

**SLEEP-WAKE**  
**Research in the Netherlands**

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# CONTENTS

PREFACE .....	9
EDITORIAL NOTE.....	11
<b>PhD Theses .....</b>	<b>13</b>
SLEEP BENEFIT IN PARKINSON'S DISEASE .....	14
M. van Gilst	
INDIVIDUAL DIFFERENCES IN SHIFT WORK TOLERANCE .....	16
H.M. Lammers-van der Holst	
<b>Research papers .....</b>	<b>21</b>
SLEEP AND PERFORMANCE IN ELITE ATHLETES .....	22
A. Nieuwenhuys	
ON-THE-ROAD DRIVING PERFORMANCE THE MORNING AFTER BEDTIME USE OF THE OREXIN ANTAGONIST SUVOREXANT .....	32
A Vermeeren	
IMPACT OF SLEEP DEPRIVATION AND CAFFEINE ON WORKING MEMORY MANAGEMENT.....	35
D.M. Sorta	
SOMNAMBULISM AND MILITARY SERVICE .....	39
A. Coenen	
<b>Abstracts .....</b>	<b>43</b>
A GROUNDED THEORY STUDY ON THE INFLUENCE OF SLEEP ON PARKINSON'S SYMPTOMS .....	44
M.M. van Gilst	
SLEEP AND FOOD CHOICE IN A DUTCH STUDENT POPULATION.....	45
CHC Leenaars	
THE LEEDS FOOD PREFERENCE QUESTIONNAIRE AFTER MILD SLEEP RESTRICTION – A SMALL FEASIBILITY STUDY.....	46
CHC Leenaars	
TIME DELAY BETWEEN CARDIAC AND BRAIN ACTIVITY DURING SLEEP.....	47
X. Long	
EFFECTS OF BETWEEN- AND WITHIN-SUBJECT VARIABILITY ON AUTONOMIC CARDIORESPIRATORY ACTIVITY DURING SLEEP AND THEIR LIMITATION ON SLEEP STAGING: A MULTILEVEL ANALYSIS .....	48
X. Long	
DETECTION OF NOCTURNAL SLOW WAVE SLEEP BASED ON CARDIORESPIRATORY ACTIVITY IN HEALTHY ADULTS .....	49
X. Long	
ESTIMATING ACTIGRAPHY FROM MOTION ARTIFACTS IN ECG AND RESPIRATORY EFFORT SIGNALS.....	50
P. Fonseca	
SLEEP STAGE CLASSIFICATION WITH ECG AND RESPIRATORY EFFORT.....	51
P. Fonseca	
CARDIORESPIRATORY SLEEP STAGE DETECTION USING CONDITIONAL RANDOM FIELDS .....	52
P. Fonseca	
DETERMINANTS OF PERCEIVED SLEEP QUALITY IN NORMAL SLEEPERS, INCLUDING NIGHT-TO-NIGHT VARIABILITY .....	53
M.S. Goelema	
SUBJECTIVE RATINGS AND PERFORMANCE IN THE HEAT AFTER SLEEP DEPRIVATION .....	54
H.A.M. Daanen	
SPATIALLY SPECIFIC CHANGES IN EEG SPECTRAL POWER IN POST TRAUMATIC STRESS DISORDER DURING REM AND NREM SLEEP .....	55
L.M. Talamini	

