AP + 2 mm, L - 2 mm, and AP - 6 mm, L +3 mm from Bregma), EOG (peri-ocular muscles) and EMG (nuchal muscles) activities.

Vigilance states and EEG power spectra determination

Online polygraphic recordings were performed for 20 hours following the subcutaneous administration of saline (n=8) and donepezil (0.3, 1, 3 mg/kg, n=8 for each dose). Six vigilance states were classified as being indicative of active wake, passive wake, light sleep,

deep sleep, intermediate stage or rapid eye movement (REM) sleep. Time spent in each vigilance state, latencies for light sleep, deep sleep and REMS (defined as the time between the beginning of the recordings and the appearance of the first sleep period lasting at least 30 s) are presented here. The accumulated profiles (minutes) of different vigilance states were computed and plotted in 60-min bins for 20 hours post-administration. Sleep loss reflected mainly in loss of deep sleep is expressed as negative accumulation and represented as negative slope, while a positive slope indicates recovery sleep. Similarly, an increase in active waking is expressed as positive accumulation values and are represented a positive slope.

Donepezil-induced changes in EEG frequency spectrums were determined in the active waking for artifact free 2 sec epochs during each of the first 4 hours of active waking. The spectral changes were calculated as the ratio of mean spectral power over frequencies between 0.5 and 50 Hz obtained following the injection of donepezil (day2) versus the mean spectral power obtained following administration of vehicle (day 1).

Statistical analysis

Time course changes in different sleep variables following each treatment were expressed as the mean \pm S.E.M and presented as mean value over 30 minutes period. The time course profile of the effects of donepezil on EEG spectral profile was expressed as a percentage of the mean spectral profile for the active waking in the baseline saline period. All data were submitted to Mann-Whitney test with Bonferroni correction, $\alpha=5\%$, 2-sided.

RESULTS

Donepezil significantly increased active waking during the 4 hrs post-administration with the effects of the middle and highest doses lasting up to 5 hrs (+62% and +197%; $p<0.05$, respectively) (Figure 1A). Consequently, reductions in light sleep, deep sleep, intermediate state and REM sleep were observed, leading to a significant reduction in total time spent asleep particularly with the middle and highest dose. Remarkably, donepezil at the lowest dose increased REM sleep time during 4 hrs post-administration (Figure 1A). No homeostatic sharp rebound of different vigilance states followed the initial sleep suppression or occurred during the subsequent dark phase (Figure 1A).

Cumulative changes indicated that donepezil rapidly reduced deep sleep evidenced by negative slope during the first 5 hours post-administration. However, the time course of the effects differed as a function the dose and vigilance state measured. The accumulated sleep deficit differed between groups i.e. at 1 and 3 mg/kg, deep sleep gradually recovered during the 20 hours post-treatment interval; however, a delayed compensatory sleep response was observed at 3 mg/kg (Figure1B).

Cumulative changes in waking indicate that donepezil (3 mg/kg) accumulated wakefulness with acute arousing effects peaks around 5hrs, and the transient arousing effect holds on longer, which may consequently delay the initial compensator deep sleep response (Figure 1B). Finally, the wake promoting effects of donepezil is consistent with lengthened sleep onset latencies with the middle and highest dose (Figure 1A bar graphs).

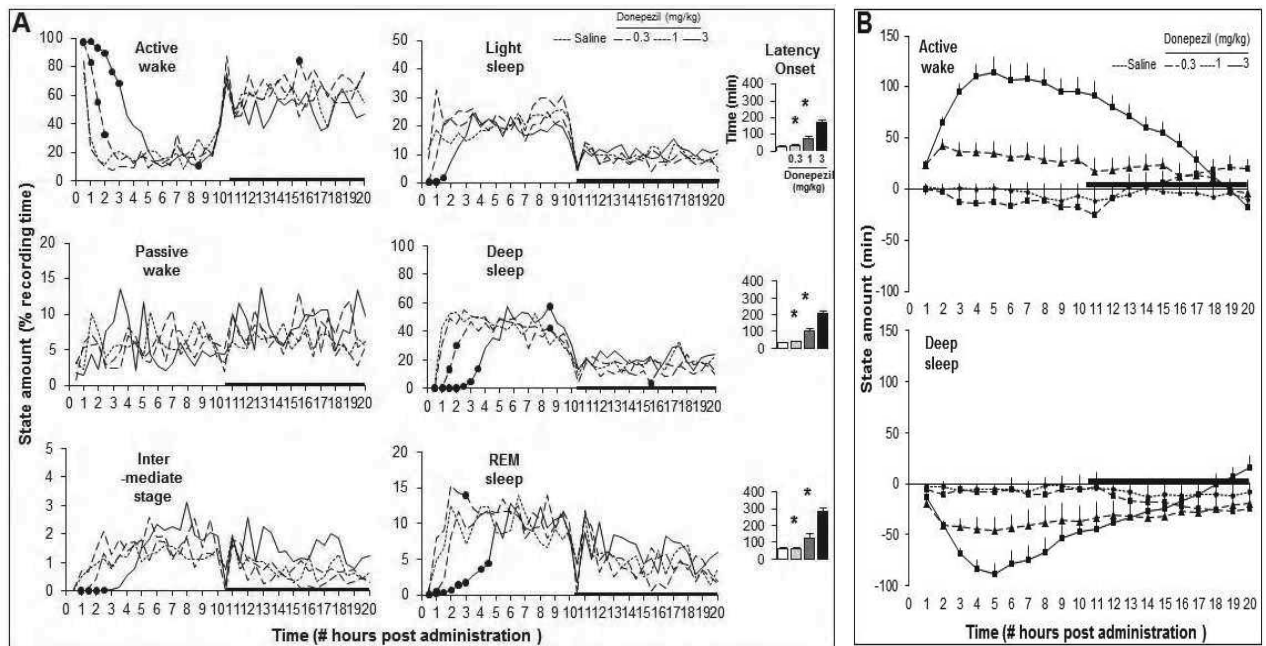


Figure 1: A/ Effects of subcutaneous administration of donepezil (0.3, 1, 3 mg/kg) or saline on sleep-wake architecture during 20 consecutive hours. The inset bar graphs indicate the latency to specific sleep state. B/ Total cumulative changes in minutes of active waking and deep sleep relative to baseline 24 h earlier after acute subcutaneous administration of donepezil (0.3, 1, 3 mg/kg) or saline; a negative slope indicates cumulative sleep loss whilst a positive slope indicates compensatory sleep. Dark square area represents the dark period. $P < 0.05$ is indicated by dots on curves.

The quantitative analysis of spectral contents during each of the first 4 hours of active waking showed that donepezil selectively enhanced the EEG power in the frequency ranges 5-8 Hz and 35-50 Hz (Figure 2).

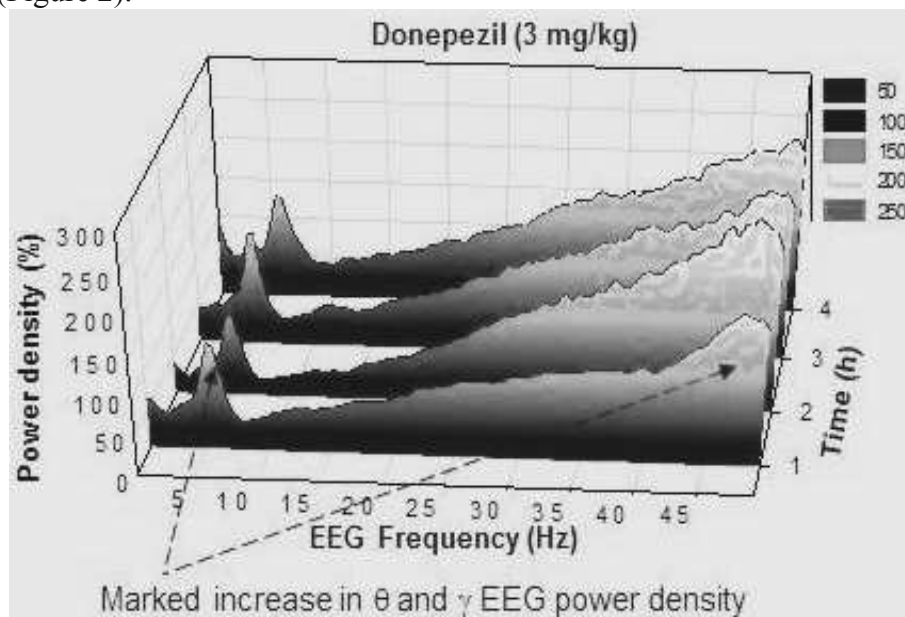


Figure 2: Sequential mean changes in spectral EEG power density (0.5-50 Hz) in active waking after subcutaneous administration of donepezil (3 mg/kg) or saline, expressed as percentage change over baseline (within-animal comparison) during each of the first 4 hours of active waking.

DISCUSSION

Donepezil markedly enhanced active waking associated with inhibition of light sleep, deep and REM sleep. Acetylcholine has been known as a key player in the ascending arousal pathways that control vigilance states and cognitive processes^{1,2}. Therefore, the idea of elevation the extracellular acetylcholine by ChEIs to elicit alertness and restore cognitive deficits has gained interest as effective therapeutic molecules for symptoms in AD⁶. In line with the current results in rats, cognitive enhancers inhibiting the acetylcholinesterase activity such as donepezil, rivastigmine, or galantamine elicited changes in sleep architecture in human and animal by increasing awakening⁷.

Cumulative changes in waking were greater and sustained over the major part of the recording time, which resulted in progressive compensatory sleep.

It is well established that sleep favors memory consolidation and sleep disturbances negatively impact various aspects of cognitive functioning⁸. Here, the arousal effect of donepezil is followed by an increased sleep drive without sharp overcompensation of sleep time as described with most wake promoting drugs. It has also been shown that donepezil led to an increase in sigma activity during stage 2 NREM sleep and delta activity during slow wave sleep, which may facilitate processes of sleep-dependent memory consolidation in older adults⁹. Therefore, it is essential that pharmacological activity of symptomatic medications should have a neutral effect on sleep, or ideally improve and maintain sleep quality.

Our results demonstrated that donepezil at the lowest dose enhanced REM sleep during the first 4 hrs post-administration. It is known that cholinergic neurotransmission contributes significantly to the generation of REM sleep and damage of cholinergic pathways, hypothalamic and brainstem nuclei is involved in the molecular basis of perturbed REM sleep in AD patients and mouse models of the disease⁷. Previous research in younger, elderly individuals and AD patients have shown that ChEIs exerted a marked effect on REM sleep parameters, by reducing REM sleep latency and increasing its density suggesting a beneficial effect on memory performance^{10,11}. In the REM activating system, mutual excitatory interactions between cholinergic, glutamatergic and GABAergic neurons serve to promote and/or maintain the state of REM sleep. It is hypothesized that donepezil at low dose induced an excitation of GABAergic neurons in the brainstem sublaterodorsal and pontine oralis nuclei to silence the aminergic pontine inhibitory system and promote REM sleep.

Donepezil enhanced waking with dominant EEG theta and gamma oscillatory activity. Contemporary research in cognitive neuroscience demonstrated that theta oscillations establish precise temporal communication between cortical and subcortical neuronal networks during processes, whereas gamma rhythm is involved in dynamic links between short distance brain areas during cognitive processing¹². EEG slowing and diminished fast oscillatory activity was found in animal models of AD and generally described prior treatment in AD patients⁷, whereas donepezil had a positive effect on theta oscillatory rhythm in temporal and centroparietal brain areas of AD patients¹³. Here, donepezil promoted both theta and gamma oscillatory rhythms (a reflection of underlying hippocampal and cortical area synchronization), which pattern was also observed with the other symptomatic treatment drugs, being the ChEIs rivastigmine, galantamine or the NMDA blocker meantime. This consolidated wake-promoting action associated with enhanced theta and gamma network oscillations may correlate with cognitive-enhancing effects at least during the period of waking state.

Base on earlier work and our data it might be reasoned that during the early stage of AD where sufficient numbers of cholinergic projection neurons remain, donepezil still has some use as a symptomatic therapeutic drug that does not cause severe abnormalities as seen in sleep-wake architecture in rats. The results highlight the specific effects of donepezil on spectral theta and gamma frequency oscillations, both of which rhythms have functional

relevance in memory and cognitive process. Novel symptomatic treatment need to aim for better efficacy in consolidating and improving cognition, while maintaining positive effects on sleep-wake EEG especially during the later stage of AD.

ACKNOWLEDGEMENTS

We thank Ms. H. Huysmans for technical assistance.

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INACTIVATION OF THE METABOTROPIC GLUTAMATE RECEPTOR (MGLUR2) EVOKES AN AROUSAL BUT NOT ANTIDEPRESSANT-LIKE PROFILE IN RODENT'S SLEEP-WAKE EEG

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INTRODUCTION

Contemporary research in the neurobiology of mood disorders has focused on a number of non-monoamine therapeutic strategies and emerging clinical and preclinical evidence suggests a potential for drugs targeting the glutamatergic system in the treatment of depression¹. The metabotropic glutamate receptor (mGluR2) is an attractive target to normalize excessive glutamate neurotransmission and thus provides a novel and promising therapeutic approach. The expression pattern of these receptors occurs highly and discretely in the presynaptic cleft in key regions of the limbic system in the forebrain such as thalamus, cortices, hippocampus and amygdala². These brain areas represent key circuit elements in the cortico-basal ganglia-cortico circuitry involved in depression³.

Sleep disturbances are an integral part of the diagnostic criteria for major depression and sleep may provide biomarkers for treatment response to antidepressant medication^{4,5}. In addition, a strong relationship exists between glutamate neurotransmission and sleep mechanisms. Moreover, sleep architecture shows clear homology among species and sleep parameters commonly measured in human subjects can also be obtained in animals. Therefore, sleep-wake EEG read-outs are most sensitive indices of functional pharmacodynamic activity and target engagement. This may provide insight in the potential therapeutic application and offers interesting options for translational medicine⁶.

The role of mGluR2 in the regulation of the sleep-wake cycle has been demonstrated thanks to availability of specific pharmacological agents of this receptor^{7,8}. The present studies sought to examine whether inactivation of mGluR2 signalling elicits changes on sleep-wake architecture in rodents different from those previously demonstrated following the activation of mGluR2¹⁴, and to what extent the drug-induced changes have an antidepressant-like signature. A case study with mGluR2 (-/-) mice is reported here.

METHODS

Animals, surgery and experimental procedure

mGluR2^{-/-} mice (n=32; Deltagen In) weighing 25-30 g at the time of surgery were used in the polygraphic studies. All animals were maintained under controlled environmental conditions throughout the study: 22°C ± 2°C ambient temperature, relative humidity 60%, standard 12:12 light cycle regime (illumination intensity: ~ 100 lux) and had free access to standard laboratory food chow and tap water. All experimental protocols were carried out in strict accordance with the European Communities Council Directive of 24th November 1986 (86/609/EEC) and were approved by the animal care and use committee of J& J PRD and local ethical committee.

In brief, surgery was performed under isoflurane anaesthesia using the protocol described earlier¹⁴.

In mice, the telemetry transmitter TA10ETA-F20 (Data Sciences International, USA), containing biopotential electrodes for monitoring the electroencephalographic (AP - 2.3 mm,

L ± 1.4 mm from bregma), were surgically implanted according to the procedure used in earlier study¹⁴. After surgery the animal were subcutaneously given 0.3 ml analgesic (Carprofen, Rimadyl, 50mg/ml, Pfizer Ltd, UK diluted 1:10) and applied local analgesic on the wounds (Lidocaine spray Xylocaine, 1 % solution, Astra Pharmaceuticals Ltd, UK). Then, animals were individually placed in their home cage, kept warm in a heating box set at 26 °C ± 2 °C to avoid hypothermia and the temperature was progressively decreased over days to reach room temperature.

Drug treatment and analysis

After two weeks recovery and adaptation to the recording conditions, the baseline sleep-wake profile was first determined in metabotropic glutamate mGluR2 (-/-) mice and their WT control littermates (n=32, 16 animals for each genotype) over 24 h spontaneous recordings. In the second experiments, we investigated the effects of subcutaneous single dose of the mGluR2 negative allosteric modulator (NAM) Ro-4491533 (40 mg/kg) on sleep-wake architecture in both genotypes. The EEG signals were digitized at a sampling rate of 200 Hz, and digitally filtered (high frequency band 50 Hz and low frequency band at 0.5 Hz) while analyzing the vigilance states.

The vigilance states were analysed in 4 s epochs using Neuroscore software (Data Sciences International) as being wakefulness, non-rapid eye movement (NREM) sleep or rapid eye movement (REM) sleep based on EEG characteristics. Different sleep-wake parameters were determined in both genotypes over 24 post-administration hours.

Statistical analysis

The time profiles of vigilance states, body temperature and activity presented as the means ± S.E.M. were analysed using repeated measures ANOVA with posthoc “by-timepoint” analyses, comparing the mean response at each dose group to that of the vehicle group, followed by a post-hoc Dunnett’s test.

RESULTS

Effects antagonizing mGluR2 on sleep-wake architecture in mice

Responses to inactivation of mGluR2 signaling on sleep architecture, locomotor activity and core body temperature were different for mGluR2 (-/-) mice and their control littermates (Figure 1). The WT mice were more sensitive in exhibiting these neurophysiological changes than mgluR2 (-/-) mice. Similar to the effects observed during the light period in rats, the wake-promoting potency of the mGluR2 NAM Ro-4491533 at 40 mg/kg p.o. was associated with a complete suppression of NREM sleep (dose effect; P < 0.05) and REM sleep (dose effect; P < 0.05) during 4 hrs.

Consistent with the wake promoting effect, mGluR2 NAM lengthened the onset to REM sleep. The enhanced waking was accompanied by an increased locomotor activity and temperature in WT but not mGluR2 (-/-) mice. It was noted that mGluR2 blockade did not immediately elevate temperature in WT mice, while locomotor behavior was increased. The maximum effect (more than +1°C) occurred about 2 hrs after the drug administration and this initial rise in locomotion and temperature returned to vehicle level at approximately 5 hrs after administration.

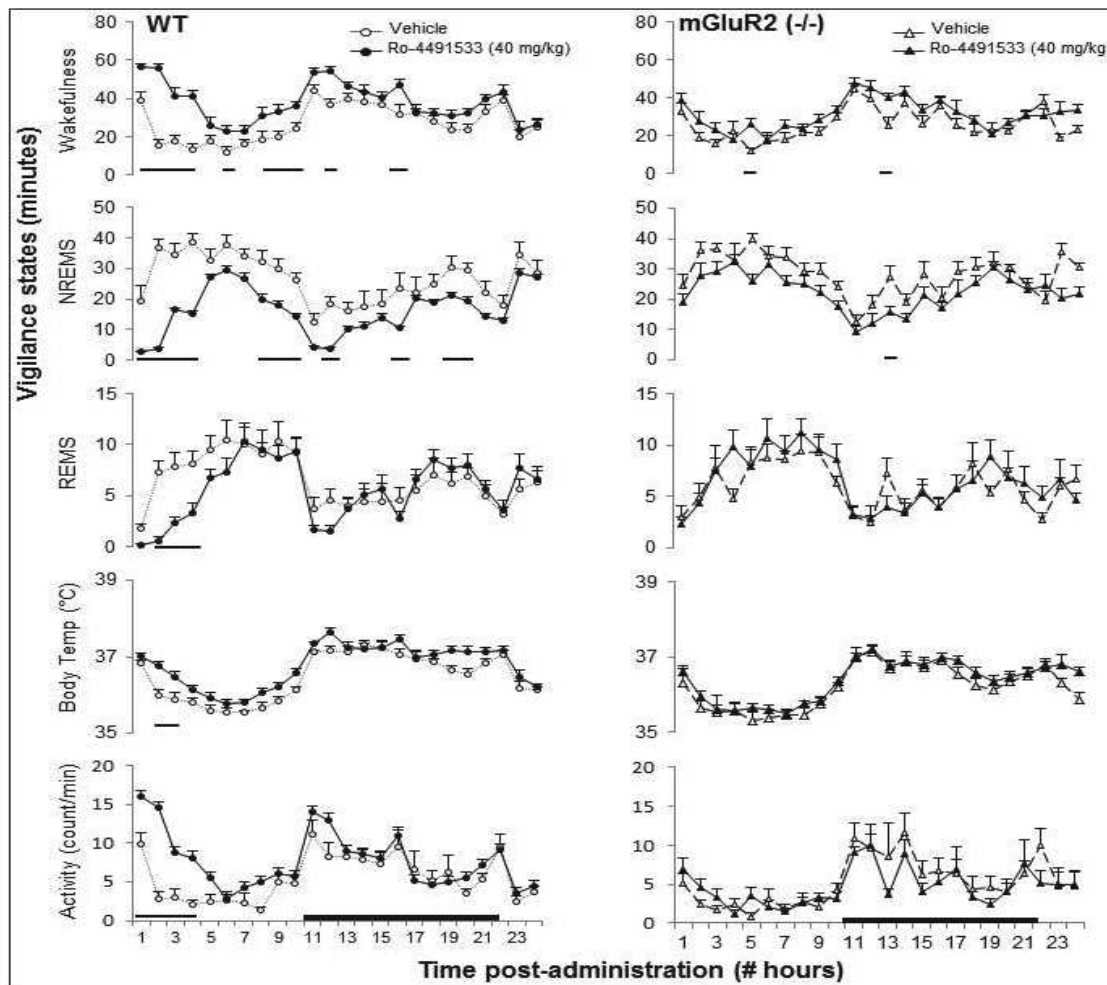


Figure 2: Effects of acute oral administration of mGluR2 NAM Ro-4491533 (40 mg/kg) and of vehicle (20% HPCD + 1HCl) on sleep-wake organization, body temperature and activity in mGluR2 (-/-) and WT mice. Mean changes per hour is indicated for each sleep-wake state, body temperature and activity. Black square areas indicate dark period. N = 8 for each group. Lines under the curves indicate significant changes vehicle vs. treatment.

DISCUSSION

The present work used the sleep-wake electroencephalogram preclinical model to study the central functional activity and target engagement following modulation of the mGluR2 signalling. We demonstrated that inactivation of mGluR2 elicits a primary arousal profile in WT but not mGluR2 (-/-) mice. Remarkably, this arousal profile was accompanied by enhanced motor behaviour and body temperature. This result confirms the specific role of mGluR2 in mediating the common robust arousal features in the rat's sleep-wake profile. Sleep disturbance such as an increased REM density and shortened deep sleep has long been known as a core symptom and recognized as a biomarker in mood disorders^{4,5}. The most consistent effects of clinically effective antidepressant drugs on sleep architecture has been the robust and immediate dose-related suppression of REM sleep and delayed its onset latency, both in animals, healthy volunteers and depressed patients⁹. The glutamatergic mechanisms became one of the major focus of contemporary research in mood disorders to overcome the limitations of monoamine-based approaches¹⁰. Earlier studies showed that

patients with mood disorders have increased plasma glutamate levels^{11,12}, which were further confirmed by imaging and post-mortem brain studies^{13,14}. Because of their unique pre-synaptic distribution in glutamatergic synapses and the regulatory roles they have in neurotransmission, mGluR2 is believed to be a mechanistically novel and promising approach to treat depression disorder¹⁰. Accordingly, we have demonstrated earlier that positive modulation of mGluR2 elicited particular changes in rodent's sleep-wake variables following attenuation glutamate release⁷. This observation raised a hypothesis on the benefits that may be brought about by normalizing excessive glutamate neurotransmission, on sleep disturbances regularly encountered in mood disorders with excessive REM sleep overdrive. In the present study, we found that negative modulation of the mGluR2 elicited a robust arousal EEG response in the rodent's sleep EEG model. Our findings are in line with earlier reports on the stimulating properties of mGluR2 blockade^{8,15}. Considering the fact that sleep disturbance such as sleepiness is one of the disabling symptoms in depression disorder, the present pharmacological pattern might have significant clinical implications as it is likely that inactivation of mGluR2 as a therapeutic approach at sleep onset may exacerbate poor sleep quality, which may have detrimental consequences on daytime cognitive functioning. However, the large unmet need for wakefulness-promoting agents associated with robust pro-cognitive profile may make mGluR2 blockade an attractive mechanism for the treatment of cognitive disorders.

mGluR2 blockade has been shown to exhibit antidepressant activity in classical screening models used to detect potential antidepressant efficacy¹. However, these animal models have shown their limitations when newer mechanism of action is involved and have lead to mis-interpretation of the behavioural response. Psychostimulant activity appears to be the most frequent cause of false positive response in these behavioral animal models of depression¹⁶. Hence our present findings raised some concerns about earlier interpretation regarding the antidepressant potential of this mechanism of action.

The present findings demonstrated that only WT mice were sensitive to mGluR2 inactivation and responded to wake-promoting effects of mGluR2 blockers, whereas mGluR2 (-/-) did not. Our results in rat and mice suggest that the wake-promoting effects of mGluR2 inactivation of these compounds do require intact glutamatergic neurotransmission through mGluR2.

It can be concluded that blockade of the mGluR2 signalling has a distinct pharmacological profile consistent with an arousal promoting pattern, which differs from a classical antidepressant-like profile in the rodent's sleep EEG paradigm. Sleep is important for optimal cognitive function, and sleep disruption results in functional impairment. The effects of mGluR2 blockade on sleep structure and quality encourages further prospective preclinical functional brain network and cognitive studies to unravel the consequence of mGluR2 inactivation on sleep related memory and consolidation process as well as the therapeutic utility in the treatment of cognitive and attentional disorders.

ACKNOWLEDGEMENTS

We thank Mrs. L. Raeymaekers and Mrs. H. Huysmans for technical assistance.

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PREOPERATIVE SCREENING FOR OBSTRUCTIVE SLEEP APNEA IN PATIENTS BEFORE BARIATRIC SURGERY.

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INTRODUCTION

Obstructive sleep apnea (OSA) is common in subjects with severe obesity. Its prevalence in patients with a body mass index (BMI) between 35-60 kg/m² was 74-83%.¹ In patients who underwent bariatric surgery (BMI 48 kg/m²), its prevalence (Apnea Hypopnea Index (AHI) >5) was 71%, while moderate to severe OSA (AHI ≥15) was present in 44% of the cases.²

Untreated OSA can cause severe postoperative complications, including nocturnal hypoxemic episodes, upper airway obstruction with necessity for reintubation, and hypertension.³ Since screening for OSA with poly(somno)graphy is time-consuming and accompanied with high costs, it is reasonable to select only those subjects who are at increased risk. Patients planned for surgery could be questioned on OSA symptoms, e.g. snoring, observed apneas or daytime sleepiness. Many screening tools have been developed to improve accurately identification of patients with high risk for OSA. For example, the Berlin Questionnaire⁴ or STOP BANG questionnaire⁵ are relatively user friendly tools (≤10 items) and have been proven highly efficient to identify moderate to severe OSA (AHI ≥15).⁶

The aim of this study was to investigate the frequency of newly diagnosed OSA in patients scheduled for bariatric surgery and referred to our sleep clinic due to anaesthesiologist's suspicion of OSA. Furthermore, we studied whether the STOP BANG questionnaire could correctly identify patients with mild to moderate/severe OSA.

METHODS

All patients scheduled for bariatric surgery, and referred to our sleep clinic by the out-clinic patients department of anesthesiology at our hospital, were included. Annually, around 500 obese patients are treated with bariatric surgery at Medical Centre The Hague. Data from the medical files (anesthesiology and sleep centre) were retrospectively collected. Only patients referred between June 2010 and January 2013 were included.

In all bariatric surgery patients the anesthesiologist gathered information on medical history, presence of snoring, observed apneas or daytime sleepiness (using a self-reported questionnaire including the Epworth sleepiness score (ESS)⁷). Subjects were referred to our sleep clinic when the anesthesiologist suspected OSA. Of these subjects only those were included for analysis when an ESS ≥11 was reported, or, in case ESS <11, when snoring was reported combined with observed apneas. Patients who were previously diagnosed with OSA were excluded from analysis.

At preoperative screening, body weight, length and blood pressure were measured. Also data on neck circumference was collected. At the sleep clinic, patients were asked again if they suffered from excessive daytime sleepiness, snoring or apnea. Consequently, a poly(somno)graphy was performed to screen for OSA. The diagnosis OSA was made according to the International Classification of Sleep Disorders-2. AHI >5 is considered mild OSA, AHI ≥15 – 30 moderate OSA, and AHI >30 severe OSA. The STOP BANG questionnaire with 8 items on Snoring, Tiredness, Observed apnea, blood Pressure, Body

mass index, Age, Neck circumference and Gender was applied.⁵ On each abnormal item one point can be scored. In our study, one point may be scored on the item blood pressure, if the diastolic blood pressure was ≥ 90 mmHg, or when the patient reported a history of hypertension or used antihypertensive drugs. A STOP BANG score of ≥ 3 corresponds with a high risk on OSA, < 3 implicates a low risk.⁵ In obese subjects, a cut-off value of 4 to 6 could also be used.⁸ In our patients, STOP BANG scores were calculated based on information from the anesthesiology patient records. When STOP BANG items were missing in these records, data were used from the sleep centre records to minimize missing values. Student's T-test or non-parametric Mann-Whitney test was used to compare means between groups. The Pearson Chi-square test or the Fischer's Exact test, the latter in case of a small sample size, was used to compare variables between groups. $P \leq 0,05$ was taken as the level of significance. Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS version 17.0, IBM, Baltimore, USA).

RESULTS

Sixty-four subjects scheduled for bariatric surgery were referred to our sleep centre. Eleven patients were excluded from further analysis because at referral the ESS was < 11 and snoring combined with observed apneas was absent, or information on these topics was missing. Another 3 subjects were excluded, since they were previously diagnosed with OSA.

Baseline characteristics of the included 50 patients are presented in table 1. Twenty-eight subjects were diagnosed with OSA (AHI > 5). A subset of these OSA patients had moderate OSA (n=5) or severe OSA (n=6).

The frequency of snoring, observed apnea or abnormal ESS differed statistically significantly between subjects with or without OSA (AHI > 5). When subjects with at least moderate OSA (AHI ≥ 15) were compared to those with an AHI < 15 , male gender was significantly more present in those with AHI ≥ 15 ($p < 0,01$). Also neck circumference was significantly higher if AHI was ≥ 15 ($p = 0,01$).

In 28 subjects, one (n=25) or two items (n=3) of the STOP BANG questionnaire were missing. Overall, a STOP BANG score $<$ or ≥ 3 could be calculated in 49 subjects. The STOP BANG score was < 3 in only 2 subjects, both did not suffer from OSA. In 28 subjects (out of 47) with a STOP-BANG score ≥ 3 (60%), OSA (AHI > 5) was found, including 5 with moderate and 6 with severe OSA. Table 2 shows the sensitivity and specificity of the STOP BANG questionnaire at diverse cut-off values.

A STOP BANG score of $<$ or ≥ 6 could be calculated in 41 subjects. Twenty-nine subjects had a score < 6 , of which ten subjects had mild OSA and one subject had severe OSA (AHI 41). Twelve subjects had a STOP BANG score of ≥ 6 , in two of these no OSA was present. The other ten subjects with a STOP BANG score of ≥ 6 suffered from moderate (n=6) or severe OSA (n=4).

DISCUSSION

Only approximately 5% of all the bariatric surgery patients at our hospital were referred to the sleep clinic. In these selected patients with a clinical suspicion of OSA, 28 out of 50 subjects were newly diagnosed with OSA (AHI > 5). subjects (22%) suffered from moderate to severe OSA (AHI ≥ 15). These numbers are extremely low compared with previously reported data in patients with a comparable degree of obesity.²

	<i>Overall</i>	<i>AHI ≤5</i>	<i>AHI >5</i>	<i>AHI ≥15</i>	<i>p-value</i>
n	50	22	28	11	
Male gender (n)	13 (26%)	3 (14%)	10 (36%)	7 (64%)	0,08
Age (years, mean ±SD [range])	42 ±9 [18 – 56]	41 ±8 [18 – 55]	43 ±9 [24 – 56]	46 ±7 [31 – 52]	0,47
Age > 50 years (n)	14 (28%)	4 (18%)	10 (36%)	4 (36%)	0,17
BMI (kg/m ² , mean ±SD [range])	45 ±6 [35 – 62]	46 ±7 [37 – 62]	45 ±6 [35 – 55]	45 ±5 [39 – 54]	0,38
BMI > 35 kg/m ² (n)	50 (100%)	22 (100%)	28 (100%)	11 (100%)	n.a.
BMI > 50 kg/m ² (n)	13 (26%)	6 (27%)	7 (25%)	3 (27%)	0,85
Neck circumference (cm, mean ±SD, n available)	42 ±4, n=24	41 ±4, n=10	43 ±4, n=14	46 ±5, n=6	0,25
Neck circumference > 40cm (n)	23 (96%)	9 (41%)	14 (50%)	6 (55%)	0,42
Diastolic blood pressure ≥ 90 mmHg (n)	13 (26%)	6 (27%)	7 (25%)	2 (18%)	0,86
History of hypertension (n)	20 (40%)	7 (32%)	3 (46%)	7 (64%)	0,30
Antihypertensive drugs (n)	20 (40%)	6 (27%)	14 (50%)	7 (64%)	0,10
Snoring (n)	42 (84%)	15 (68%)	27 (96%)	11 (100%)	0,03*
Observed apneas (n)	31 (62%)	9 (41%)	22 (79%)	10 (91%)	<0,01*
Tiredness or sleepiness (n)	35 (70%)	14 (64%)	21 (75%)	8 (73%)	0,28
ESS (median [range])	11 [2-19]	12 [7 -17]	11 [2 – 19]	10 [4 – 19]	0,21
ESS ≥11 (n)	35 (68%)	19 (86%)	15 (54%)	5 (46%)	0,01*
AHI (median [range])	5,8 [0 – 96,9]	1,0 [0 – 4,9]	12,5 [5,3 – 96,9]	30,2 [15,3 – 96,9]	<0,01*

Table 1. Baseline characteristics of bariatric surgery patients (n=50) screened for obstructive sleep apnea (OSA), SD = standard deviation, BMI = Body Mass Index, n.a. = not available (no statistics could be performed), ESS = Epworth Sleepiness score, AHI = apnea hypopnea index; * statistically significant difference between AHI≤5 and AHI >5 .

<i>STOP BANG score</i>	<i>Sensitivity % [95% CI]</i>	<i>Specificity % [95% CI]</i>
AHI > 5 (at least mild OSA)		
≥ 3 (n = 49)	100,0 [0,85 – 1,00]	9,5 [0,01 – 0,32]
≥ 4 (n = 42)	100,0 [0,85 – 1,00]	17,6 [0,05 – 0,44]
≥ 5 (n = 38)	95,2 [0,74 – 1,00]	58,8 [0,33 – 0,81]
≥ 6 (n = 41)	47,6 [0,26 – 0,70]	90,0 [0,67 – 0,98]
AHI ≥ 15 (moderate and severe OSA)		
≥ 3 (n = 49)	100,0 [0,68 – 1,00]	5,3 [0,01 – 0,19]
≥ 4 (n = 42)	100,0 [0,68 – 1,00]	8,8 [0,02 – 0,25]
≥ 5 (n = 38)	100,0 [0,63 – 1,00]	34,4 [0,19 – 0,53]
≥ 6 (n = 41)	90,9 [0,57 – 1,00]	93,3 [0,76 – 1,00]

Table 2. Sensitivity and specificity of the STOP BANG questionnaire at different cut-off values. OSA = obstructive sleep apnea, n = number of patients available to calculate the STOP BANG score at a cut-off point, AHI = apnea hypopnea index, CI= confidence interval.

Limitations of our study were the referral method, the small sample size and the retrospective design. Since not all bariatric surgery patients were screened with poly(somno)graphy, it is possible that in some subjects OSA was not identified by the anesthesiologists, since typical symptoms were lacking. The last few years the STOP BANG questionnaire has been shown

to be a reliable screening tool.^{5,6,8} In non-obese surgery patients sensitivity and specificity of STOP BANG (with cut off value of ≥ 3) to identify moderate/severe OSA (AHI ≥ 15) was 93% and 43% respectively.⁵ In morbid obese patients (BMI 40 ± 5 kg/m²) these percentages are 97% and 7% respectively.⁸ When a cut off value ≥ 6 was used in morbid obese patients the sensitivity and specificity to identify moderate/severe OSA was 42% and 87% respectively.⁸ We found better results when a cut off value of ≥ 6 was used, with a sensitivity and specificity of 91% and 93% respectively. Again, our small sample size should be taken into account. On the other hand, our results confirm that STOP BANG questionnaire has a high sensitivity at different cut off values.^{6, 8} Further research with a prospective design should be conducted to find the optimal cut off value in morbidly obese subjects.

CONCLUSIONS

This retrospective study illustrates that, when screening for OSA in morbid obese patients is only performed in those with high score on ESS (≥ 11) or presence of snoring and observed apneas, probably only a subset of OSA patients will be identified. Recent publications suggest that STOP BANG questionnaire might be a good screening strategy.³ Our study results confirms a high sensitivity of the STOP BANG questionnaire in morbid obese patients. More research is needed to determine the optimal cut off value with acceptable sensitivity and specificity in patients with obesity. The optimal cut off value of the STOP BANG score might be higher than 3 points in (morbid) obese subjects to efficiently identify patients with high risk on OSA.

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CHANGES IN SLEEP ARCHITECTURE AFTER AN EPILEPTIC SEIZURE THE DAY BEFORE

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INTRODUCTION

Sleep disturbances are common in people with epilepsy. A Dutch study showed a prevalence of two times higher in people with partial epilepsy compared to controls¹. That nocturnal epileptic seizures result in fatigue and daytime drowsiness is comprehensible, but what about daytime seizures. Do they also disturb the sleep pattern? If so, is this the reason that some people show for a long period, up to several days, post-ictal complaints, such as feeling unwell, strong fatigue and alertness problems? The duration of these post-ictal complaints can only partly be explained by the type of seizure.

The effect of daytime seizures on sleep has only been studied in small groups^{2,3}.

The aim of this study was to investigate the effect of generalized seizures during daytime on the sleep architecture the next night and its relation to the origin and type of the epileptic seizures.

METHODS

A total of 425 longterm video-EEG-recordings (339 people with epilepsy) of 15 years or older were studied after excluding all recordings with (a) a total time in bed (TIB) of less than 6 hours, (b) in which partial night sleep deprivation was performed as seizure provocation, (c) in which a nocturnal seizure occurred, (d) made in people with a severe intellectual disability, (e) which were incomplete and (f) which was performed after an unclassified seizure 24 h before the night of interest. These recordings were divided in a group *Seizure Free* with 331 recordings in 290 individuals who experienced a seizure free period of at least 24 h and a group *Daytime Seizure* with 94 recordings in 74 individuals who suffered one or more (secondarily) generalized seizures during the daytime or early evening before the night of investigation (Study I). Furthermore, the recordings of individuals who had a least one day with a daytime seizure as well as one day without (N=23) during EEG recording over many consecutive days were studied also (Study II).

Data of every recording concerning demography, epilepsy and sleep, assessed according the American Academy of Sleep Medicine (AASM) rules⁴, were collected.

The seizures were classified according to the International League Against Epilepsy (ILAE) seizure semiological terminology⁵. Only (secondarily) generalized seizures of at least 30 s were included. Less severe or subtle daytime seizures were excluded as we assumed that they have no influence on sleep.

In the recordings, performed primarily for epilepsy diagnostic reasons, the full 10-20 electrode system with extra electrodes on temporal regions according 10-10 system were used. In addition polygraphy was performed including ECG, EMG-submental, EOG and reparatory effort (abnominal). Sleep scoring was performed by specialized technicians.

For comparisons of both groups (Study I) the independent-sample t-test for normally distributed data and Mann-Whitney U test in not normally distributed data were used. Sleep variables which measure duration and frequency, which are by definition asymptotically distributed, were (log-) transformed to a normalized distribution. For comparisons of the sleep variables in Study II paired sample t-tests were used. Linear regression analysis was used to

correct for confounding. ANOVA with Bonferroni's correction was used to perform sub-analyse. Differences were considered statistically different at $p < 0.05$.

RESULTS

Study I: the groups *Daytime Seizure* and *Seizure Free* did not differ in age (36.9 vs. 36.2; $p = 0.73$), gender (Male: 45.7% vs. 45.0%; $p = 0.90$), number of antiepileptic drugs (AED) ($p = 0.26$) and type of epilepsy ($p = 0.66$). Table 1 shows comparisons between both groups.

Table 1. Central values of the sleep variables of all recordings in the *Seizure Free* and *Daytime Seizure* groups

Total recordings: <i>N</i> =425	Group <i>Daytime Seizure</i> <i>N</i> =94 recordings		Group <i>Seizure Free</i> <i>N</i> =331 recordings		Differences <i>Daytime Seizure</i> minus <i>Seizure Free</i>	T-test (2-sided)
Time in Bed (TIB) (min)	524.0 ^a	(439.0-755.5)	508.5 ^a	(379.0-714.0)	15.5	$p = 0.001$
Total Sleep Time (TST) (min)	433.8 ^a	(189.0-688.5)	415.5 ^a	(138.5-644.0)	18.3	$p = 0.068$
Sleep Efficiency (SE) (%)	79.1 ^b	(14.2)	79.1 ^b	(14.1)	0	$p = 0.998$
Sleep Onset Latency (SOL) (min)	19.8 ^a	(2.0-240.0)	19.5 ^a	(1.5-255.0)	- 0.3	$p = 0.499$
Awakenings (n)	18.0 ^a	(1-71)	18.0 ^a	(0-83)	0	$p = 0.974$
Wake After Sleep Onset (WASO) (min)	62.0 ^a	(5.5-355.5)	59.0 ^a	(8.0-333.0)	3.0	$p = 0.700$
Stage Changes (StCh) (n)	84.0 ^a	(20-206)	79.0 ^a	(26-216)	5.0	$p = 0.437$
REM latency (min)	110.8 ^a	(9.0-613.5)	93.0 ^a	(8.0-373.5)	17.8	$p = 0.010$
NREM 1 (%)	16.6 ^b	(12.9)	14.8 ^b	(9.9)	1.8	$p = 0.150$
NREM 2 (%)	42.5 ^b	(12.1)	39.7 ^b	(10.2)	2.8	$p = 0.023$
NREM 3 (%)	23.3 ^b	(9.8)	26.2 ^b	(9.7)	- 2.9	$p = 0.012$
REM (%)	17.6 ^b	(7.5)	19.3 ^b	(6.8)	- 1.7	$p = 0.037$

The central values (with range or sd) of sleep variables of all recordings in people who suffered a (secondarily) generalized seizure the day before the night of interest (*Daytime Seizure*) and those who were seizure free for at least 24 hours before night of interest.