SIGMA FLUCTUATIONS IN POLICE OFFICERS AND COMBAT VETERANS WITH PTSD .....	56
L.M. Talamini	
HITTING THE RIGHT SPOT: A NEW CLOSED-LOOP STIMULATION PROCEDURE FOR OSCILLATORY PHASE TARGETING.....	57
L.M. Talamini	
A NEW MINIMAL ASSUMPTION, SPINDLE ANALYSIS METHOD, APPLIED TO PTSD SLEEP .....	58
L.M. Talamini	
THE IMPACT OF TRAINING LOAD ON SLEEP PARAMETERS IN ELITE ATHLETES .....	59
M. Knufinke	
PREVALENCE OF PHYSICIAN-DIAGNOSED ASTHMA IN PATIENTS WITH SUSPECTED OBSTRUCTIVE SLEEP APNEA SYNDROME: A CROSS-SECTIONAL ANALYSIS OF THE ESADA DATABASE.....	60
G. Lo Grasso	
REM REBOUND DURING CPAP TITRATION AS A PREDICTOR OF CHRONIC CPAP COMPLIANCE.....	61
T. Vranken	
UPPER AIRWAY STIMULATION FOR OBSTRUCTIVE SLEEP APNEA: QUALITY OF LIFE OUTCOME AFTER 30 MONTHS OF FOLLOW UP .....	62
J. Verbraecken	
SLEEP DISTURBANCES ARE ASSOCIATED WITH REDUCED HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SUBSTANCE USE DISORDER.....	63
E.H. Magnée	
SLEEP DEPRIVATION AND HIPPOCAMPAL VULNERABILITY: CHANGES IN NEURONAL PLASTICITY, NEUROGENESIS AND COGNITIVE FUNCTION .....	64
J. Kreutzmann	
EARLY-LIFE ORIGIN OF ADULT INSOMNIA: DOES PRENATAL EARLY-LIFE STRESS PLAY A ROLE? .....	65
L. Palagini	
SLEEP DEPRIVATION CAUSES MEMORY DEFICITS BY NEGATIVELY IMPACTING NEURONAL CONNECTIVITY IN HIPPOCAMPAL AREA CA1 .....	66
R. Havekes	
TIMING OF EXAMS AFFECTS SCHOOL PERFORMANCE DIFFERENTLY IN EARLY AND LATE CHRONOTYPES .....	67
V. van der Vinne	
SLEEP RESTRICTION IN RATS LEADS TO CHANGES IN OPERANT BEHAVIOR INDICATIVE OF REDUCED PREFRONTAL CORTEX FUNCTION.....	68
J. Kamphuis	
THE TWO-PROCESS MODEL OF SLEEP REGULATION: A REAPPRAISAL.....	69
A. A. Borbély	
MODELING SLEEP ALTERATIONS IN PARKINSON'S DISEASE: HOW CLOSE ARE WE TO VALID TRANSLATIONAL MODELS? .....	70
K. Fifel	
PLASTICITY OF CIRCADIAN CLOCKS AND CONSEQUENCES FOR METABOLISM.....	71
C. P. Coomans	
THERMOREGULATION IN SLEEP AND HIBERNATION .....	72
K. Kräuchi	
CAFFEINE INCREASED LIGHT RESPONSIVENESS OF THE MOUSE CIRCADIAN PACEMAKER .....	73
T. Deboer	
DIM LIGHT AT NIGHT CHANGES SLEEP PATTERNS IN MICE .....	74
M. Panagiotou	
AGING IS ASSOCIATED WITH ALTERED NON-RAPID-EYE MOVEMENT SLEEP SLOW-WAVE CHARACTERISTICS IN MICE.....	75
M. Panagiotou	
LONG TERM EFFECTS OF SLEEP DEPRIVATION ON HYPOTHALAMIC NUCLEI.....	76
K. Fifel	

CORTICAL NETWORK DYNAMICS DIFFER AFTER TORPOR AND SLEEP DEPRIVATION IN DJUNGARIAN HAMSTERS.....	77
V. Vyazovskiy	
CIRCADIAN AND HOMEOSTATIC MODULATION OF MULTI-UNIT ACTIVITY IN DOPAMINERGIC AND STRIATAL STRUCTURES .....	78
K. Fifel	
DIM LIGHT AT NIGHT DISTURBS THE DAILY SLEEP-WAKE CYCLE AND SLEEP ARCHITECTURE IN RATS .....	79
D.J. Stenvers	
THE EFFECT OF AGING ON NREM SLEEP EEG SLOW WAVES IN MICE.....	80
M. Panagiotou	
CHRONIC HIGH FAT DIET INCREASES RAPID EYE MOVEMENT SLEEP IN MICE.....	81
M. Panagiotou	
TIRED OF BLUNT TOOLS? SHARPENING THE CLINICAL ASSESMENT OF FATIGUE AND SLEEPINESS .....	82
O. Mairesse	
EMOTION REGULATION MEDIATES THE RELATIONSHIP BETWEEN PERSONALITY AND SLEEP QUALITY .....	83
I. Vantieghem	
EXERCISE DURING SHORT-TERM AND LONG-TERM CONTINUOUS EXPOSURE TO HYPOXIA EXACERBATES SLEEP-RELATED PERIODIC BREATHING .....	84
H.F. Tellez	
INDIVIDUAL DIFFERENCES IN SUBJECTIVE CIRCADIAN FLEXIBILITY .....	85
N. Marcoen	
COMPLEX SLEEP APNEA AT AUTO TITRATING CPAP INITIATION: PREVeLANCE, SIGNIFICANCE AND PREDICTIVE FACTORS .....	86
D. Neu	
ALTITUDE AND SEASONALITY IMPACT ON SLEEP IN ANTARTICA.....	87
G. Collet	
DOES MORE SLEEP MATTER? DIFFERENTIAL EFFECTS OF NREM- AND REM-DOMINANT SLEEP ON SLEEPINESS AND VIGILANCE .....	88
D. Neu	
WHOSE CLOCK MAKES YOURS TICK? HOW MATERNAL CARDIORESPIRATORY PHYSIOLOGY INFLUENCES NEWBORN'S HEART RATE VARIABILITY .....	89
M. Van Puyvelde	
SLOW WAVE SLEEP IN THE CHRONICALLY FATIGUED: POWER SPECTRA DISTRIBUTION PATTERNS IN CHRONIC FATIGUE SYNDROME AND PRIMARY INSOMNIA .....	90
D. Neu	
eAMI: A QUALITATIVE QUANTIFICATION OF PERIODIC BREATHING BASED ON AMPLITUDE OF OSCILLATIONS .....	91
H.F. Tellez	
RUMINATION IS ASSOCIATED WITH A REDUCED EFFICIENCY IN COGNITIVE CONTROL AND PERCEIVED SLEEP QUALITY .....	92
C. Muscarella	
VALIDATION AND PSYCHOMETRIC PROPERTIES OF THE 'BRUGMANN FATIGUE SCALE' (BFS): A NEW INSTRUMENT FOR THE CLINICAL ASSESSMENT OF PERCEIVED FATIGUE .....	93
D. Neu	
PRELIMINARY DATA ON THE EFFECTIVENESS AND COMPLIANCE OF A SLEEP POSITIONING PILLOW IN THE TREATMENT OF POSITIONAL SLEEP RELATED BREATHING DISORDERS .....	94
J. Newell	
EFFECTS OF LIGHT AND TEMPERATURE ON ALERTNESS AND THERMOPHYSIOLOGICAL RESPONSES.....	95
M. te Kulve	