In addition, the differences between the central values of both groups and the p -value, obtained using the unpaired t-test are shown (log-transformation was used in non-normally distributed variables before statistical analysis)

^a Central value = median (minimum – maximum)

^b Central value = mean (standard deviation)

Table 2: Central values of the sleep variables in individuals with one recording after daytime seizure and one recording after a seizure free period of at least 24 h.

Total recordings <i>N</i> = 23	<i>Daytime Seizure</i>		<i>Seizure Free</i>		Differences <i>Daytime Seizure</i> Minus <i>Seizure Free</i>	Paired T-test (2-sided)
TIB (min)	523.0 ^a	(470.5-743.5)	507.0 ^a	(440.0-584.0)	26.0	$p = 0.021$
TST (min)	431.5 ^a	(238.0-688.5)	447.0 ^a	(317.5-529.5)	- 10.0	$p = 0.574$
SE (%)	78.4 ^b	(17.26)	84.4 ^b	(8.95)	- 6.0	$p = 0.008$
SOL (min)	15.5 ^a	(3.5-45.0)	17.0 ^a	(5.0-97.5)	- 0.5	$p = 0.478$
Awakenings	16.0 ^a	(6-40)	18.0 ^a	(7-34)	- 1.0	$p = 0.725$
WASO (min)	53.5 ^a	(11.5-355.5)	51.0 ^a	(11.0-126.5)	22.8	$p = 0.004$
StCh (n)	81.0 ^a	(33-127)	80.0 ^a	(35-123)	2.0	$p = 0.962$
REM-Latency (min)	110.5 ^a	(9.0-485.0)	97.4 ^a	(8.0-261.5)	25.3	$p = 0.119$
NREM 1 (%)	15.4 ^b	(9.5)	13.1 ^b	(8.5)	2.3	$p = 0.183$
NREM 2 (%)	43.1 ^b	(12.1)	41.6 ^b	(9.7)	1.5	$p = 0.474$
NREM 3 (%)	23.1 ^b	(7.0)	25.5 ^b	(9.7)	- 2.4	$p = 0.176$
REM(%)	18.5 ^b	(8.6)	19.7 ^b	(5.7)	- 1.2	$p = 0.386$

The central values (range or sd) of the sleep variables in the recordings in individuals with both one recording after a seizure-free period of at least 24 hours and one recording during the night following a (secondarily) generalized seizure during the day.

In addition, the differences between the central values of both groups (with confidential interval) are shown. The p -value was obtained using the paired T-test (log-transformation was used in non-normally distributed variables before statistical analysis)

^a Central value = median (minimum – maximum)

^b Central value = mean (standard deviation)

Compared to people in *Seizure Free* group, people in the *Daytime Seizure* group were longer in bed (TIB, 15.5 min, CI_{95%}: 3.50 to 31.00, $p=0.001$), had a longer REM-latency (17.8 min, CI_{95%}: 3.0 to -29.0, $p=0.01$), significantly more light sleep (NREM 2(%):2.8%, CI_{95%}: 0.4 to 5.2, $p=0.023$) and less deep sleep (NREM 3(%): -2.9%, CI_{95%}: -5.0 to -0.6, $p=0.012$ and REM(%) (-1.7%, CI_{95%}: -3.3 to -0.1), $p=0.037$). After correction for age, TST was longer as well. The number of AEDs taken had no influence on the results. The localisation of the epileptogenic zone proved to be no significant confounder.

All 23 individuals in Study II (mean age 36.7 yrs) had partial epilepsy with a localization: temporal (20), frontal (1) or unclassified (2). Three individuals did not use AEDs, 6 only one AED, 12 two AEDs and 2 individuals three AEDs. Comparing sleep after a daytime seizure of sleep after a seizure free period of at least 24 h resulted in a longer TIB (26 min, $p=0.021$) and WASO (22.8min, $p=0.004$) and a higher sleep efficiency (SE) (6.0%, $p=0.004$) in the *Daytime Seizure* group. These results did not change after correction for age, number of AEDs, day of recording nor type of seizure as potential confounder.

DISCUSSION

In the cohort study (Study I) sleep in the group *Daytime Seizure* was characterized by a longer TIB and REM latency, and after correction for age as potential confounder TST as well. This was conform earlier findings^{6,7}. The differences in our study are small and therefore of dubious value in clinical practice. In the group *Daytime Seizure* also more NREM 2, less NREM 3 and less REM sleep were found than in the group *Seizure Free*. These findings correspond for duration of NREM 3 and REM sleep with an often cited case study of a woman with status epilepticus during the daytime³. A decrease of REM sleep is previously found in people with temporal lobe epilepsy². However we could not confirm this in our group which contains mostly people with partial epilepsy. Our study provided insufficient data to study the differences in sleep architecture in people with generalized epilepsy.

In the follow-up study (Study II) the individual was his own control, with sleep assessment after days with and without seizures, during the same long-term monitoring. We found longer TIB and WASO, resulting in a lower SE the night after a seizure. These findings were described in previous studies, but in these studies nocturnal seizures were no reason for exclusion^{6,8}. The distribution of sleep stages was similar for both situations. Correction for age, number of AEDs taken, and localization of the origin of the seizures did not change the results. Study II shows that the differences between night after a daytime seizure or after a seizure free day, when measured in the same persons are small. There were some limitations. The study took place in a tertiary-care epilepsy clinic. Mental retardation, which is often a co-morbid disorder in people with epilepsy, was reason for exclusion. This could bias the generalizability of the findings. Although the influence of the number of different AEDs was controlled for, change of medication during consecutive recordings was not included as variable in this study. As this was a retrospective study based on recording of sleep, judgments on the quality of sleep by the individuals themselves which provides insight in an important aspect of quality-of-life is lacking.

CONCLUSION

In people with epilepsy only small changes of the sleep architecture can be expected the night after a daytime (secondarily) generalized seizure.

ACKNOWLEDGEMENTS

This work was supported by the 'Christelijke Vereniging van Lijders aan Epilepsie' and a grant from UCB Pharma B.V.

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INCREASED PREVALENCE OF RESTLESS LEGS SYNDROME IN CROHN'S DISEASE.

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INTRODUCTION

Crohn's Disease (CD) has been associated with manifestations of other organ systems than the gastro-intestinal tract, affecting up to 36% of the patients with CD.

These extra-intestinal manifestations, include inflammatory arthropathies; osteoporosis; mucocutaneous, ophthalmologic and hepatobiliary manifestations; and anemia¹. Weinstock et al. suggested a new extra-intestinal manifestation, i.e. Restless Legs Syndrome (RLS)².

As it is not known whether the presence and severity of RLS in CD patients are associated with the severity and extension of CD and as neither is known how RLS influences the quality of life within patients with CD.

We investigated the prevalence of CD patients in our hospital population compared to that of the general population and whether the prevalence of RLS is higher in patients with more severe CD. Furthermore, the influence of RLS on the quality of life of CD patients was studied.

METHODS

Study Population

Patients were randomly selected from our database of CD patients. A cross-sectional study was performed by sending all patients a questionnaire. Patients were asked to complete this questionnaire and send it back. A control group was provided by requesting all patients to ask their partner or a friend, without CD, to complete and return an alternative questionnaire.

Contents of questionnaire

The questionnaire consisted of questions about the presence and severity of RLS, severity of CD, quality of life, comorbidity, lifestyle and current medication use. The diagnosis of RLS was made according to the four criteria provided by the International Restless Legs Syndrome Study Group³. Prevalence of RLS was defined as satisfying all four criteria of RLS when completing the questionnaire. The severity of RLS over the last four weeks was determined according to a Dutch translation of the International Restless Legs Study Group Rating Scale. To determine the severity of CD, questions based on the Harvey Bradshaw Index were used⁴. Questions about CD-related surgery, duration of CD and CD-related medication use, were used as alternative markers for the severity of CD. Quality of life, over the last four weeks, was established using the Dutch version of the RAND 36-item Health Survey⁵.

Statistical Analysis

Differences between CD patients and controls in categorical variables were tested for statistical significance using the Chi-square test. Continuous variables were checked for a normal distribution using the Kolmogorov – Smirnov test. Variables with a normal distribution were further analysed using the Independent-T test. Variables that did not have a normal distribution were further analysed using the Mann-Whitney U test. P-values <0.05 were considered statistically significant. Logistic regression was performed to establish whether CD increased RLS prevalence in a model adjusted for age, sex, smoking, use of alcohol, and daily intake of caffeine. β -coefficients were used to compute odd ratios. 95% confidence intervals with a lower limit >1 were considered statistical significant.

RESULTS

A total of 238 persons(49.6%) sent back the questionnaire; 153 patients with CD (63.8% response rate) and 85 controls (35.4% response rate). Nine patients were excluded because they were not diagnosed as having CD or there was doubt about the diagnosis, based on the questionnaire. In the control group 5 subjects were excluded, because they nonetheless were diagnosed as having CD or ulcerative colitis (UC). Eventually 144 patients with CD and 80 controls were included (table1).

The prevalence of RLS in patients with CD (25.7% ; $n = 37$) was higher than (12.5%; $n = 10$) in the control group ($p=0.02$). The crude prevalence odds ratio (POR) for RLS in patients with CD was 2.42 (95% CI: 1.13 – 5.18) compared to subjects without CD. After adjusting for age, sex, smoking, alcohol use and caffeine use, the POR of RLS was 2.48 (95% CI: 1.09- 5.62) for patients with CD compared to subjects without CD.

Mean severity of RLS did not differ significantly between patients with CD (12.43 ± 6.12 , $n=37$) and the control group (11.55 ± 2.59 , $n=10$) ($p=0.66$). Both scores indicate moderate severity of RLS.

In patients with CD, a statistically significant increased risk of RLS in patients using caffeine on a daily base and in patients with arthralgias was shown.

Within the control group 3/10 people with RLS used selective serotonin re-uptake inhibitors (SSRIs) compared to 4/68 people without RLS ($p=0.013$). This association was also found for persons using benzodiazepines (3/10 versus 3/68 respectively, $p=0.005$) and GABA-like medication (1/10 versus 0/68 respectively, $p=0.009$).

Within the group of CD patients no effect for medication use on the risk of RLS was found.

Measuring severity of CD by questions based on the Harvey Bradshaw index and CD-related surgery showed a significant association with a higher prevalence of RLS. Also severity of RLS was increased with a score of $13,8 \pm 6,7$ for patients with RLS that did have CD-related surgery compared to $9,2 \pm 2,3$ for patients with RLS who did not have CD-related surgery ($p=0,004$). Other markers for measuring severity of CD did not show significant association with a higher prevalence of RLS. Also, no associations were found between severity of CD and severity of RLS.

Quality of life scores are summarized in table 2. Mean physical functioning was significantly lower in patients with CD and RLS, compared to patients with CD but without RLS. Also within the control group there was a significant difference in mean physical functioning between persons with RLS compared to persons without RLS.

	<i>N</i> =	Crohn +	<i>N</i> =	Crohn -	P-Value
Age yrs ± SD	142	45.8 ± 15.7	77	48.6 ± 15.1	.20 NS
<i>(range)</i>		(18 - 90)		(23 - 88)	
Sex	142		76		
Male, % (n)		36.6% (52)		46.1% (35)	.18 NS
Female, % (n)		63.4% (90)		53.9% (41)	
Alcohol Use	144		77		
Currently, % (n)		63.2% (91)		71.4% (55)	.22 NS
Units/day ± SD	86	1.0 ± 0.96	51	1.24 ± 1.50	.38 NS
<i>(range)</i>		(0 - 5)		(0 - 10)	
Smoking					
Currently, % (n)	144	33.3% (48)	78	23.1% (18)	.11 NS
Units/day ± SD	47	11.08 ± 6.63	18	11.50 ± 6.87	.76 NS
<i>(range)</i>		(0 - 25)		(0 - 23)	
Caffeine Use					
Currently, % (n)	142	88.7% (126)	77	87.0% (67)	.71 NS
Units/day ± SD	126	3.94 ± 2.22	67	4.29 ± 2.16	.33 NS
<i>(range)</i>		(0 - 10)		(0 - 12)	
Medication, % (n)	140		78		
Risk medication					
- SSRI		9.3% (13)		9.0% (7)	.94 NS
- TCA		4.3% (6)		0.0% (0)	.06 NS
- Anti Psychotics		2.1% (3)		0.0% (0)	.19 NS
- Anti Histamine		7.6% (11)		10.3% (8)	.55 NS
- Dopamine antagonists		0.7% (1)		0.0% (0)	.45
Favourable effect					
- Opioids		7.1% (10)		2.6% (2)	.16 NS
- Anti Epileptics		2.1% (3)		1.3% (1)	.65 NS
- Benzodiazepines		3.6% (5)		7.7% (6)	.18 NS
Crohn +: patients diagnosed with CD					
Crohn -: persons not diagnosed with CD, control group					
N: number of patients / persons					
SD: Standard Deviation					
SSRI: Selective Serotonin Re-uptake Inhibitor					
TCA: Tricyclic Antidepressant					
NS: Not Significant					

Table 1. Baseline characteristics

<i>Quality of life</i>	<i>N</i>	<i>CD</i>		<i>N</i>	<i>Controls</i>		<i>P</i>
		<i>RLS +</i>	<i>RLS -</i>		<i>RLS +</i>	<i>RLS -</i>	
Physical functioning	143	70.6 ±24.7	80.5 ±19,7	79	72.5 ±18.3	81.8 ±24.4	.03
Social functioning	144	71.6(19.5)	73.9 ± 24.1	80	76.3 ± 19.0	81.1 ± 22.2	.32
Role limitations physical ¹	135	52.2 ± 37.1	63.0 ± 42.8	79	60.0 ± 35.7	76.4 ± 38.6	.07
Role limitations emotional ²	135	75.5 ± 36.1	76.9 ± 38.2	80	70.0 ± 48.3	86.0 ±31.0	.34
Emotional well being	141	68.7 ± 17.6	70.0 ± 17.5	79	70.8 ± 17.4	74.9 ± 14.6	.42
Energy / Fatigue	142	44.7 ± 19.1	51.5 ± 18.1	79	50.5 ± 25.2	61.4 ± 19.2	.11
Pain	143	75.7 ± 20.6	72.8 ±24.5	80	71.4 ± 21.6	82.0 ± 22.6	.09
General health perception	136	44.2 ± 16.6	50.5 ± 21.3	79	58.0 ± 20.7	66.7 ± 18.1	.35
Health change	144	50.7 ± 25.3	49.8 ± 22.4	80	50.0 ± 20.4	46.8 ± 17.5	.90

Table 2. Quality of life. CD: Crohn’s disease SD: standard deviation
N: number of patients / persons 1Physical: caused by physical health problems
RLS +: Restless Legs Syndrome present 2Emotional: caused by emotional problems
RLS -: Restless Legs Syndrome absent

DISCUSSION

In our population of CD patients, RLS was almost 2.5-fold more prevalent than in the control group. This difference was statistically significant also after adjusting for known RLS-risk factors. Severity of RLS did not differ between CD-patients with RLS compared to controls with RLS. A more severe course of CD seemed associated with a higher prevalence of RLS. Furthermore the presence of RLS had a negative effect on “physical functioning”, one of the subcategories for quality of life.

The prevalence ratios found in patients with CD (25.7%) and in the control group (12.5%) in this study are in line with previous research by Weinstock et al. They established a prevalence

of 30% within CD patients compared to 9% in the control group(2). Within our control group a relatively high prevalence of RLS was found, compared to other studies concerning prevalence of RLS in Western Europe. A Dutch epidemiological study of Rijsman et al. demonstrated a prevalence of RLS of 7.1% in people older than 50⁶.

This study is the first study to demonstrate a decrease in quality of life in patients with RLS compared with persons without RLS, mainly within the subcategory “physical functioning”. A negative impact of RLS on quality of life has previously been demonstrated⁷. However, since a more severe course of CD is associated with an increased prevalence of RLS, it is difficult to differentiate which part of the decrease in quality of life is associated with RLS and which part is associated with a more severe course of CD.

The reason why RLS is increased in CD is unknown. Bacterial overgrowth in CD is associated with an increased production of interleukine-6, which increases the production of Heptacidin. This protein influences iron transportation, which could induce shortage of iron in the central nervous system, associated with RLS². Another explanation could be a possible linkage between a leaky gut and central nervous system diseases. Several studies have shown that diseases characterized by an increased permeability of the intestine (e.g. CD) are associated with CNS disorders including depression, autism and migraine⁸⁻¹¹. This possible association between intestinal diseases and CNS disorders could be explained by leakage of lipopolysaccharides from the intestinal lumen into the circulation (leaky gut), resulting in the release of pro-inflammatory cytokines. These cytokines can act on relevant receptors of the CNS¹².

CONCLUSION

Because of its increased prevalence, as far as can be concluded from a 35 % response rate, awareness of the presence of RLS CD patients is recommended, not least because the syndrome seems to be often underdiagnosed and poorly treated, while treatment is often successful¹³.

Future RLS research is also warranted in other patients with chronic diseases, i.e. ulcerative colitis and rheumatic diseases. In these patients, etiological factors contributing to RLS and the effects of RLS on quality of life can be further investigated. This could be of clinical importance by focusing on effectiveness of RLS treatment and to improve quality of life in these patients.

The hypothesis that RLS could be the consequences of a leaky gut could be investigated by measuring the permeability of the gut, using the glucose mannitol test¹⁴.

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AMBULATORY AUTOMATED AUDITORY PARTIAL SLEEP DEPRIVATION AFFECTS SUBJECTIVE SLEEPINESS WITHOUT AFFECTING SLEEP MACRO STRUCTURE

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INTRODUCTION

Sleep plays a crucial role in our daily lives since its duration, timing and depth are considered to be critical for health and well-being.¹ Sleep has been identified as a major factor in physical functioning, metabolic regulation, brain recuperation processes, emotion regulation, cognitive functioning, learning and memory consolidation.² Given this role of sleep, it is no surprise that a lack of sleep can have major health consequences. A direct consequence of short sleep duration and poor sleep quality is increased daytime sleepiness and lower alertness, which in turn contributes to occupational and medical errors, workplace injuries, impaired driving, and motor vehicle accidents.¹ It has also been shown that insufficient sleep is associated with increased risk for the development of psychiatric disorders, heart disease, hypertension, glucose intolerance, obesity, and diabetes.¹ Most of the evidence on the relation between sleep deprivation and health status in men is derived from correlation studies, not allowing for causal interpretation or derived for experimental animal research. In recent years, several studies have experimentally restricted or disrupted sleep for up to 4 or 5 days, but merely in a setting in which it was needed to attend to a sleep laboratory to be subjected to the deprivation. In order to systematically study the causal effects of sleep deprivation in men under real life conditions, a standard experimental method should be in place to test its effects. In this study we explore the use of an ambulatory system to selectively deprive deep sleep in the habitual sleep setting; the bedroom at home. We aimed to selectively deprive deep sleep in an automated way using auditory stimuli and test its efficacy in altering objective and subjective sleep.

METHODS

20 subjects, aged 18 - 53 (Mean \pm SD: 24.5 \pm 7.02 yr; 10 male), all without subjective sleep complaints (HSDQ³ < 2.02, PSQI⁴ < 6) participated in the study.

Sleep data were collected using the wireless Zeo system (Zeo Inc., Newton, USA). This system is validated for measuring sleep in healthy adults (Shambroom et al., 2012), quantifying sleep based on the recording of a single bi-polar channel located at the forehead (EEG position Fp1-Fp2) using a headband. A four stage classification of sleep in 30 second epochs is automatically derived and classifies the data into Wakefulness, REM sleep, Light sleep or Deep sleep. Total sleep time (TST), time in bed (TIB), sleep period time (SPT; defined as time available for sleep after sleep onset), sleep efficiency (SE, defined as TST/TIB), and the percentage of each sleep stage (defined as time spent in a certain sleep stage relative to the time in bed), as well as frequency of sleep stage shifts/TST and sleep stage shifts in total, were calculated.

Subject sleep was evaluated within 15 minutes after the final awakening using the Groningen Sleep Quality Scale (GSQS)⁶ and the Global Vigor & Affect Scale (GVA)⁷.

For the purpose of selective auditory deep sleep deprivation, the open source computer program ZeoScope (<https://github.com/dancodru/Zeo-Scope>) was used. The ZEO classified the forehead signal immediately into a sleep stage and this served as input for the ZeoScope. Whenever deep sleep was classified, a 30 sec., 1000Hz tone with a gentle fade-up at the start ranging from 37 dB(A) to 55 dB(A) maximum, was played. See figure 1 for the setup.

Automated auditory partial sleep deprivation was applied using a cross-over, placebo controlled, single blind design. The study consisted of two nights - one deep sleep deprivation night and one control night. Participants were informed that during both nights sounds would be played, and that for both nights the sounds might go unnoticed. Participants were instructed on the use of the system prior to the 2 test nights. At both test nights, all equipment were self-installed by the participants and the subjects had to follow identical procedures. To achieve a single blind placebo condition, the audio settings of the ZeoScope was switched according to the condition (i.e. audio on/off) by the researcher during backup of the Zeo data between the 2 nights. The control night (CN) and the deep sleep deprived night (SWSD) were statistically compared using a paired sample t-test, $\alpha=5\%$, 1-sided.

The study was approved by the Internal Committee of Biomedical Experiments (ICBE) of Philips and informed consent was signed by all subjects.

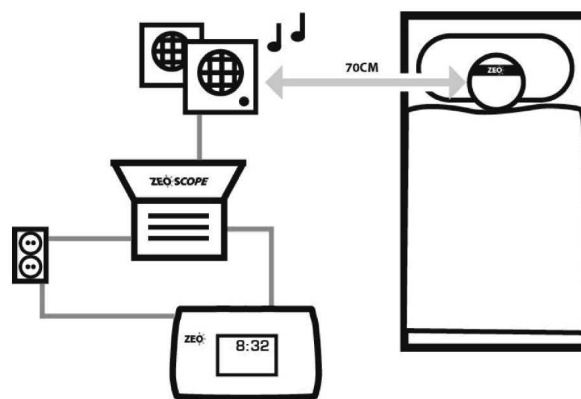


Figure 1. Technical setup of the ambulatory automated auditory partial sleep deprivation system. The Zeo was connected to an HPmini notebook (Hewlett-Packard Company, California, USA) on which the ZeoScope extension program ran. The HPmini notebook was used to send the auditory signal via USB to speakers located at a distance of 70cm beside the bed, approximately at the same height as the pillow.

RESULTS AND DISCUSSION

The evaluation of the subjective sleepiness in the morning showed a lower subjective sleep quality after deep sleep deprivation on the GSQS ($p = .02$) and a more negative affect after sleep deprivation on the GVA, ($p = .026$) (see Table 1).

The analyses of the objective sleep parameters showed a clear trend towards less deep sleep during SWSD ($p = .06$). Other than this, the deep sleep deprived condition, as compared to the control night, showed hardly any disturbance of the macro structure of sleep (see Table 2).

To our surprise, the number of sleep stage transitions was reduced in the SWSD condition, as compared to the CN condition ($p = .03$), mostly determined by a reduced number of deep sleep – light sleep transitions ($p = .01$). However, only in the SWSD condition, transitions from deep sleep to wake were observed.

Table 1. Mean (\pm S.E.) of GSQS and GVA, for each night separately and statistical comparison between nights.

<i>Questionnaire</i>	<i>SWSD</i>	<i>CN</i>	<i>t</i>	<i>df</i>	<i>P</i>
	(<i>Mean \pm S.E.</i>)	(<i>Mean \pm S.E.</i>)			
GSQS	4.33 \pm 1.08	1.5 \pm .50	2.32	11	.02
GVA vigor	54.54 \pm 6.65	60.80 \pm 7.34	-.90	9	.19
GVA affect	68.41 \pm 4.36	74.14 \pm 3.96	-2.20	10	.02

Note. SWSD = slow-wave sleep deprivation; CN = control night; M = Mean; S.E. = Standard Error of Mean; t = t-value; df = degrees of freedom.

Table 2. Mean (\pm S.E.) of Zeo sleep parameters for each night separately and statistical comparison between nights.

	<i>SWSD</i>	<i>CN</i>	<i>t</i>	<i>df</i>	<i>P</i>
	(<i>Mean \pm S.E.</i>)	(<i>Mean \pm S.E.</i>)			
Wake % of TIB	4.11 \pm .77	3.85 \pm .65	.44	11	.33
Light Sleep % of TIB	54.62 \pm 1.75	53.67 \pm 2.92	.38	11	.35
Deep Sleep % of TIB	15.46 \pm .96	18.07 \pm 1.53	-1.74	11	.06
REM Sleep % of TIB	25.23 \pm 2.28	23.75 \pm 1.59	.78	11	.22
Undefined % of TIB	.56 \pm .44	.67 \pm .67	-.12	11	.45
TST (minutes)	447.0 \pm 12.24	433.29 \pm 22.63	.58	11	.28
TIB (minutes)	469.46 \pm 13.90	472.41 \pm 18.79	-.19	11	.42
SPT (minutes)	461.75 \pm 12.96	463.33 \pm 17.90	-.09	11	.46
SE (%)	95.31 \pm .67	95.52 \pm .77	-.26	11	.40

Note. SWSD = slow-wave sleep deprivation; CN = control night; M = Mean; S.E. = Standard Error of Mean; t = t-value; df = degrees of freedom; TST = Total sleep time; TIB = Time in bed; SPT = sleep period time; SE = sleep efficiency.

Table 3. Mean (\pm S.E.) of sleep stage shifts for each night separately and statistical comparison between nights.

	<i>SWSD</i>	<i>CN</i>	<i>t</i>	<i>df</i>	<i>P</i>
	(<i>Mean \pm S.E.</i>)	(<i>Mean \pm S.E.</i>)			
Transition Total	43.08 \pm 2.99	52.00 \pm 5.72	-2.05	11	.03
Deep – Undefined	.07 \pm .07	.00 \pm .00	1.0	11	.17
Deep – Light	1.5 \pm .27	2.11 \pm .21	-2.58	11	.01
Deep – REM	.10 \pm .06	.24 \pm .06	-1.29	11	.11
Deep – Wake	.083 \pm .03	.00 \pm .00	2.8	11	.01
Deep-Light & Deep-Wake	1.58 \pm .27	2.11 \pm .21	-2.13	11	.03
REM, Deep, Light-Wake	.57 \pm .14	.58 \pm .16	.14	11	.45

Note. SWSD = slow-wave sleep deprivation; CN = control night; M = Mean; S.E. = Standard Error of Mean; t = t-value; df = degrees of freedom.

The results support the view that deep sleep deprivation impairs subjective sleep quality and impacts affect negatively. In addition, this study shows that the method used is effective in achieving sleep deprivation at a subjective level. On the macro structure of sleep, hardly any effect of sleep deprivation was observed. These results are in line with previous findings of Van der Werf et al.⁸ who reported that the use of an automated mild acoustic sleep-perturbation approach to induce a mild sleep disruption, using a full PSG setup, mostly affected SWA, but did hardly impact sleep efficiency, total sleep duration and the number of sleep state transitions.

Applying louder acoustic stimuli might be used to result in a stronger effect on sleep, both on the subjective and objective level. Of note is that the current method of mild sleep deprivation is rather elegant by forcing people to a lighter sleep stage rather than to wake.

CONCLUSIONS

The applied ambulatory automated mild acoustic sleep perturbation approach affected subjective sleepiness without affecting sleep macro structure. This method can be easily applied for field studies to test the effects of disturbed sleep. Increasing the volume of the auditory intervention might be used to get a more fierce sleep disruption.

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RECHARGE YOURSELF; RECHARGE INTERVENTIONS DURING FESTIVAL- INDUCED SLEEP LOSS

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INTRODUCTION

There are instances where we voluntarily deprive ourselves of sleep for entertainment reasons. Night festivals and parties are a common commodity among the younger generations, and in the Netherlands not only dance parties last throughout the night, but also museum and art exhibitions (Museumnacht, Kunst de Nacht), movie festivals (Pluk de Nacht), and other cultural arrangements (Culturele Nacht, Discovery Festival) occur during night time. Though often being intrinsically activating, such a night without sleep can have negative effects on sleepiness and alertness. The buildup of sleepiness impairs the experience, and the public could benefit with a recharge intervention. In worst case scenario, it might also lead to increased aggression [1] during the event and traffic incidents [2] after the event.

We studied the impact of an activating, or recharging, intervention that could counteract the buildup of sleepiness and increase alertness during a nighttime festival event. A placebo controlled, within subject and between groups experimental protocol was set up to detect the effects of four different recharging interventions: bright light, powernap, caffeine, or decaffeinated coffee. Secondly, we wanted to provide festival participants an insight to scientific sleep research by giving them the possibility to participate in a research protocol. A protocol, albeit here shorter and during ongoing festival activities, could have been executed in a real scientific experiment.

METHODS

Participants visited the Recharge Bar during a nighttime science and art festival in Eindhoven (Discovery, Eindhoven 2012; <http://www.discoveryfestival.nl>). Enrollment to the Research Bar was open between 20:30 and 02:00, and participants could start at any moment, only restricted by the availability of test-devices. Participants were randomly assigned to one out of three recharge options, a 15 minutes nap opportunity, a 15 minutes light intervention or a free coffee or espresso. The third recharge option was placebo-controlled, i.e. participants received either a cup of coffee with caffeine, or a decaffeinated cup of coffee. The recharge options were located in distinct chambers, separated by light blocking curtains. In the nap condition participants spent their time lying on a bed, wearing noise cancelling head phones and with the option of using blankets. The area was dimly lighted with red light. In the light intervention, participants were seated in an area lighted by 5 Philips Energy lights as well as a Strato light (Philips Electronics, Amsterdam, the Netherlands). The area was cooled to compensate for the heat production of the lamps. In the coffee conditions, participants were served their coffee at the espresso bar, located next to the recharge bar, where they stayed for 15 minutes.

Participants completed a 5 minute psychomotor vigilance task (PVT) [4, 5], a computerized version of the Global Vigor and Affect scale (GVA; GV and GA) [3] the Karolinska Sleepiness Scale (KSS) [6], and the 4-point Effort to Stay Awake scale immediately before and after the recharge intervention. During the task subjects wore headphones and main stream pop music was played, in order to minimize the effects of environmental noise.

All variables were tested with independent t-tests for group differences before the intervention and paired t-tests were used for analyzing intervention effects ($\alpha = 0.05$, two sided). Analyses were performed with SPSS 17 (IBM SPSS, Armonk, USA). The mean reaction time over the 5 minute period of the PVT and the standard variation of the reaction time over the 5 minute period of the PVT was analyzed.

RESULTS

111 participants were enrolled in the study, of whom 96 completed the two test sessions. The mean (\pm SD) age of the 96 participants was 33.1 (\pm 30.0) years and 40 (41.7%) were female. There were no significant differences reported between the intervention groups in cumulative alcohol (all $p > 0.43$) or caffeine (all $p > 0.26$) intake before the test. There were no differences in sex distribution (χ^2 $p > 0.16$) or age (all $p > 0.16$) between groups.

Subjective Sleepiness

None of the intervention groups scored significantly different on the KSS (all $p > 0.08$) or on the Effort to Stay Awake (all $p > 0.61$) before intervention. Participants felt significantly less sleepy after intake of a caffeinated cup of coffee as reflected by the KSS scores (5.2 ± 2.0 versus 3.9 ± 2.0 , $p = 0.01$). A significant reduction in sleepiness, albeit to a much lesser extent, was also found after intake of a decaffeinated cup of coffee (5.7 ± 1.9 versus 5.13 ± 2.5 , $p = 0.05$). Neither Bright Light nor the 15 minute nap produced any sleepiness reducing effects (figure 1). Participants indicated to have less trouble to stay awake after drinking a caffeinated cup of coffee, as reflected by the Effort to Stay Awake score (1.8 ± 0.7 versus 1.6 ± 0.7 , $p = 0.04$).

Subjective Vigor and Affect

The groups did not score significantly different on the GA before intervention (all $p > 0.45$), but there was a significant difference between the caffeine and decaf group on the GV (63.2 ± 21.1 versus 49.9 ± 19.3 , $p = 0.03$). People felt significantly more vigorous after drinking a caffeinated cup of coffee (63.2 ± 21.1 versus 72.2 ± 17.1 , $p = 0.01$), but showed no significant changes in affect ($p = 0.85$).

Bright Light, a 15 minute nap, or drinking decaffeinated coffee did not produce significant changes in vigor or affect.

PVT

There were no significant differences in the mean reaction time (all $p > 0.21$) or reaction time variation (all $p > 0.06$) between groups before interventions. Neither the PVT mean reaction time (all $p > 0.09$) nor the reaction time standard variation (all $p > 0.05$) changed significantly after the interventions.

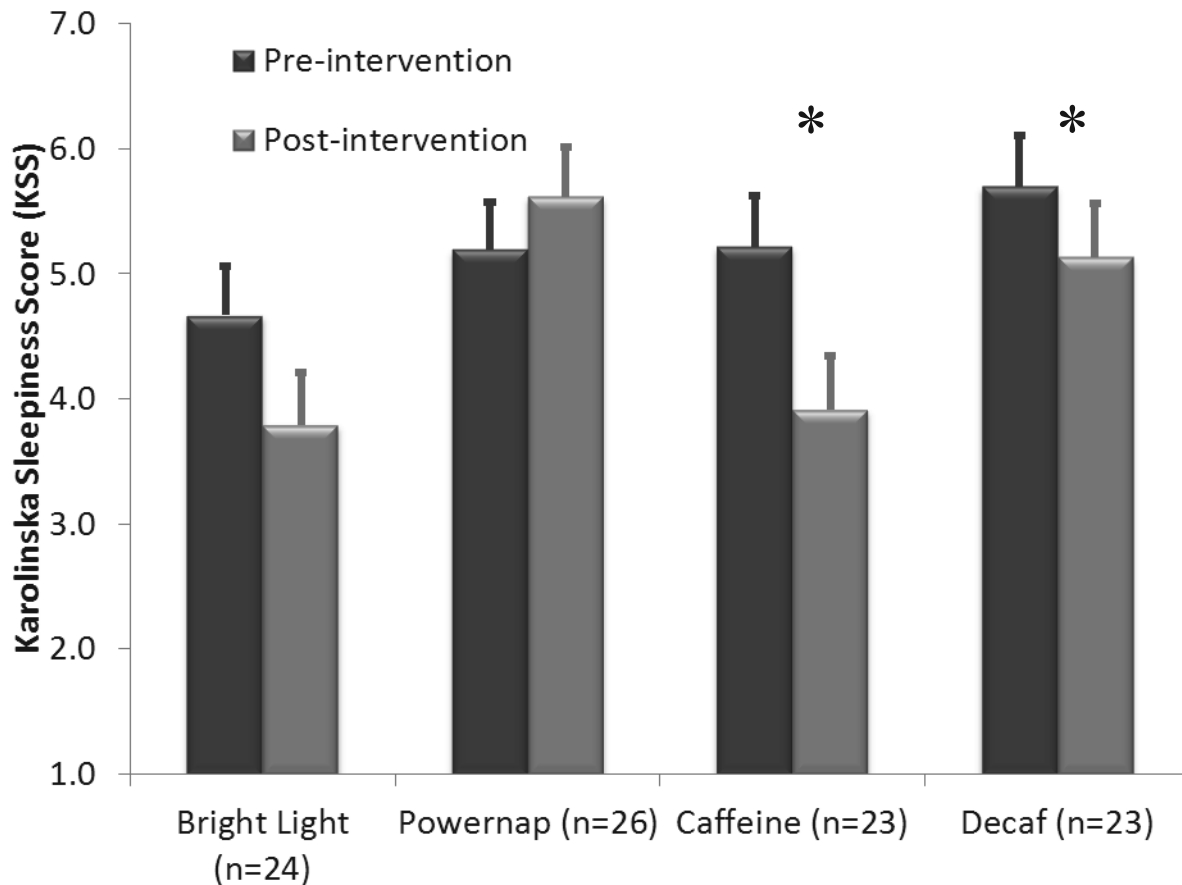


Fig. 1 Average KSS score before (grey) and after (black) intervention. Significant differences ($p < 0.05$) are marked with a star. Values are presented as averages \pm S.E.M.

DISCUSSION AND CONCLUSION

The current study shows that during a festival night, a caffeine intervention decreases subjective sleepiness and increases vigor on short term, while this was not evident in the objective PVT measures. The bright light and nap intervention did not change neither subjective nor objective parameters significantly.

There was a significant reduction of the KSS scores in the decaf intervention. This could be the result of the expectancy of the participants towards the activating effects of coffee. Previously, bright light has been shown to have an activating effect during night time [7]. The results of the present study can not confirm these effects. Yet, there was a trend in the bright light condition for increased vigor (GV $p = 0.06$) and a reduced feeling of sleepiness (KSS $p = 0.07$). It could be that the timing of the light intervention was too early, as light interventions have been reported to be more effective in the early morning [8]. Potentially, a combination intervention of caffeine and bright light might prove more effective [8]. We did not establish whether people actually fell asleep in the nap condition. It is possible that participants only got the chance to rest, and not sleep, which could influence the slim effects of this condition. In addition, and this holds true for all interventions, it must be taken into account that they were implemented continuously to participants over a timespan of about five hours. Small effects which are time dependent would not have been detected in this protocol set-up.

Although we controlled for alcohol and caffeine intake before the start of the study, we did not check for nicotine intake or the use of any other drugs. It is possible that these factors may

have varied between the intervention groups. Furthermore, the sound level during the festival was loud and changed over time. In order to minimize the effects of environmental, mainstream pop music was played during testing.

To conclude, a recharge intervention during a nighttime festival is possible; the caffeine intervention successfully decreased subjective sleepiness and increased vigor in adults attending a late night festival. In contrast, bright light or a 15 minute nap do not appear to be effective to counteract those feelings of sleepiness. Participating in an experiment during festivals serves an educational function, showing that science is possible everywhere and can be fun to do.

Acknowledgments

The authors thank Edith Dourleijn, Raymond van Ee, Marieke van der Hoeven, Björn Vlaskamp for their support; Philips Lighting for contributing the Strato Light and Philips Lifestyle Entertainment for their contribution of the headphones; Annemiek Swinkels of Straffe Bak for the coffee/espresso and the Discovery Festival for the decoration set up.

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COMPARISON OF THE SPANE AND PANAS SCALES FOR MEASURING SELF-REPORTED AFFECT DURING TOTAL SLEEP DEPRIVATION

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INTRODUCTION

Sleep loss leads to changes in self-reported affect and mood. In a study involving sustained sleep restriction to 4 hours per day, decreases in positive affect were found.¹ In two studies of total sleep deprivation (TSD), decreases in positive affect were observed as well^{2,3}; one study also reported increases in negative affect.³ The present study used the Scale of Positive and Negative Experience (SPANE) and the Positive and Negative Affect Schedule (PANAS) to measure subjective positive affect (PA) and negative affect (NA) during sleep deprivation.

The SPANE is a 12-item questionnaire with six questions measuring PA and six questions measuring NA. Each item is scored on a scale of 1 (very rarely or never) to 5 (very often or always). The total PA and NA scores on the SPANE each range from 6 to 30.⁴ The PANAS is a 20-item questionnaire with ten questions measuring PA and ten questions measuring NA. Each item on the PANAS is scored on a scale of 1 (very slightly or not at all applicable) to 5 (extremely applicable to the way the individual is feeling). The total PA and NA scores on the PANAS each range from 10 to 50.⁵ We examined changes in PA and NA during TSD and compared the results obtained with the two scales.

METHODS

Twenty-six healthy subjects (ages 22–37; 10 females) spent 6 consecutive days and nights in a sleep laboratory. All subjects had two baseline days with 10 hours time in bed (TIB) for sleep at night (22:00–08:00). They were then randomized to a 62-hour TSD condition (n=13) or a control condition with 10 hours TIB (22:00–08:00; n=13). All subjects subsequently had two recovery days with 10 hours TIB (22:00–08:00).

At 2-hour intervals during most of the scheduled waking periods in the study, subjects filled out a paper-and-pencil version of the SPANE, performed a battery of cognitive tests, and then filled out a computerized version of the PANAS. There were 42 test times in the TSD condition and 32 in the control condition. Each subject was asked to fill out the questionnaires according to how they felt at that moment.

Scores on the PA and NA subscales of both the SPANE and the PANAS were analyzed using mixed-effects analysis of variance (ANOVA) with a fixed effect of time and a random effect on the intercept over subjects. In these analyses, F tests for the effect of time were performed to assess the statistical significance of temporal changes. Additional analyses included mixed-effects ANOVAs with fixed effects of time, condition (TSD or control) and their interaction, or fixed effects of time, affect dimension (PA or NA) and their interaction, and a random

effect on the intercept over subjects. In these latter analyses, F tests for interaction were performed to assess the statistical significance of differential temporal changes between the TSD and control conditions or between PA and NA. For testing the interaction of time by condition, only test bouts included in both the TSD and control conditions were used.

One subject did not complete the last PANAS of the study and another subject did not complete the full set of NA items in one PANAS, resulting in a few missing data points. Our statistical analyses did not require imputation of these missing data.

RESULTS AND DISCUSSION

Figure 1 shows the group-average data for PA and NA as measured with the SPANE and PANAS in the TSD and control conditions of the study. Table 1 shows the results of statistical testing.

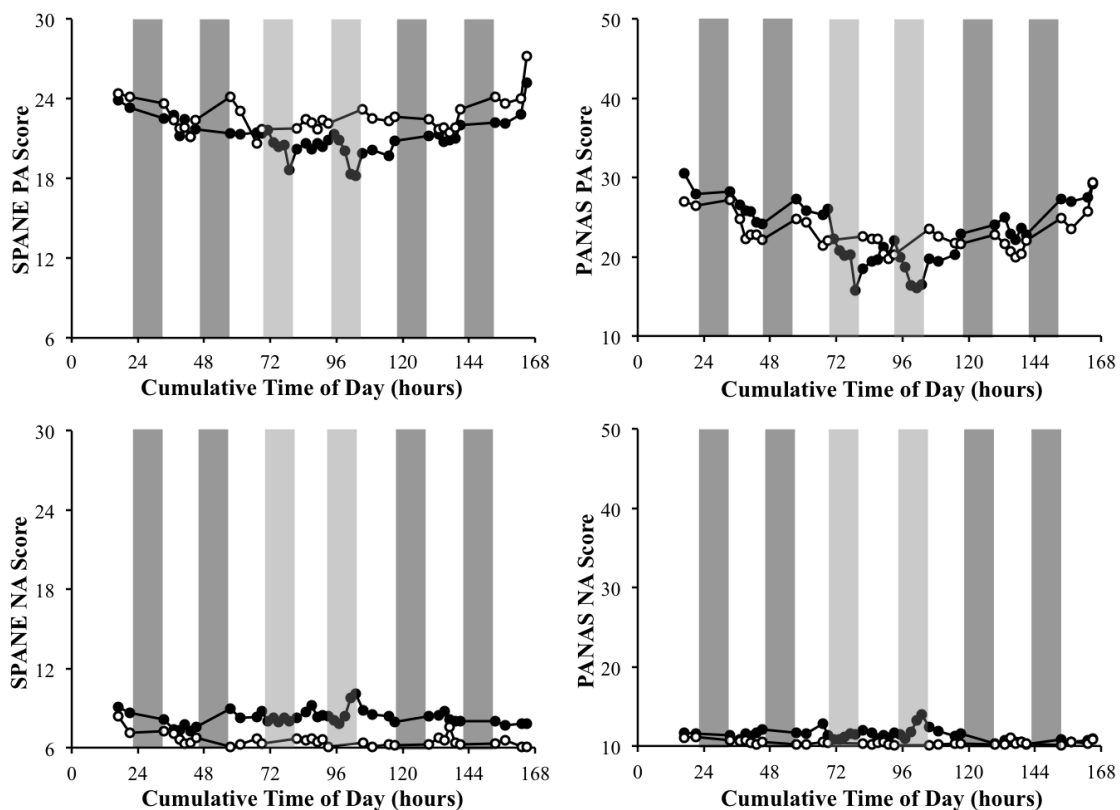


Figure 1. Group-average data for positive affect (PA; top panels) and negative affect (NA; bottom panels) on the SPANE (left) and PANAS (right) as a function of cumulative time of day in the study. Curves show the total sleep deprivation condition (closed circles) and the control condition (open circles); tick marks indicate midnight. Dark gray bars represent TIB periods in both the TSD and control conditions. Light gray bars represent additional TIB periods in the control condition only.

For PA, there were significant effects of time for the SPANE and for the PANAS in the TSD condition and in the control condition. These results reflect marked decreases in PA during the TSD period – especially during the nights and early mornings. Although there were also decreases in PA during the middle days of the study in the control group, these were not as pronounced as in the TSD condition, as evidenced by significant interactions of time by condition.

For NA, there were likewise significant effects of time for the SPANE in the TSD condition and in the control condition. There was also a significant effect of time for the PANAS in the TSD condition, but not in the control condition. These results reflect that TSD was associated with minor increases in NA, as observed on both the SPANE and PANAS. However, these same increases were not seen in the control condition, as evidenced by significant interactions of time by condition.

The effects of the study on self-reported affect were more pronounced for PA than for NA on both the SPANE and the PANAS – see Figure 1. This observation was corroborated by significant interactions of time by dimension (PA versus NA), although in the TSD condition this interaction showed only a trend for the SPANE – see Table 1.

Table 1. Statistical effects of time, and interactions of time by condition and time by PA versus NA, as derived using mixed-effects ANOVA. *df* = degrees of freedom.

<i>Dimension</i>	<i>Instrument</i>	<i>Condition</i>	<i>F</i>	<i>df</i>	<i>P</i>
PA	SPANE	TSD	3.5	41, 492	<0.001
		control	3.9	31, 372	<0.001
		TSD versus control	3.1	31, 864	<0.001
	PANAS	TSD	9.4	41, 492	<0.001
		control	6.2	31, 371	<0.001
		TSD versus control	3.9	31, 863	<0.001
NA	SPANE	TSD	1.6	41, 492	0.017
		control	3.5	31, 372	<0.001
		TSD versus control	2.3	31, 864	<0.001
	PANAS	TSD	2.4	41, 491	<0.001
		control	1.3	31, 371	0.14
		TSD versus control	1.8	31, 862	0.004
PA versus NA	SPANE	TSD	1.4	41, 996	0.071
		control	1.8	31, 756	0.005
	PANAS	TSD	5.1	41, 995	<0.001
		control	2.0	31, 754	0.001

Across the TSD and control conditions, SPANE PA covaried significantly with PANAS PA ($F_{1,934}=242.8$, $P<0.001$) and SPANE NA covaried significantly with PANAS NA ($F_{1,933}=28.6$, $P<0.001$). The overall correlation between SPANE and PANAS was 0.55 for PA and 0.30 for NA. Thus, changes in PA and NA measured with the SPANE paralleled those measured with the PANAS fairly well. The correlation between the two scales was higher for PA than for NA, but this observation should be interpreted with caution, as there was more variability across the study (and thus greater potential for correlation between the two scales) for PA than for NA.

CONCLUSIONS

In this laboratory study, TSD caused a substantial drop in PA, especially at night and in the early morning, as observed on the SPANE as well as on the PANAS. In line with research showing independence of the positive and negative dimensions of affect,⁴ the changes in PA during TSD were only marginally mirrored by changes in NA.

The relatively small magnitude of changes in NA during TSD would suggest that the subjects in our study did not experience the sleep deprivation period as particularly aversive. However,

in a recent laboratory study by another group,³ which employed the Mood Scale II,⁶ subjects exposed to TSD reported more substantively increased NA besides reduced PA. Subjects in the control condition of the study reported increased intensity of feelings of depression.³ This suggests that increased NA may have been a symptom associated with the laboratory circumstances of that particular study per se, regardless of condition assignment. Findings of impaired performance in the absence of sleep loss reported by the same group,⁷ not normally seen in the control conditions of sleep deprivation studies in other laboratories, would seem to support this explanation.

It is noteworthy that our findings contrast with reported changes in affect among medical residents exposed to sleep loss,⁸ who have been found to exhibit both reduced PA and increased NA on the PANAS. The difference in the effect on NA may be related to the fact that the subjects in our study, unlike most medical residents, underwent sleep deprivation by voluntary choice alone.

ACKNOWLEDGMENTS

We thank the staff of the Sleep and Performance Research Center at Washington State University for conducting the laboratory sleep deprivation study. The research was supported by NIH grant HL105768 and FAA grant DTFAAC-11-A-00003.

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RESTLESS LEGS SYNDROME OR WILLIS-EKBOM DISEASE: WHAT IS IN A NAME?

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For many articles on Restless Legs Syndrome (RLS) published in the last two years, one can see a change in the name of the disorder from RLS to Willis-Ekbom Disease (WED). This new name for the disorder is chosen by the International Restless Legs Syndrome Study Group (IRLSSG) during the meeting of the World Association for Sleep Medicine (WASM) in Quebec in September 2011 and is endorsed by some national patient organizations. There are however, still some remarks on WED as the new name which is apparently promoted by the Journal. These remarks concern the “D” of disease and the change from RLS to WED itself.

Admittedly in the last decades, major progress is made in understanding the disorder from various points of view, ranging from epidemiology and diagnostic criteria to pathophysiology and therapy. As to pathophysiology, many theories are available: for example genetic abnormalities, dopaminergic dysfunction, disorders of iron metabolism, a role for the central opiate system, etc. No one knows exactly what happens and which regions in the central or even peripheral nervous system are the real culprits. In a recent article on the role of inflammation and the immune system by Weinstock et al., another theory is given¹. The article provides again a new point of view, but as such only expands the range of possibilities without giving firm proof how to integrate all knowledge to a clear pathophysiological principle. As the term disease suggests at least a common and understandable idea about pathophysiology of the disorder, one can only decide that RLS is still a disorder with no uniform ideas on its origin and as such does not deserve the “D” of disease as suggested by WED.

In the discussion on change of the name of the disorder another issue has been important. This has nothing to do with science, but is meant to circumvent and hopefully end, nasty discussions about restless legs. In many countries, people, including physicians and insurance companies, have made the disorder a laughing matter or even not to be taken seriously. The arguments for such opinions are: patients complain about strange feelings which can often not be described in detail, moving of the legs is thought to be harmless, prevalence figures are too high to be true, there is no uniform idea how therapy works, etc. We all know that these points are not true or can be unnerved at least partially.

So, regarding the change of the name, we are talking not about science, but about promoting the disorder. In the opinion of some experts and patient organizations, the name change should stop jokes and ridiculing the disorder. Of course, it does not. The same points remain and -worse- what had been built up over the years about what we know about RLS, will be lost when we are talking about what will be seen as the new disorder WED. There is another point. In nearly all fields of medicine there is a strong tendency to name well described diseases without using the name of people who were first to describe the disorder. Doing the opposite looks outdated. Furthermore, for most physicians the name Willis is associated with the circle of Willis, which has nothing in common with RLS. Only a few insiders know that the same Willis may have described symptoms of RLS. Ekbom's disorder has been well known in the medical world and is probably part of a psychiatric syndrome. The same few insiders know that Ekbom had a major influence on the description of symptoms of RLS, but this is not enough. Finally, the following anecdote out of everyday practice gives

another point of view: the patient has all symptoms of RLS and is told that she has Willis-Ekbom Disease. She is flabbergasted and says: “What? Do I have the disease of Willis-Sexbom(b)? Maybe this is the next laughing matter around RLS.

Willis-Ekbom Disease is not a good choice and it will take much energy to implement this new name. It is probably better to spend this effort in explaining what Restless Legs Syndrome really is.

ACKNOWLEDGEMENTS

This text was previously published as a Letter to the Editor of Sleep Medicine ²

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SLEEP-WAKE
Research in The Netherlands

Annual Proceedings of the NSWO
Volume 24, 2013

Abstracts

IS A QUESTIONNAIRE A USEFUL SCREENING METHOD FOR SLEEP APNEA IN STROKE?

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ABSTRACT

Introduction: Sleep apnea syndrome (SAS) is a highly prevalent sleep disorder in stroke patients and is associated with decreased functional recovery, increased risk of recurrent stroke and mortality. Screening for SAS in stroke rehabilitation settings is limited, despite the high prevalence. Standard self-report symptom questionnaires for SAS, such as the Berlin Questionnaire, are often administered, but were found to be of limited diagnostic value in the stroke population. The objective of this study was to identify predictive self-report symptoms, socio-demographic and clinical variables for the detection of stroke patients with a high probability of SAS.

Methods: 438 stroke patients, admitted to the neurorehabilitation unit of Heliomare rehabilitation center, were assessed with a SAS questionnaire and underwent pulse oximetry to determine their oxygen desaturation index (ODI). Patients with an ODI ≥ 15 were classified as having a high probability of SAS. The SAS questionnaire included self-reported symptoms (e.g. snoring, apneas, falling asleep during daytime, fatigue, concentration loss and mood changes), socio-demographic (e.g. age, gender and smoking) and clinical variables (e.g. body mass index (BMI), stroke type and blood pressure). With univariate logistic regression analysis, the associations between potential questionnaire items and ODI ≥ 15 were examined. Significant variables (p -value ≤ 0.20) were selected for a backward multivariate logistic regression.

Results: Thirty-one percent of the stroke patients had a high probability of SAS (ODI ≥ 15). The prediction model for ODI ≥ 15 consisted of the self-report symptoms apneas and falling asleep during daytime, socio-demographics characteristics age and male gender, and the clinical variable BMI (see Table).

Conclusion: A high probability of SAS is common in stroke patients and is insufficiently predicted by self-report symptoms alone. Socio-demographic and clinical variables improve the diagnostic value of the questionnaire. Therefore, socio-demographic and clinical variables should be incorporated in SAS self-report symptom questionnaires to improve SAS screening in stroke rehabilitation.

Table: Multivariable model with predictors of ODI ≥ 15 . The odds ratio, 95% confidence interval and p -value for the predictive values are presented

<i>Variables</i>	<i>OR</i>	<i>95% CI</i>	<i>p-value</i>
Age	1.04	1.01-1.07	.002
Gender	2.32	1.39-3.85	.001
BMI	1.17	1.10-1.24	<.001
Self reported apneas	2.32	1.23-4.37	.009
Falling asleep during daytime	1.81	1.12-2.91	.015

OR = odds ratio; CI = confidence interval

Presented at the second international Sleep and Breathing conference in Berlin, April 12th 2013.

AUDITORY SENSORY MEMORY AND MISMATCH NEGATIVITY DEFICITS IN RATS: ASSESSMENT OF DRUGS WITH PRO-COGNITIVE POTENTIAL

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Objectives: Auditory event related potentials (AEPs) are commonly affected in neurological and psychiatric disorders with cognitive deficits. The mismatch negativity component (MMN), typically measured in an oddball paradigm, indexes attention and sensory memory processing. MMN generation has been linked to glutamatergic and cholinergic transmission, pathways that are significantly implicated in Alzheimer's Disease, Parkinson Disease and Schizophrenia. Here, we investigate the potency of cognitive enhancers to normalize pharmacologically-induced disruption in MMN.

Methods: In conscious rats, MMN was elicited by rare changes in the acoustic environment. AEPs were recorded in different cortical areas, under baseline, following administration of scopolamine (0.64 mg/kg) and ketamine (10 mg/kg), and a combination thereof with cognitive enhancers Donepezil (3 mg/kg) and Memantine (3 mg/kg), respectively.

Results: In an oddball paradigm, MMN-like activity was elicited as a response to violations of auditory frequency regularities. Deviant stimuli evoked a prominent response of negative polarity peaking at 40-100 ms after stimulus onset, particularly in frontal areas. Smaller MMNs with shift in peaks and network oscillations were found after scopolamine and ketamine. Donepezil and memantine, which augment acetylcholine levels and NMDA receptor function, respectively, each increased MMN amplitude by its own, while the scopolamine and ketamine-induced disruptions in MMN-response were attenuated.

Conclusions: The present studies confirm the contribution of cholinergic and glutamatergic networks to MMN generation. The findings encourage the utility of MMN and late endogenous AEP components to study in rodents (reversal of) impaired synaptic plasticity and memory, which may facilitate the selection of drugs with cognitive enhancing potential in preclinical drug discovery

AD/PD2013, Florence, Italy.

MISMATCH NEGATIVITY (MMN) AND P300 CORRELATES IN EPIDURAL AUDITORY EVOKED POTENTIALS IN AWAKE RATS: OPPORTUNITIES FOR PRECLINICAL EVALUATION OF DRUGS WITH PRO-COGNITIVE POTENTIAL

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Introduction: Deficit in Mismatch negativity (MMN) and P300-like amplitudes as well as latencies represent robust neurophysiological markers in schizophrenia and Alzheimer's disease (AD). These events related potentials components, typically measured in an oddball paradigm, are associated with cognitive domain that index deviance detection process, orienting or shift in attention. MMN amplitude reduction is highly associated with impairment in psychosocial functioning and positive symptoms in schizophrenia, whereas negative symptoms and executive functions were related to MMN longer peak latency. Smaller peak amplitude and longer latency of late P300 component were proved reliable and sensitive to early cognitive decline or disease progression in AD. Rodent auditory event potentials (AEPs) measures share similarities with human; therefore MMN and P300 correlates in awake rats could be useful measures to assess the central effects of drugs on different domains of early cortical processing.

Here, we investigated whether 1) MMN and P300 correlates occurred in awake rats, 2) could be sensitive to drug known to impair cognitive process, 3) cognitive enhancers would normalize pharmacologically-induced abnormalities in MMN-like activity generation.

Methods: In awake rats, MMN is elicited to rare changes in the acoustic environment "Deviant" in a series of otherwise regularly repeating stimuli "Standard". Epidural potentials were recorded in different cortical areas in awake rats, under baseline or following acute administration of scopolamine (0.16 mg/kg) or ketamine (10 mg/kg).

Results: In an oddball condition, MMN-like activity elicited by difference between Standard vs. Deviant response was observed. Deviant stimuli evoked a prominent response of negative polarity peaking at 40-100 ms after stimuli onset, particularly in frontal areas. Subsequently, we explored possible effects of drugs on deviance-related activity. MMN-like activity was sensitive to scopolamine and ketamine, associated with reduction and shift in peak latency of the negative deflection to deviant stimulus. Additional experiments are ongoing to evaluate the potency of cognitive enhancers to normalize alterations in the MMN-like response.

Conclusions: The present studies demonstrate possible preclinical evidence at the electrophysiological level to generate and exploit genuine MMN-like component as a preclinical marker in translational research and efficacy assessment of novel drugs on early cognitive process. Efforts are currently underway to elicit a P300-like component to deviant target stimuli in the active oddball task, which requires a behavioral response such as pressing a lever for a reward.

SFN2012, New Orleans, USA.

EEG NETWORK OSCILLATIONS: A TARGET FOR SCREENING DRUGS WITH COGNITION ENHANCING AND ANTIPSYCHOTIC POTENTIAL

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Objectives: Abnormalities in functional network connectivity between brain areas have been postulated as an important pathophysiological mechanism underlying dysfunctional cognition processes in neuropsychiatric and neurological disorders. The present study addressed the potential of electroencephalographic (EEG) network oscillations in rats, as a suitable translational tool for assessment of efficacy of drugs with pro-cognitive and antipsychotic potential.

Methods: EEG network oscillations abnormalities of positive and negative symptoms of schizophrenia and cognitive impairment in patients were modeled in rats by using the N-methyl-D-aspartate (NMDA) and the muscarinic receptor antagonists, respectively. Subsequently, we examined the efficacy to reverse disruptions in network oscillations, of marketed antipsychotics (APs) (olanzapine, risperidone, clozapine) and of cognitive enhancers (donepezil, rivastigmine, tacrine and memantine), which are approved for symptomatic treatment of Alzheimer's Disease.

Results: Cognitive enhancers resulted in systematic "fingerprint" enhancement of lower theta (4.5-6 Hz) and lower gamma (30.5-50 Hz) cortical network oscillations. Quantification of functional coupling revealed consistent elevated theta coherence among parieto-occipital and between interhemispheric pairs of cortical areas, whereas coherence marginally increased between frontal and posterior sites. When administered after the injection of scopolamine, the cognitive enhancers normalized the scopolamine-induced leftward shift and increased coherence in slow delta network oscillatory activity. APs commonly decreased activity in the alpha1 and higher gamma EEG oscillations in different cortical regions. NMDA antagonists increased the synchrony of gamma EEG oscillations. Combined treatment with APs attenuated abnormalities in functional network oscillatory pattern induced in NMDA treated animals. Chronically blockade of NMDA receptor elicited decrease coherent activity in higher gamma oscillations.

Conclusions: The impairment in network functional connectivity following acute or chronic disruption of glutamatergic and cholinergic transmission are hypothesized to be fundamental components underlying cognitive impairment. EEG abnormalities modeled in conscious rats, makes EEG network oscillations a valuable tool to measure the efficacy drugs with cognition enhancing and antipsychotic potential on neural communication at large spatial scale.

SFN2013, San Diego, USA.

PRO-COGNITIVE POTENTIAL OF METABOTROPIC RECEPTORS (MGLUR5) BLOCKADE: EVIDENCE FROM SLEEP BEHAVIOR AND CORTICAL NETWORK OSCILLATIONS IN RODENTS

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Objectives: Pharmacological manipulation of the metabotropic glutamate (mGlu5) receptors may be critical for the treatment of many neurological and psychiatric disorders. MGLu5 receptor blockade limits neuronal damage induced by a hyperactivity of N-methyl-d-aspartate (NMDA) receptors, therefore linked to process of neurodegeneration/neuroprotection. Whereas, positive modulation of mGlu5 receptors may alleviate the profound glutamatergic hypo-function observed in schizophrenia. Sleep has a primary role in the regulation of brain plasticity and cognition, hence cognitive impairment associated with sleep disturbances is a core feature of patients with Alzheimer and schizophrenia diseases. The mGlu5-NMDA receptors signaling is fundamentally involved in cognitive functions; therefore the present studies used mGlu5 receptor antagonists (MTEP and MPEP) and positive allosteric modulators (ADX and AZ) to clarify whether blockade or allosteric activation of mGlu5 receptor signaling would have beneficial effects on sleep and facilitates oscillatory indexes of cortical networks communication in rats.

Methods: Effects of systemic MPEP and MTEP (1, 3 and 10 mg/kg) and oral ADX and AZ (10, 30 and 100 mg/kg) were characterized on sleep-wake architecture, electroencephalogram variables and cortical network oscillations in rats.

Results: MGLu5 receptor blockade consistently consolidated deep sleep and enhanced sleep efficiency, whereas allosteric activation increased waking and decreased deep sleep. Cortical oscillations in the theta (4.5-6 Hz) and gamma (30-50 Hz) frequency ranges were prominent in field potentials following blockade of the mGlu5 receptor, whereas only theta oscillations were promoted after allosteric activation. Future studies will address the circadian profile of vigilance states in mutant mice deficient in mGlu5 receptor as well as changes of the receptors density in the rat brain using [3H]MPEP autoradiography in order to examine the functional interaction between receptor activity and biological effects.

Conclusions: Our pharmacological evidence highlights the ability to differentiate the pharmacology of mGlu5 blockade from that of allosteric activation, and furthermore suggest that sleep and cortical network oscillations may provide a valuable animal-clinical interface for studying mGlu5 receptor signaling. The beneficial effect on sleep and the dynamic changes in cortical oscillations might underpin cognitive potential of mGlu5 receptor blockade.

ESRS2012, Paris, France.

TRANSLATIONAL VALIDITY OF EEG OSCILLATIONS IN SCHIZOPHRENIA

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Objectives: There is growing recognition that aberrant electroencephalographic (EEG) oscillations are core features of a wide range of neuropsychiatric and neurological disorders. Synchronous oscillatory activities in spatially distributed neural networks represent essential dynamic mechanisms for temporal coordination of multiple brain networks to coordinate higher-order cognitive functions. Electrophysiological and anatomical reports suggest that abnormalities in neuronal oscillations may play a key role in the pathophysiology of schizophrenia, in which failure in gamma oscillatory synchrony seems to be a specific functional component underlying cognitive deficit and symptoms of the disorder. Clinical reports in schizophrenic patients have described complexity and opposite changes in gamma oscillatory response, which have been correlated with chronic versus psychosis state of the disease. Deficit in gamma power is generally correlated with negative symptoms, whereas increased gamma oscillation propensity is found during psychotic episode and hallucinations state.

Methods: N-methyl-D-aspartate (NMDA) receptor antagonists have utility recapitulating positive, negative and cognitive deficit in healthy man and laboratory animals.

Results: In preclinical studies, acute blockade of NMDA receptors enhances aberrant EEG gamma oscillations, thus recreates a pattern postulated to be linked to positive symptoms of the disease state. However, a major challenge remains in modeling the negative symptoms of the disease following blockade of NMDA neurotransmission.

Conclusions: To ensure optimal translational relevance of the model in preclinical drug discovery research, repeated blockade of NMDA receptors is expected to lead to reduction in gamma oscillatory activity. This emphasizes the notion that pharmacological studies have to be conducted in ways that closely resembles acute versus chronic clinical states.

IPEG2012, New York. USA

GEOGRAPHIC VARIATION IN THE PREVALENCE OF ADHD: THE SUNNY PERSPECTIVE.

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Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common psychiatric disorder of childhood with average worldwide prevalence of 5.3%, varying by region.

Methods: We assessed the relationship between the prevalence of ADHD and solar intensity (SI: kWh/m²/day) based on multinational and cross-state studies. Prevalence data for the US were based on self-report of professional diagnoses, for the other countries, on diagnostic assessment. SI data were obtained from national institutes.

Results: In three datasets (across 49 US States for 2003 and 2007 and across 9 non-US countries) a relationship between SI and the prevalence of ADHD was found, explaining 34-57% of the variance in ADHD prevalence, with high SI having an apparent preventative effect. Controlling for low birth weight, infant mortality, average income (SES), latitude, and other relevant factors did not change these findings. Furthermore, these findings were specific to ADHD, not found for the prevalence of autism spectrum disorders nor major depressive disorder.

Conclusions: In this study we found a lower prevalence of ADHD in areas with high SI for both US and non-US data. This association has not been reported before in the literature. The preventative effect of high SI may be related to an improvement of circadian clock disturbances, which have recently been associated with ADHD. These findings likely apply to a substantial sub-group of ADHD patients and have major implications in our understanding of the etiology and possibly prevention of ADHD by medical professionals, schools, parents, and manufacturers of mobile devices.

Arns, M., van der Heijden, K. B., Arnold, L. E., & Kenemans, J. L. (2013). Geographic variation in the prevalence of attention-deficit/hyperactivity disorder: The sunny perspective. Biological Psychiatry. doi:10.1016/j.biopsych.2013.02.010.

TRAVELING SLOW WAVES IN THE AVIAN BRAIN

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Introduction: Recent studies have shown that slow waves propagate across the neocortex as a traveling wave during mammalian slow wave sleep. Although waves tend to originate in frontal regions, they can originate in virtually any part of the neocortex. To determine whether the behavior of slow waves described in mammals reflects a fundamental aspect of slow wave sleep, we examined whether slow waves also act as traveling waves in birds, the only other taxonomic group to exhibit unequivocal slow wave sleep.

Methods: Adult female zebra finches (*Taeniopygia guttata*) were anesthetized with 1-1.25% isoflurane. Local field potentials (LFP) and multiunit activity (MUA) were recorded using a 64-channel NeuroNexus

silicon probe (8 x 8, 200 micro-m array of electrodes) inserted into the anterior hyperpallium and underlying mesopallium and nidopallium. LFP and MUA were recorded (sampled at 14 kHz) while the birds remained under anesthesia. Probe placement was verified histologically using a fluorescent tracer.

Results: The LFP recordings revealed high amplitude slow waves associated with bursts of MUA across most recording sites. This activity swept across the plane of the electrode array as a traveling wave. Although activity tended to appear first in deeper sites, it could appear first in any part of the array. The wave usually reached all electrode sites, but in some cases only involved specific brain regions. The speed with which the waves crossed the array varied from wave to wave.

Conclusion: Several characteristics of avian slow waves are similar to those described in mammals; 1) slow waves are associated with alternating periods of MUA and neuronal quiescence, 2) slow waves are more likely to appear first in certain electrode sites, but can appear first in virtually any part of the brain covered by the electrode array, and 3) slow waves propagate as traveling waves. In addition, the apparent variable propagation speed across the 2-D array suggests that the waves actually propagate in 3 dimensions with some wave fronts occurring orthogonal and others parallel to the surface of the array. Wave propagation in 3 dimensions is consistent with the nuclear arrangement of stellate-shaped neurons in the avian pallium. The traveling nature of slow waves appears to be a fundamental feature of slow wave sleep.

APSS abstract, Sleep 36; A397.

NMDA RECEPTOR BLOCKADE: EVIDENCE FROM AEP MISMATCH NEGATIVITY IN RATS ON LACK OF NR2B-SUBUNIT CONTRIBUTION TO COGNITIVE DISRUPTION

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Objectives: N-methyl-d-aspartate (NMDA) receptor hypofunction contributes to dysfunctional brain network organization and cognitive information processing in neuropsychiatric and neurological disorders. The NR2B-subunit of NMDA receptors has been indicated to be an important factor in synaptic plasticity and cognitive behavior. Impaired Mismatch Negativity (MMN) generation is one of the most robust indices of dysfunctional pre-attentive and sensory memory components in schizophrenia and Alzheimer's disease. Rodent auditory evoked potentials (AEPs) share similarities with human counterparts; therefore analysis of MMN in conscious rats is considered a useful assessment of central effects of drugs on different domains of early cortical sensory and memory processes. The present study investigated whether selective blockade of the NR2B subunit containing receptors contributes to changes in higher-order cognitive information processing as found with the NMDA antagonist, ketamine.

Methods: MMN is a neurophysiological index of the ability of the brain to extract relevant information from an irrelevant background. In an oddball paradigm, MMN waveforms and network oscillatory responses were assessed in different cortical areas of conscious rats, following the administration of ketamine (10 mg/kg, sc), or of the specific NR2B-selective NMDA receptor antagonists Ro 25-6981 and CP-101606 (each at 1, 3 and 10 mg/kg; ip).

Results: Acute and chronic ketamine respectively enhanced and inhibited MMN waveforms and network oscillatory response by accelerating and impairing auditory change detection to frequency deviants. Neither Ro25-6981 nor CP-101606 disrupted event related MMN response and had no effect on gamma oscillatory network. Behavioral observations indicate that NR2B blockade had no adverse effects on motor coordination.

Conclusions: Changes in the MMN response following NMDA receptor blockade have important implications for understanding the role of NMDA subtypes in cognition. The non-selective NMDA antagonist, ketamine, effectively disrupted sensory information processing, whereas the NR2B subunit function does not contribute to this disruption. Assessment of the NR2A-subunit function may help to further explain the differential role in pre-attentive/deviance detection deficits. The findings encourage the use of the MMN paradigm to assess the integrity of early sensory processing in translational research.

SFN2013, San Diego, USA.

MODULATION OF NICOTINIC ACETYLCHOLINERGIC RECEPTORS MAY DIFFERENTIALLY AFFECT AUDITORY EVENT RELATED POTENTIALS COMPONENTS IN AWAKE RATS

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Introduction: Schizophrenics and Alzheimer's disease (AD) patients exhibit marked cognitive dysfunctions with similar profiles in clinical tests of cognition. Dysfunction of sensory pathways is believed to play a prominent role in the underlying cognitive symptoms. Event-related potentials (ERPs) and event-related oscillations (EROS), which are both indices of sensory information processing, are extensively used to study the disruption of neural systems of attention and cognitive process. Rodent AEPs share many specific similarities with humans AEPs, therefore deviance-related AEPs components in rodents offer unique translational opportunities to study pharmacologic strategies for treating cognitive deficits. Nicotinic acetylcholinergic receptors (nAChR) have been implicated extensively in human and animal studies of attention, learning and memory, and recognized targets for drug development in cognitive and neuro-degenerative disorders.

Methods: The current studies, undertaken in the double click paradigm, examined deviancies in the amplitudes, latencies, and gating of the AEP P1, N1 and P2 components and evoked oscillations from different cortical areas in awake rats treated with different nAChR drugs. In the dose-response and combined pharmacological treatments studies, nicotine, varenicline (a partial alpha4beta2 nAChR agonist and full agonist at the alpha7 nAChR) and mecamylamine (a non-selective nicotinic receptor antagonist) were administered subcutaneously.

Results: Acute nicotine administration (0.16 and 0.64 mg/kg) significantly decreased the peak amplitudes of the cortically generated AEPs components P1, N1 and P2, while the mean latencies windows were not modified. Additionally, nicotine evoked slow gamma oscillations following an auditory stimulus over cortical areas. Varenicline (3 mg/kg) elicited similar pattern as nicotine, except that the peak amplitude of the early P1 component of the AEP was increased in the parietal region. Mecamylamine (0.5 and 1 mg/kg) had no consistent effects on AEP waveforms and related oscillations. However, pre-treatment with mecamylamine blocked nicotine-induced changes in the AEP waveform components and related oscillations. Further studies are ongoing to evaluate the effect of mecamylamine on varenicline-mediated changes in AEP components, to reveal the partial contribution of alpha4beta2 nAChR subtype in the mechanism associated with nicotine. Given the importance of alpha7 nAChR in mediating sensory information processing, a number of specific agonists and allosteric modulators are under development as potential therapeutic drugs that may improve cognitive functioning. Further studies are underway to investigate the influence of alpha7 nAChR on AEP and EROS components and to evaluate which subtype of nAChRs drugs could normalize early indices of attention and sensory information processing following pharmacological disruption of cortical processes.

Conclusions: the present results suggest that modulation of nAChRs may influence the early stages of sensory processing in awake rats, and further underline remarkable possibilities of the used paradigm for a direct translational research application.

ECNP 2012 Vienna, Austria.

CYP1A2 POLYMORPHISMS IN SLOW MELATONIN METABOLISERS: A POSSIBLE RELATIONSHIP WITH AUTISM SPECTRUM DISORDER?

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Introduction In some of our patients with intellectual disabilities (ID) and sleep problems, the initial good response to melatonin disappeared within a few weeks after starting treatment. In these patients melatonin levels at noon were extremely high (>50 pg/ml). We hypothesize that the disappearing effectiveness is associated with slow metabolism of melatonin due to a single nucleotide polymorphism (SNP) of CYP1A2.

Methods In this pilot study we analysed DNA extracted from saliva samples of 15 consecutive patients with disappearing effectiveness of melatonin. Saliva was collected at noon and 4pm for measuring melatonin levels. Patients were considered to be a possible CYP1A2 poor metaboliser if melatonin level at noon was >50pg/ml, both noon and 4pm values were >50pg/ml or both levels were >20pg/ml and calculated melatonin half-life was >2h.

Results In all patients salivary melatonin levels at noon were >50 or melatonin half time was >5h. A SNP was found in 8 of 15 patients. The allele *1C was found in 2 patients and in 7 patients the *1F allele was found. Of 15 patients with disappearing effectiveness of melatonin, 7 were diagnosed with autism spectrum disorder, and in 4 of them a SNP was found. The other 8 patients were known with a genetic syndrome. In 6 of them behaviour was considered to be autistic-type and in 3 of them a SNP was found.

Conclusion Finding a SNP in 8 of 15 patients with salivary melatonin levels at noon >50 pg/ml or a half life of melatonin > 5h, gives support to our previous hypothesis that patients with disappearing effect of melatonin and high melatonin at noon are CYP1A2 poor metabolisers. Of 15 consecutive patients with disappearing efficacy of exogenous melatonin 13 were diagnosed with autism spectrum disorder or a genetic syndrome with autistic-type behaviour. We hypothesize that slow melatonin metabolism may be associated with mechanisms that cause autism. This finding may give a new direction for research into the genetic background of autism.

This study was supported by a research grant from 's Heeren Loo Zorggroep Steunfonds and the Governor Kremers Centre.

Journal of Intellectual Disability Research. 2012 Jul 23. doi: 10.1111/j.1365-2788.2012.01595.x.

INTERNET TREATMENT OF ADOLESCENTS WITH INSOMNIA

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Introduction

Many adolescents suffer from chronic sleep reduction and insomnia symptoms due to insufficient or unsatisfactory sleep, but adolescents are less inclined than adults to seek treatment. Online ehealth programs have shown to be as effective as other methods of treatment, and offer a viable alternative to reach youth and provide adequate treatment.

Methods

We developed a website for cognitive behavioral therapy for insomnia (CBT-I), and adapted the protocol for use in an internet setting with age-appropriate exercises for adolescents from 12-19 years old. Participants were recruited through newspaper articles and online newsletters for youth healthcare professionals. Two groups of 61 adolescents in total (mean age 15.4, SD 1.33; boys 18%) were randomly assigned to a waiting list control condition or a treatment condition. The treatment group was treated with the online CBT-I protocol in 6 weekly consults. Both groups were assessed at baseline and post treatment. Insomnia complaints and chronic sleep reduction were measured with questionnaires, and sleep parameters were measured with objective (actigraphy) and subjective (sleep logs) measurements.

Results

There was significantly more decrease of scores on the insomnia scale of the Holland Sleep Disorder Questionnaire ($p < .01$) and of the scores on the Chronic Sleep Reduction Questionnaire ($p < .05$) for the treatment condition. Results from sleep parameters show a significant decrease in sleep onset latency ($p < .001$), and a significant increase in total sleep time ($p < .05$) and sleep efficiency ($p < .001$) for the treatment condition but not for the waiting list condition. Furthermore the majority of the participants commented favorably on the content and mode of treatment through an online website.

Conclusion

Internet treatment of sleep problems of adolescents shows strong improvements in sleep parameters and a large decrease of insomnia complaints and symptoms, and is a feasible alternative for care-as-usual.

This study was conducted with a grant provided by ZonMW, The Netherlands Organisation for Health Research and Development.

This study is presented at the 6th World Congress “Medicine 2.0”, London, England, September 23-24, 2013.

HOW SLEEP, WAKE AND OTHER IMPOSED ACTIVITY PATTERNS FEED BACK ON THE CLOCK

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Sleep is regulated by a homeostatic process and a circadian clock. The homeostat keeps track of the duration of prior waking and the clock provides a circadian framework which not only regulates the timing of sleep and waking, but also other behaviors and physiological processes. The circadian clock in mammals is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The physical location of the sleep homeostat is not known, but its level is reflected in the the slow-waves (< 5 Hz) of the non-rapid eye movement (NREM) sleep electroencephalogram (EEG). This slow-wave activity (SWA) in the NREM sleep EEG, increases and decreases in a predictable way, as a function of prior waking duration.

Light is a very powerful input to the circadian clock. It can shift the phase of the clock, enabling the clock to adapt its timing to the environmental light-dark cycle. It has been shown in the past that non-photoc stimuli, like increased behavioral activity or sleep deprivation, also can influence the phase and period of the clock. When combined with light these stimuli seemed to interact, preventing the light pulse from shifting the clock. Recent data obtained in phase shift and forced desynchrony experiments suggested similar interactions between sleep and circadian clock functioning in humans.

By recording electrical activity of SCN neurons in rodents it was shown that light generally increases neuronal activity within the SCN. Also vigilance state changes modulate the firing rate of SCN neurons. In rats, at entrance into NREM sleep, neuronal activity decreased, whereas at the start of REM sleep or waking neuronal activity increased. SCN neuronal activity showed a negative correlation with SWA in NREM sleep and sleep deprivation further increased SWA and decreased SCN neuronal activity. In addition, behavioral activity can influence SCN neuronal activity. Spontaneous activity in mice and rats can decrease neuronal activity in a subset of SCN neurons. In contrast, induced activity was recently shown to increase neuronal activity within the SCN of mice.

The combined data suggest that SCN neuronal firing is changed by prolonged waking, sleep deprivation and increased activity. This may change circadian clock functioning, hampering adaptation to the environmental light dark cycle and possibly influencing circadian clock dependent performance.

Presented at the first INSPIRE meeting, Viareggio, Italy, March 2013.

THE EFFECTS OF SLEEP EXTENSION ON SLEEP AND COGNITIVE PERFORMANCE IN ADOLESCENTS WITH CHRONIC SLEEP REDUCTION: AN EXPERIMENTAL STUDY

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Objective: To investigate the effects of gradual sleep extension in adolescents with chronic sleep reduction. Outcome variables were objectively measured sleep and cognitive performance.

Methods: Participants were randomly assigned to either a sleep extension group (gradual sleep extension by advancing bedtimes in the evening) or to a control group (no instruction). Our sample consisted of 55 adolescents (mean age, 15.44 y; 85.5% girls) with symptoms of chronic sleep reduction (loss of energy, shortness of sleep, sleepiness, and irritation). Sleep was monitored with actigraphy over 3 weeks; the first week was the baseline week and the last two weeks were the experimental weeks. Participants in the experimental group were instructed to extend their sleep during the week by gradually advancing their bedtimes by 5 minutes each night. Additionally participants were asked to prevent bedtime shifts on weekend nights. Cognitive performance was assessed before and after the experimental manipulation.

Results: During the last week of the experiment, adolescents in the sleep extension group had earlier bedtimes, earlier sleep onsets, spent more time in bed, and slept longer than adolescents in the control group. These results indicate that the experimental manipulation was successful and that adolescents in the experimental group fell asleep earlier and slept longer than adolescents in the control group. Furthermore some aspects of cognitive performance, especially visuospatial processing, significantly changed in the sleep extension group.

Conclusion: Gradual sleep extension has beneficial effects on adolescents' sleep and is related to changes in some aspects of cognitive performance.

Dewald-Kaufmann, J.F., Oort, F.J., & Meijer, A.M. (2013). The effects of sleep extension on sleep and cognitive performance in adolescents with chronic sleep reduction: An experimental study. Sleep Medicine, 14, 510-517.

SLEEP DEPRIVATION INHIBITS LIGHT RESPONSIVENESS OF THE CIRCADIAN PACEMAKER

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The timing and depth of sleep wake cycles are regulated by a homeostatic process and a circadian process. The homeostatic process mediates the increasing sleep propensity during wakefulness and its dissipation during sleep. The location of the sleep homeostat within the central nervous system is unknown, but is thought to be reflected in the slow-waves of the non-rapid eye movement sleep electroencephalogram. The circadian process originates from the suprachiasmatic nuclei (SCN) and determines the timing of sleep as well as daytime alertness. The daily sleep-wake cycle is regulated by an interplay between the two processes, but the mechanism of this interaction remains unclear.

Light exposure at the beginning of the active period delays the rest-activity rhythm. Light induced phase shifts are mediated by the light responsive SCN neurons. These neurons respond with a sustained response for the full duration of the stimulus with characteristic fast-transient components occurring at the light transitions. This sustained response is significantly larger when the pulse is applied during the night, when light is able to phase shift the clock, compared to during the day. Sleep deprivation attenuates the phase-shifting effect of light on behavioral activity. Recent evidence indicates that vigilance state changes affect SCN neuronal electrical activity and that sleep deprivation significantly decreases SCN neuronal activity. These results show that SCN neuronal activity and clock functioning is strongly modified by changes in sleep pressure.

In the present study we examined the role of sleep deprivation on the acute modulation of SCN electrical activity by light in freely moving mice in the beginning of the night. In addition, we examined the phase-delaying effect of this light pulse on their rest-activity rhythm. We found an attenuated phase-shift of the circadian rhythms of mice after a 6-hour sleep deprivation. The SCN electrical activity recordings revealed that the sustained response in SCN electrical activity was attenuated after a 6-hour sleep deprivation prior to light exposure. These data confirm previous studies showing that sleep deprivation affects the light induced phase shifts in behavioral activity. The present data suggest that changes in circadian pacemaker function due to increased homeostatic sleep pressure may be mediated by a reduced responsiveness to light of SCN neurons.

Presented at the first INSPIRE meeting, Viareggio, Italy, March 2013.

SLEEP DEPRIVATION AND CAFFEINE INFLUENCE LIGHT RESPONSIVENESS OF CIRCADIAN PACEMAKER NEURONS

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The timing and depth of sleep are regulated by homeostatic and circadian processes. The circadian process originate from the suprachiasmatic nuclei (SCN) and determines the timing of sleep, whereas the homeostatic process mediates the increasing sleep propensity during wakefulness and its dissipation during sleep. One of the substances thought to be involved in the homeostatic regulation of sleep is adenosine, which increases in the brain in the course of sleep deprivation and decreases during recovery sleep.

Light induced phase shifts are mediated by light responsive SCN neurons, which respond with a sustained increase in electrical activity for the full duration of the light pulse, with characteristic fast- transient components occurring at light onset and offset. This sustained response is significantly larger during the night, a time when light is able to phase shift the clock, compared to during the day. Sleep deprivation is known to significantly decrease SCN neuronal activity and attenuates the phase-shifting effect of light on behavioral activity. In addition, application of adenosine agonists and antagonists mimic and block the effect of sleep deprivation, respectively. These results show that sleep pressure strongly modifies SCN activity and clock functioning.

In the present study we examined the role of sleep deprivation and the effect of caffeine on the acute modulation of *in vivo* SCN electrical activity by light in the beginning of the night in freely moving mice. The electrophysiological recordings showed that the sustained response to light in SCN neuronal activity was attenuated after a 6-hour sleep deprivation prior to light exposure. Subsequent i.p. application of caffeine, an adenosine receptor antagonist, was able to restore the response to light.

The sleep deprivation data suggest that increased homeostatic sleep pressure changes circadian pacemaker functioning by reducing SCN neuronal responsiveness to light input. The experiments with caffeine indicate that this reduced responsiveness is mediated by increased adenosine levels. Consuming caffeinated beverages may therefore increase clock sensitivity to light, when sleep deprived.

Presented at the XIII EBRS meeting, Munich, Germany, August 2013.

RISK OF AUTOMOBILE ACCIDENTS ASSOCIATED WITH THE USE OF BENZODIAZEPINE RECEPTOR AGONISTS HYPNOTICS

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Introduction: The most commonly used hypnotics are the benzodiazepine receptor agonists (BzRAs) which differing in half life. The shorter acting BzRAs induce sleep and have limited residual effects. In contrast, the longer acting BzRAs induce and maintain sleep but may cause significant impairment in ability to drive the morning or even the afternoon after taking medication. There is both laboratory and epidemiological data evaluating the effects of BzRAs on driving. The purpose of this report is to review epidemiological literature on BzRA related driving risk.

Methods: In May 2012 a literature search (Medline, Pubmed, and Embase) was conducted, using search terms: “hypnotics and crashes”, “hypnotics and driving” and “benzodiazepines and crashes”, to gather information on road accident associated with BzRA hypnotics. Data was abstracted as to drug, age, presence or absence of blood level data, OR, single or multiple drugs, and case identification method.

Results: 37 articles were identified and of these 13 met criteria for inclusion. The overall analysis showed that BzRA hypnotic use was associated with a significantly increased crash risk (OR= 1.751; 95% CI +1.496 -2.048). The half-life of the various drugs was evaluated by trichotomizing all the drugs into three bins (short: <6hrs, intermediate: 6-12hrs, long: >12hrs). The results show that both intermediate acting (OR= 1.406; 95% CI=1.114- 1.774) as well as the long acting drugs (OR=1.451; 95% CI= 1.198-1.758) represent a significant risk for crashes. This was not the case for the short acting drugs. In secondary analyses we found that in terms of demographics age is negatively related to increased risk while gender does not alter accident risk.

Conclusion: The analysis of the epidemiological data is consistent with laboratory data showing overall BzRAs risk for impaired driving/accidents, and that this risk increases with the half life of the drug.

Financial support provided by Merck, Inc.

APSS abstract, Sleep 36; A429.

AGING OF THE SUPRACHIASMATIC CLOCK

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

In Press in The Neuroscientist.

ON THE IMPACT OF AROUSALS ON THE PERFORMANCE OF SLEEP AND WAKE CLASSIFICATION USING ACTIGRAPHY

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We evaluated the impact of arousals on the performance of actigraphy-based sleep/wake classification. Using a dataset of 15 healthy adults and a threshold optimized for this task we found that the percentage of sleep epochs with activity counts above that threshold was significantly larger in epochs with and following arousals. We also found that 41.1% of all false positive classifications occurred in these epochs. Finally, we determined that excluding these epochs from the evaluation led to a maximum precision increase of 17.2%. Considering wake detections in those epochs as correct led to a maximum precision increase of 31.3%. We concluded that unless arousals can be automatically identified or at least distinguished from wake, the performance of actigraphy-based sleep/wake classifiers is limited by their presence.

Published in Proc. 35th Ann. Int. Conf. IEEE EMBS (EMBC), Osaka, Japan, July, 2013.

ASSOCIATION OF EVENINGNESS WITH PROBLEM BEHAVIOR IN CHILDREN: A MEDIATING ROLE OF IMPAIRED SLEEP

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Eveningness, the preference of being active during the evening in contrast to the morning, has been associated with markedly increased problem behavior in adolescents, however, the underlying mechanisms are still not understood. This study investigates the association of eveningness with behavior and cognition in children aged 7-12 years, and explores the potential mediating role of a variety of sleep factors.

Parents of 333 school-aged children (mean age 9.97 years, 55% girls), completed a sleep log and several questionnaires regarding eveningness, sleep habits, and behavioural problems. Intellectual abilities, working memory, and attention were assessed using the short-form of the WISC and subtasks of the Amsterdam Neuropsychological Tasks.

Results showed that eveningness predicted behavioral problems over and above the effects of demographic variables (age, gender and familial socioeconomic status) ($p = .003$). Significant partial correlation was found for eveningness and sleep duration during weekdays ($p = 0.005$), and not during weekends. Furthermore, evening-orientation was associated with a reduced rested feeling on weekday mornings ($p < .001$), but not on weekends. The most important sleep characteristic that showed association with many cognitive and behavioral measures, was the subjective feeling upon awakening - particularly during weekdays. Bootstrap mediation analyses demonstrated that sleep significantly mediated the effects of eveningness on behavioral problems, working memory, and sustained attention. Interestingly, mediation was only significant through the subjective feeling upon awakening on weekdays.

The current findings indicate that the subjective feeling upon awakening is a much better predictor of daytime problems, than subjective sleep quantity. Furthermore the data suggest that negative outcomes in evening types are due to the fact that they wake up before their circadian drive for arousal and prior to complete dissipation of sleep pressure during weekdays. Interventions are discussed which target the misalignment of endogenous circadian rhythms and imposed rhythms.

The authors want to thank Sabine van Wijck for her assistance. Furthermore, we are grateful to all schools and families who participated, and to the students of our department for collecting data.

Van der Heijden K.B., de Sonnevile L.M., Swaab H. (In Press). Association of eveningness with problem behavior in children: a mediating role of impaired sleep. Chronobiology International.

PARENTAL EDUCATION IN CHILDREN WITH ADHD AND SLEEP ONSET INSOMNIA

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Introduction: Sleep onset insomnia(SOI) is a highly prevalent symptom in children with Attention Deficit Hyperactivity Disorder (ADHD). Chronic SOI in ADHD can be caused by a Delayed Sleep Phase Syndrome (DSPS). This diagnosis is confirmed by assessment of endogenous melatonin levels in saliva, showing a delayed dim light melatonin onset (DLMO). Melatonin treatment effectively reduces sleep onset latency in children with DSPS. Consequently, many children with ADHD and SOI receive melatonin treatment. However, other causes of SOI that are highly prevalent during childhood may be overlooked, such as poor sleep hygiene or behavioral problems. We studied DLMO in a consecutive series of 64 children with ADHD and SOI. Furthermore, we studied the effect of parental education on the insomnia symptoms.

Methods: A consecutive series of 64 children with ADHD and SOI, merely between 6 and 12 years were studied. They were referred by child psychiatrists to their colleague with special interest in sleep (JH). In all patients, DLMO was measured, and all parents received education on sleep physiology, sleep hygiene and management of behavioral bedtime problems by a nurse practitioner (RB). Evaluation took place after 6 weeks by means of DLMO results and a parental rating of the insomnia symptoms on a 3 point scale (improved, no change, worsened).

Results: 1 parent reported the insomnia symptoms had worsened since the education. DLMO in this child was normal. 37/64 (58%) reported the education had no influence on the symptoms, in this group DLMO was delayed in n= 30 children (81%). 26/64 parents (41%) reported the sleep of the child had improved since the education, in n= 20 (77%) DLMO was delayed.

Conclusion: In summary, in this population of children with ADHD and SOI, DLMO was delayed in 80%. Parental education improved the symptoms in 40%.

Presented at the poster session of the International Pediatric Sleep Association congress 2012 December 5-7 Manchester UK.

FRANCTAL PATTERNS OF NEURAL ACTIVITY EXIST WITHIN THE SUPRACHIASMATIC NUCLEUS AND REQUIRE EXTRINSIC NETWORK INTERACTIONS

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The mammalian central circadian pacemaker (the suprachiasmatic nucleus, SCN) contains thousands of neurons that are coupled through a complex network of interactions. In addition to the established role of the SCN in generating rhythms of ~24 hours in many physiological functions, the SCN was recently shown to be necessary for normal self-similar/fractal organization of motor activity and heart rate over a wide range of time scales--from minutes to 24 hours.

To test whether the neural network within the SCN is sufficient to generate such fractal patterns, we studied multi-unit neural activity of *in vivo* and *in vitro* SCNs in rodents.

In vivo SCN-neural activity exhibited fractal patterns that are virtually identical in mice and rats and are similar to those in motor activity at time scales from minutes up to 10 hours. In addition, these patterns remained unchanged when the main afferent signal to the SCN, namely light, was removed. However, the fractal patterns of SCN-neural activity are not autonomous within the SCN as these patterns completely broke down in the isolated *in vitro* SCN despite persistence of circadianrhythmicity.

Thus, SCN-neural activity is fractal in the intact organism and these fractal patterns require network interactions between the SCN and extra-SCN nodes. Such a fractal control network could underlie the fractal regulation observed in many physiological functions that involve the SCN, including motor control and heart rate regulation

PLoS One 7, e48927, 2012.

ANTAGONISM VERSUS POSITIVE ALLOSTERIC MODULATION OF METABOTROPIC GLUTAMATE (MGLU5) RECEPTORS: EEG AND SLEEP-WAKE BEHAVIOR INDICES FOR POTENTIAL PRO-COGNITIVE DRUG PROPERTIES IN RODENTS

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Objectives: Pharmacological manipulation of metabotropic glutamate (mGlu5) receptors can be valuable in the treatment of several neurological and psychiatric disorders. mGlu5 receptor blockade limits neuronal damage induced by a hyperactivity of N-methyl-d-Aspartate (NMDA) receptors and has been associated with neurodegeneration/neuroprotection. Furthermore, sleep has an instrumental role in the regulation of brain plasticity and cognition, while cognitive impairment associated with sleep disturbances is a core feature found in Schizophrenics and Alzheimer patients. Moreover, mGlu5-NMDA receptors signaling is clearly involved in cognitive functions; therefore the present studies in rats used mGlu5 receptor antagonists (MTEP and MPEP) and positive allosteric modulators (ADX and AZ) to clarify whether blockade or allosteric activation of mGlu5 receptor signaling has beneficial effects on sleep and can facilitate oscillatory indexes of cortical neuronal communication.

Methods: The influence of MPEP and MTEP was first investigated on brain slices to validate their effects on synaptic transmission and synaptic plasticity. Next, consequences of systemic administration of MPEP and MTEP (1, 3 and 10 mg/kg) and oral administration of ADX and AZ (10, 30 and 100 mg/kg) were characterized for sleep-wake architecture, electroencephalographic variables and cortical network oscillations in rats.

Results: MPEP and MTEP showed similar effects in hippocampal brain slice. In freely moving rats, mGlu5 receptor blockade consistently consolidated deep sleep and enhanced sleep efficiency, whereas allosteric activation increased waking and decreased deep sleep. Cortical oscillations in the theta (4.5-6 Hz) and gamma (30-50 Hz) frequency ranges were prominent in field potentials following blockade of the mGlu5 receptor, whereas only theta oscillations were promoted after allosteric activation. Studies are underway to address the circadian profile of vigilance states in mutant mice deficient in mGlu5 receptor as well as changes of the receptors density in the rat brain using [3H]MPEP autoradiography in order to examine the functional interaction between receptor activity and biological effects.

Discussion: Our pharmacological evidence highlights the ability to differentiate the pharmacology of mGlu5 blockade from that of allosteric activation, and furthermore suggests that sleep and cortical network oscillations may provide a valuable animal-clinical interface for studying mGlu5 receptor signalling. The beneficial effect on sleep and the dynamic changes in cortical oscillations seem to support a cognitive potential of mGlu5 receptor blockade.

SFN2012, New Orleans, USA.

GUIDELINES FOR THE RECORDING AND EVALUATION OF PHARMACO-SLEEP STUDIES IN MAN: THE INTERNATIONAL PHARMACO-EEG SOCIETY (IPEG)

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The International Pharmacology-EEG Society (IPEG) presents guidelines summarising the requirements for the recording and computerised evaluation of pharmacology-sleep data in man. Over the past years, technical and data-processing methods have advanced steadily, thus enhancing data quality and expanding the palette of sleep assessment tools that can be used to investigate the activity of drugs on the central nervous system (CNS), determine the time course of effects and pharmacodynamic properties of novel therapeutics, hence enabling the study of the pharmacokinetic/pharmacodynamic relationship, and evaluate the CNS penetration or toxicity of compounds. However, despite the presence of robust guidelines on the scoring of polysomnography recordings, a review of the literature reveals inconsistent aspects in the operating procedures from one study to another. While this fact does not invalidate results, the lack of standardisation constitutes a regrettable shortcoming, especially in the context of drug development programmes. The present guidelines are intended to assist investigators, who are using pharmacology-sleep measures in clinical research, in an effort to provide clear and concise recommendations and thereby to standardise methodology and facilitate comparability of data across laboratories.

Neuropsychobiology 2013; 67: 127-167.

GUIDELINES FOR THE RECORDING AND EVALUATION OF PHARMACO-EEG DATA IN MAN: THE INTERNATIONAL PHARMACO-EEG SOCIETY (IPEG)

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The International Pharmaco-EEG Society (IPEG) presents updated guidelines summarising the requirements for the recording and computerised evaluation of pharmaco-EEG data in man. Since the publication of the first pharmaco-EEG guidelines in 1982, technical and data processing methods have advanced steadily, thus enhancing data quality and expanding the palette of tools available to investigate the action of drugs on the central nervous system (CNS), determine the pharmacokinetic and pharmacodynamic properties of novel therapeutics and evaluate the CNS penetration or toxicity of compounds. However, a review of the literature reveals inconsistent operating procedures from one study to another. While this fact does not invalidate results per se, the lack of standardisation constitutes a regrettable shortcoming, especially in the context of drug development programmes. Moreover, this shortcoming hampers reliable comparisons between outcomes of studies from different laboratories and hence also prevents pooling of data which is a requirement for sufficiently powering the validation of novel analytical algorithms and EEG-based biomarkers. The present updated guidelines reflect the consensus of a global panel of EEG experts and are intended to assist investigators using pharmaco-EEG in clinical research, by providing clear and concise recommendations and thereby enabling standardisation of methodology and facilitating comparability of data across laboratories.

Neuropsychobiology 2013; 66: 201-220.

PREVALENCE AND RELEVANCE OF SLEEP DISTURBANCES IN FORENSIC PSYCHIATRIC PATIENTS

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INTRODUCTION: Sleep problems are very common in psychiatric patients and are often considered as secondary symptoms to the psychiatric disorder. However, disrupted sleep itself may affect emotional function. For example, a chronic lack of sleep is considered to be a risk factor for the development of mood disorders. Sleep loss is not only associated with depressive mood, but also with emotional instability, hostility and aggression. Thus, sleep problems may not only be of high importance to individuals with affective disorders, but also to aggressive individuals, such as forensic psychiatric patients. Despite this, epidemiological data on sleep difficulties in forensic psychiatric populations are lacking. Whether these sleep problems are related to aggression- and impulsivity levels in these patients is also not known.

METHODS: In this study we investigated the prevalence of sleep disorders, poor subjective sleep quality and the relation with aggression/impulsivity by means of the Sleep Diagnosis List (SDL), the Pittsburgh Sleep Quality Index (PSQI), the Aggression Questionnaire (AQ) and the Barrat Impulsiveness Scale (BIS-11) in 96 patients admitted to a forensic psychiatric hospital.

RESULTS: Almost half of the participants (49.1%) had a total PSQI score >5, indicating that they considered themselves to be poor sleepers. According to the SDL, one or more sleep disorders were present in 29.1% of the participants. In most cases, this was insomnia (18.2%). A worse sleep quality and higher SDL insomnia scores were significantly and independently associated with higher self-reported aggression and impulsivity.

CONCLUSIONS: Sleep disturbances are experienced by a large part of clinical forensic psychiatric patients, despite intensive clinical treatment. The results of this study support to a large extent the hypothesis that sleep problems are a risk factor for aggressive, impulsive behaviour in forensic psychiatric patients. Future studies should focus on the effect of sleep improving interventions on the aggression regulation capacities in forensic psychiatric individuals. The treatment of sleep problems may be a valuable, innovative element in aggression-reducing and crime-preventing treatment programmes.

Kamphuis J, Karsten J, de Weerd A, Lancel M. Sleep disturbances in a clinical forensic psychiatric population. Sleep Medicine, in press.

EFFECTS OF CLINICALLY APPROVED, PRO-COGNITIVE PHARMACOLOGICAL AGENTS ON ELECTROENCEPHALOGRAPHY (EEG) IN ALZHEIMER'S DISEASE-MODEL MICE: POTENTIAL FOR TRANSLATIONAL BIOMARKERS

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Objectives: The development of novel symptomatic treatments for Alzheimer's Disease (AD) requires continued efforts in biomarker discovery, coupled with preclinical models that have high predictive capacity. Cortical EEG is a useful translational tool for these efforts because it can detect neurophysiological biomarkers for treatment response in sleep/wake maintenance and spectral frequency modulations. The current studies compared cortical EEG measures in wildtype and three transgenic mouse strains which express human mutated AD-associated genes. The four gold standard symptomatic AD treatments donepezil, rivastigmine, galantamine, and memantine were administered to the mice to determine if similar and reliable biomarkers for treatment response are detected.

Methods: Mice were chronically implanted with epidural EEG screw electrodes over the frontal and parietal cortices, and electromyogram (EMG) wires were placed in the dorsal neck muscle. Drugs were administered subcutaneously 2 hours after lights off (i.e. the active circadian phase). Wireless telemetric recordings of EEG/EMG were analyzed offline and the effects of the drugs on vigilance state maintenance and spectral frequency components were investigated.

Results: Dose response studies showed that all four drugs caused dose-dependent increases in the duration of wakefulness and suppression of rapid-eye-movement (REM) and non-REM sleep. Several changes in spectral frequency power were also observed. Notably, the acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) enhanced theta (4-8Hz) and gamma (32-100Hz) power and reduced alpha (8-14Hz) power. Similarly, memantine (an NMDA_R antagonist) reduced the alpha power and enhanced gamma power. In the transgenic mice, baseline EEG recordings had abnormalities in delta (1-4Hz), theta, and gamma powers compared to wild-type counterparts. Preliminary analysis has shown that memantine (10mg/kg) increased vigilance and concomitantly reversed the deficient gamma power observed during the baseline. Analysis of the donepezil and memantine in the other AD-model mice is ongoing.

Conclusions: Overall, the findings indicate that the four drugs had a similar profile of effects on increased vigilance and synchronization of specific brain frequency ranges. of specific brain rhythms despite differences in the mechanisms of action. These changes can be related to the established cognitive enhancing properties of these clinically approved AD treatments. The studies in the transgenic mice suggest that these biomarkers have validity in translational research models. Thus, our findings further substantiate the utility of sensitive EEG biomarkers that can aid the drug discovery process for pro-cognitive AD treatments.

ECNP2013, Barcelona, Spain.

ASSESSMENT OF HUMAN SLEEP DEPTH IS BEING DE-STANDARDIZED BY RECENTLY ADVISED EEG ELECTRODE LOCATIONS

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Introduction.

Human sleep depth was traditionally assessed by scoring electro-encephalographic slow-wave amplitudes at the globally standardized C4-M1 electrode derivation. Since 2007, the American Association of Sleep Medicine (AASM) has accepted three additional derivations for the same purpose. These might well differ in slow wave amplitudes which would bias the scorings. Some derivations might also introduce large inter-individual variability.

Methods.

We compared mean and variability of slow wave amplitudes between six derivations including the four AASM ones. Slow wave amplitudes in those derivations were simultaneously measured using automated analysis in 29 patients. Each amplitude was divided by the average from the six derivations, thus removing shared factors such as age, gender and sleep depth while retaining factors that differ between the derivations such as caused by local skull characteristics, electrode distance and neuronal dipole orientation.

Results.

The remaining inter-individual variability differed significantly and up to a factor of two between the AASM derivations. The amplitudes differed significantly and up to 60% between the AASM derivations.

Conclusion.

Substantial scoring bias occurs between centres using different derivations. The resulting de-standardization most likely affects any patient group because the amplitude differences were consistent over diagnoses, genders, and age. Derivation-dependent amplitude thresholds were proposed to reduce the scoring bias. However, it would be better to settle on just one derivation, for instance Cz-Oz or Fpz-Cz because these have lowest variability while matching the traditional C4-M1 amplitudes.

Kemp B, van Someren P, Roessen M, van Dijk JG (2013) Assessment of Human Sleep Depth Is Being De-Standardized by Recently Advised EEG Electrode Locations. PLoS ONE 8(8): e71234. doi:10.1371/journal.pone.0071234.

BASELINE DEPRESSION LEVELS DO NOT AFFECT EFFICACY OF COGNITIVE-BEHAVIORAL SELF-HELP TREATMENT FOR INSOMNIA

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Introduction: Cognitive-behavioral therapy can effectively treat insomnia (CBTI). Randomized controlled trials have shown efficacy of self-help CBT-I, but unclear is whether excluding depressive patients boosted treatment effects.

Method: We administered unsupported self-help CBT-I to insomnia patients with low and high depression levels. Based on the validated Centre of Epidemiological Studies-Depression (CES-D) scale, the internet-recruited sample ($N = 479$) was divided into three groups: low depression scores ($n = 198$), mild depression scores ($n = 182$), and high depression scores ($n = 99$). Follow-ups were 4 and 18 weeks after completion of the treatment.

Results: At 4-week follow-up, all groups had a similar amelioration on the primary sleep measures ($d = 0.1-0.7$; $P < 0.05$) and the secondary insomnia ratings ($d = 1.2$; $P < 0.001$). The only difference was that the high/mild depression groups had a steeper reduction in depression ($d = 1.0-1.1$; $P < 0.001$) and anxiety scores ($d = 0.7-0.8$; $P < 0.001$) than the low depression group (depression and anxiety: $d = 0.3$; $P < 0.01$), possibly due to floor effects in the latter group. The observed effects were sustained at the 18-week follow-up.

Conclusions: This study showed that CBT-I is effective regardless of baseline depression levels. Treating the combination of insomnia and depression is an extra challenge since it is associated with increased sleep problems. These data may help us understand the relationship between insomnia and depression and indicate that self-help CBT-I may be a promising addition to regular depression treatment.

Lancee, J., van den Bout, J., van Straten, A., & Spoormaker, V.I. (2013). Baseline depression levels do not affect efficacy of cognitive-behavioral self-help treatment for insomnia. Depression and Anxiety, 30, 149-156.

THE ASSOCIATION BETWEEN NIGHTMARES AND DAILY DISTRESS

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Introduction Nightmares are a prevalent disorder with negative consequences.

Method This study investigated the association between nightmares and daily distress. Fifty-six participants with frequent nightmares filled out questionnaires and a 10-day diary. The questionnaire concerned: sleep, nightmare distress, depression, neuroticism, posttraumatic stress, and anxiety; the diary: nightmares, sleep, and sleep related distress.

Results Multilevel analyses revealed that nightmare nights, sleep quality, baseline nightmare distress, and depression were significantly associated with daily sleep related distress ($P < 0.05$).

Discussion This is the first study that prospectively shows that nightmares are independently associated with daily sleep related distress.

Lancee, J. & Schrijnemaekers C.M.L. (2013). The association between nightmares and daily distress. Sleep and Biological Rhythms , 11, 14-19.

RESPIRATION AMPLITUDE ANALYSIS FOR REM AND NREM SLEEP CLASSIFICATION

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In previous work, single-night polysomnography recordings (PSG) of respiratory effort and electrocardiogram (ECG) signals combined with actigraphy were used to classify sleep and wake states. In this study, we aim at classifying rapid-eye-movement (REM) and non-REM (NREM) sleep states. Besides the existing features used for sleep and wake classification, we propose a set of new features based on respiration amplitude. This choice is motivated by the observation that the breathing pattern has a more regular amplitude during NREM sleep than during REM sleep. Experiments were conducted with a data set of 14 healthy subjects using a linear discriminant (LD) classifier. Leave-one-subject-out cross-validations show that adding the new features into the existing feature set results in an increase in Cohen's Kappa coefficient to a value of $\kappa = 0.59$ (overall accuracy of 87.6%) compared to that obtained without using these features (κ of 0.54 and overall accuracy of 86.4%). In addition, we compared the results to those reported in some other studies with different features and signal modalities.

Published in Proc. 35th Ann. Int. Conf. IEEE EMBS (EMBC), Osaka, Japan, July, 2013.

NOCTURNAL MOVEMENTS IN PARKINSON'S DISEASE PATIENTS AND SUBJECTS AT-RISK, AND CONTROLS

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Introduction: The pattern of nocturnal movements is commonly different in patients with Parkinson's disease (PD) compared to healthy subjects. Some nocturnal problems can be present early in the course of PD. Here, we examined whether abnormal nocturnal movements may represent an early marker for PD. We compared nocturnal movements between PD patients, clinically unaffected subjects with a high risk of PD (HR-PD), and healthy controls.

Methods: Three groups participated: 11 PD patients; 33 HR-PD, based on substantia nigra hyperechogenicity together with slight signs of motor impairment or two of the following markers: unilateral reduced arm swing, depression, olfactory dysfunction or family history of PD; and 13 healthy controls. Two nocturnal registrations of every subject analyzed. Nocturnal movements were registered using a tri-axial accelerometer. Mean movement intensity, total movement time and frequency, size, duration and speed of axial turns were compared between groups.

Results: Mean intensity of movements was significantly lower in PD patients compared to controls (PD: 0.048 g (0.035-0.079), control: 0.080 g (0.049-0.108), $p < .001$). This was not found in HR-PD subjects (HRPD: 0.071 g (0.047-0.116), $p = .098$). Movements of PD patients were significantly smaller compared to controls (PD: 32.55° (17.54-46.94), control: 46.72° (22.66-73.86), $p < .001$). Moreover the duration of the movements was shorter (PD: 5.68 s (4.07-8.81), control: 6.96 s (5.62-10.18), $p = .001$). Again these differences were not found in the HR-PD subjects (HR-PD: size 51.19° (18.83-77.03), $p = 0.52$; duration 7.82 s (3.39-15.56), $p = .134$). Total movement time, frequency and speed of turns were not significantly different between groups.

Conclusion: PD patients have a lower intensity of nocturnal movements compared to controls, which could be a marker of nocturnal hypokinesia. In addition axial rotations are smaller and take less time in PD patients. However, these changes do not seem to be an early marker for PD.

APSS abstract, Sleep 36; A260.

SUBJECTIVELY IMPAIRED BED MOBILITY IN PARKINSON DISEASE AFFECTS SLEEP EFFICIENCY

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BACKGROUND:

Impaired bed mobility (IBM) may be an important reason for the high prevalence of sleep insomnia in Parkinson disease (PD). Here we assessed the influence of subjectively IBM on objective sleep parameters in insomnia PD patients with (PD+IBM) and without (PD-IBM) concerns of IBM.

METHODS:

We included 44 PD patients with sleep initiation or maintenance concerns and 44 control subjects with primary insomnia. Polysomnographic sleep parameters, activity data, and the number of body position changes were compared between PD patients and controls as well as within the PD group between PD+IBM vs PD-IBM subjects.

RESULTS:

There were 54.5% of PD subjects who reported having IBM. In the PD+IBM group, the number of body position changes was significantly lower than in PD-IBM (0.4/h [0.0-1.8] vs 1.4/h [0.0-4.6], $P=.015$). Sleep efficiency (SE) was lower in PD+IBM patients (63.5; 26.2-85.6) compared to PD-IBM patients (78.4; 54.8-92.6; $P<.001$).

CONCLUSION:

PD patients who report IBM have fewer sleep-related body position changes (i.e., nocturnal hypokinesia) than PD patients without such concerns. Furthermore, objective SE is significantly diminished in these patients.

Sleep Medicine (2013) 14: 688-674.

MEASURING SLEEP DEFICIT THROUGH SELF-REPORT IN ADOLESCENTS: DEVELOPMENT AND VALIDATION OF THE CHRONIC SLEEP REDUCTION QUESTIONNAIRE-SHORT FORM (CSRQ-SF)

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Introduction

Chronic sleep reduction, resulting from insufficient and/or poor sleep over a long time period, is a common phenomenon in adolescents. Due to its severe negative psychological and behavioral daytime consequences, it is important to have a reliable and valid measure of symptoms of chronic sleep reduction. This study aims to validate an adapted, short form version of the Chronic Sleep Reduction Questionnaire (CSRQ), measuring universal symptoms of chronic sleep reduction.

Methods

Various samples from the general population and clinical cases were included in the study. The CSRQ was adapted on the basis of principal components analysis, item-total correlations, and substantive consideration. The adapted, short form version (CSRQ-SF) was validated by calculating correlations with self-reported and objective sleep and self-reported daytime functioning, and by determining how well the CSRQ-SF discriminates between general and clinical samples, which are assumed to differ in the extent of chronic sleep reduction.

Results

Internal consistencies of the CSRQ-SF were good. Correlations with self-reported sleep, daytime functioning and objective sleep variables were similar to the correlations with the original questionnaire. Furthermore, the CSRQ-SF has been found to discriminate well between clinical and non-clinical cases, further supporting its validity.

Conclusion

The CSRQ-SF appears to be a reliable and valid questionnaire. Due to the limited number of items referring to universal symptoms of chronic sleep reduction only, and the availability of cut-off scores, it is a practical tool for clinical and research purposes.

EFFECTS OF A SINGLE NIGHT OF SLEEP DEPRIVATION ON CEREBROSPINAL FLUID AMYLOID-BETA DYNAMICS IN HEALTHY MALE VOLUNTEERS

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Introduction: In epidemiological studies, sleep disturbances have been linked to an increased risk of Alzheimer's disease (AD), a neurodegenerative disorder in which the accumulation of amyloid proteins plays an essential pathophysiological role. Recent mechanistic studies in rodent models showed that extended wakefulness is associated with increased production and deposition of amyloid β ($A\beta$) proteins in the brain, and that sleep leads to a marked fall in their production. We investigated the relation between sleep and $A\beta$ levels in human subjects, using sleep deprivation and repeated cerebrospinal fluid (CSF) sampling.

Methods: Using an indwelling intrathecal catheter, CSF samples were collected from 26 healthy male volunteers (40-60 yrs) before and after a night with unrestricted sleep (n=13) and before, during and after a night of total sleep deprivation (n=13). $A\beta_{42}$ and $A\beta_{40}$ concentrations were determined at 10 time points (sleep deprivation group) or 6 time points (control group) divided over 24 hours. Polysomnographic recordings were performed during the entire study period.

Results: The sampling procedure was well tolerated. Control subjects slept on average 382 minutes (SD 58.5), with a sleep efficiency of 77.3 +/- 12.1%. Total sleep time in the deprivation group was 19.1 +/- 31.9 minutes; 1 subject accumulated a little over 90 minutes of sleep during the sampling period. A first analysis of $A\beta_{42}$ levels showed that after unrestricted sleep, levels decreased to 91% of baseline. In contrast, sleep deprived subjects showed an increase in CSF $A\beta_{42}$ levels to 109% (p<0.05).

Conclusion: We succeeded in translating an animal model to study short-term effects of sleep and sleep deprivation on $A\beta_{42}$ levels into a continuous CSF sampling method in healthy volunteers. Preliminary data support the hypothesis that during unrestricted sleep CSF $A\beta_{42}$ levels decline, resulting in diurnal rhythm in $A\beta$ dynamics; and that sleep deprivation prevents this nocturnal decrease.

APSS abstract, Sleep 36; A329.

SLEEP AND CIRCADIAN RHYTHMICITY IN ADULT ADHD AND THE EFFECT OF STIMULANTS: A REVIEW OF THE CURRENT LITERATURE

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Introduction: This review updates information on sleep and circadian rhythmicity in adult ADHD especially as to circadian rhythmicity and the influence of stimulants.

Method: Investigations into sleep, chronotype and circadian rhythm in adult ADHD were searched in the Cochrane Library, Embase, Medline, and PsycInfo databases.

Results: ADHD in adults is associated with longer objective sleep latency, irrespective of insomnia complaints. Sleep maintenance is disturbed and waking up time is delayed. Adult ADHD is associated with increased eveningness, delayed dim light melatonin onset, and later waking up time. Stimulant treatment induces delay of nonparametric circadian parameters, whereas light therapy induces shifts towards morningness which is associated with a reduction of ADHD symptoms.

Conclusion: Adult ADHD is associated with delayed circadian rhythmicity and analogous sleep characteristics, which are typical of a delayed sleep phase disorder (DSPD). Stimulants induce delay of circadian rhythmicity.

Snitselaar, M. A., Smits, M. G., van der Heijden, K. B., & Spijker, J. (2013). Sleep and Circadian Rhythmicity in Adult ADHD and the Effect of Stimulants : A Review of the Current Literature. J.Atten.Disord.

EFFECT OF LABORATORY SLEEP DEPRIVATION ON SELFREPORTED POSITIVE AND NEGATIVE AFFECT

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Introduction: The Positive and Negative Affect Schedule (PANAS) is a 20-item subjective scale of mood from which composite measures of positive affect (PA; 10 items) and negative affect (NA; 10 items) are

derived. It is believed that PA items tap 4 content categories captured by subscales labeled Attentive, Strong, Excited, and Proud. Here we explore the effect of laboratory sleep deprivation on PANAS composite measures as well as content categories.

Methods: Twelve healthy adults (aged 27.4 ± 4.5 y; 5F) spent 6 consecutive 24h days in a sleep laboratory with continuous behavioral monitoring. Psychiatric and medical health was screened by a psychiatrist.

Subjects experienced 62h total sleep deprivation (TSD), preceded (baseline) and followed (recovery) by 2 days with 10h time in bed for sleep (22:00-08:00). Across each day, subjects filled out the PANAS at 09:00, 13:00, 19:00 and 21:00. Composite PA and NA as well as PA subscale scores were analyzed with mixed-effects ANOVA with fixed effect for study phase (baseline, TSD, recovery) and random effect for intercept over subjects.

Results: NA showed a significant but small increase with sleep deprivation (average scores increased from 11.0-12.0 on a scale of 10-50; $F[1,22]=10.4$, $P=0.004$). PA was significantly reduced during TSD compared to baseline and recovery (average scores reduced from 23.9 to 18.1; $F[1,22]=30.3$, $P<0.001$). There was between-subjects variability in the magnitude of this effect, with subjects' raw self-reported PA score dropping by 1.5-12.1 points during TSD. Further, 3 of the 4 PA subscales were significantly reduced: Attentive ($F[1,22]=39.5$, $P<0.001$), Strong ($F[1,22]=22.4$, $P<0.001$) and Excited ($F[1,22]=17.1$, $P<0.001$). There was no significant change in Proud ($F[1,22]=1.4$, $P=0.25$).

Conclusion: In previous studies involving one night of sleep deprivation, self-reported PA decreased while NA did not change appreciably. Similarly, across this laboratory study with two days (62h) of TSD, negligible amounts of NA were endorsed while PA showed a more substantial decline with considerable variation between subjects. Further, TSD significantly reduced 3 of 4 content categories of PA: Attentive, Strong and Excited (but not Proud). Low PA is thought to confer vulnerability for certain psychiatric disorders such as depression, and as such may constitute a mechanism by which sleep loss is related to the onset and course of these disorders.

CDMRP award W81XWH-05-1-0099 and NIH grant CA167691

APSS abstract, Sleep 36; A96.

THE EFFECTS OF BENZODIAZEPINE RECEPTOR AGONISTS ON DRIVING PERFORMANCE AS ASSESSED BY STANDARD DEVIATION OF LATERAL POSITION

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Introduction: The most commonly used hypnotics are the benzodiazepine receptor agonists (BzRAs) with the shorter acting agents only inducing sleep while the longer acting compounds induce and maintain sleep. The objective of this analysis is to determine the effects of hypnotics on driving performance and to identify predictors of this impairment.

Methods: In April 2012 a literature search (Medline, Pubmed, and Embase) was conducted, using search terms “driving test”, “SDLP”, “on-the-road” and “benzodiazepine”. All double-blind, placebo-controlled

studies that used standard deviation of lateral position (SDLP) as the primary endpoint were selected. Data were categorized according to drug dose, half life, and time of drug administration relative to driving. These data were subjected to a meta-analysis.

Results: Fourteen studies were included. Across hypnotics significant impairment was found. All hypnotics, except zolpidem and zaleplon, were associated with significant impairment. Relative to morning driving, afternoon driving was a significantly less impaired. However, several drugs impaired driving in the afternoon. When “high” and “low” doses were compared, there was a dose dependent impairment in SDLP. While zolpidem did not impair driving performance when administered at bedtime it did impair driving when administered in the middle of the night. Middle of the night administration of zopiclone, but not zaleplon, also caused significant impairment. Finally, trichotomizing all the drugs into three half life bins (short: <6hrs, intermediate: 6-12hrs, long: >12hrs) revealed that both intermediate and long acting drugs caused significant morning driving impairment, while short acting hypnotics did not.

Conclusion: These analyses indicate that duration of action (half-life, dose) and drug ingestion time relative to driving all have to be taken into account before driving after ingestion of BZRAs.

Financial support provided by Merck, Inc

APSS abstract, Sleep 36; A221.

THE SEROTONIN TRANSPORTER 5-HTTLPR POLYMORPHISM MODERATES THE ASSOCIATION BETWEEN SUBJECTIVE SLEEP QUALITY AND POSITIVE AFFECT

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Introduction Sleep and affect are closely intertwined. The neurotransmitter serotonin (5HT) is both associated with sleep and affect regulation. This study investigated whether the 5-HTTLPR polymorphism in SCL6A4 modulates the association between subjective sleep quality and affect.

Methods A sample of 361 5-HTTLPR genotyped women from the general population underwent a 5-day experience sampling protocol assessing ambulatory positive and negative affect ten times a day, along with daily sleep quality ratings upon awakening.

Results There was a significant two-way interaction between allelic variation and sleep quality for the L/L vs. S/S comparison ($b=-.03$, $p<.05$) as well as the L/L vs. S/L comparison ($b=-.03$, $p<.05$) for positive affect. Carriers of one or two S alleles had a significantly steeper slope compared to L/L carriers ($\chi^2=4.15$, $p<.05$ and $\chi^2=3.90$, $p<.05$, respectively).

Conclusion 5-HTTLPR allelic variation interacts with sleep quality to predict positive affect the next day. The association between subjective sleep quality and positive affect the next day was stronger in carriers of at least one copy of the S-allele compared to in L/L carriers, supporting the notion of a link between sleep and affect regulation, in which serotonin may play a role.

Presented at Update@Kempenhaeghe.nl, International Clinical Symposium, Heeze, March 22nd 2013.

EEG ALPHA POWER AS AN INTERMEDIATE MEASURE BETWEEN BDNF VAL66MET AND DEPRESSION SEVERITY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Major depressive disorder (MDD) has a large impact on patients and society and is projected to be the second greatest global burden of disease by 2020. The Brain Derived Neurotrophic Factor (BDNF) gene is considered to be one of the important factors in the aetiology of MDD. In a recent study, alpha power was found to mediate between BDNF Met and subclinical depressed mood. The current study looked at a population of MDD patients (N=107) to examine the association between the BDNF Val66Met polymorphism, resting state EEG alpha power and depression severity. For this purpose repeated-measures ANOVA, partial correlation and multiple linear models were used. Results indicated a negative association between parietal-occipital alpha power in the eyes open resting state and depression severity. Also, Met/Met patients showed lower global absolute alpha power in the eyes closed condition compared to Val-carriers. These findings are in accordance with the previously uncovered pathway between BDNF Val66Met, resting state EEG alpha power and depression severity. Additional research is needed for the clarification of this tentative pathway and its implication in personalized treatment of MDD.

J of Clin Neurophysiology 2013 (in press).

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**Annual Proceedings of the NSWO
Volume 24, 2013**

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