CIRCADIAN RHYTHMS IN GLUCOSE AND LIPID METABOLISM IN NOCTURNAL AND DIURNAL MAMMALS .....	96
P.K. Jha	
SEROTONIN, A POSSIBLE INTERMEDIATE BETWEEN DISTURBED CIRCADIAN RHYTHMS AND METABOLIC DISEASE .....	97
R.I. Versteeg	
EFFECTS OF CENTRAL GASTRIN-RELEASING PEPTIDE ON GLUCOSE METABOLISM .....	98
P.K. Jha	
THE ROLE OF FEEDING RHYTHM, ADRENAL HORMONES AND NEURONAL INPUTS IN SYNCHRONIZING DAILY CLOCK GENE RHYTHMS IN THE LIVER.....	99
Y. Su	
EFFECTS OF 6-MEALS-A-DAY FEEDING AND 6-MEALS-A-DAY FEEDING COMBINED WITH ADRENALECTOMY ON DAILY GENE EXPRESSION RHYTHMS IN RAT EPIDIDYMAL WHITE ADIPOSE TISSUE.....	100
Y. Su	
SUPRACHIASMATIC NUCLEUS NEUROPEPTIDES AND THEIR CONTROL OF ENDOGENOUS GLUCOSE PRODUCTION .....	101
E. Foppen	
ABSENCE OF DIURNAL VARIATION IN VISCEROMOTOR RESPONSE TO COLORECTAL DISTENTION IN NORMAL LONG EVANS RATS.....	102
S. Botschuijver	
INDIVIDUAL DIFFERENCES IN SLEEP TIMING RELATE TO MELANOPSIN-BASED PHOTOTRANSDUCTION IN HEALTHY ADOLESCENTS AND YOUNG ADULTS.....	103
W.P. van der Meijden	
SLEEP RESTRICTION ACUTELY IMPAIRS GLUCOSE TOLERANCE IN RATS.....	104
P.K. Jha	
NUTRITION IN THE SPOTLIGHT: METABOLIC EFFECTS OF ENVIRONMENTAL LIGHT .....	105
R.I. Versteeg	
SLEEPINESS AND MELATONIN SUPPRESSION DURING EVENING EXPOSURE TO BLUE-DEPLETED AND VIOLET-ENRICHED WHITE LIGHT .....	106
J. Souman	
CIRCADIAN RHYTHM DISRUPTION AS A LINK BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY? .....	107
S.W.N. Vogel	
INDIVIDUAL AND FAMILIAL SUSCEPTIBILITY TO MPTP IN A COMMON MARMOSSET MODEL FOR PARKINSON'S DISEASE .....	108
S. Franke	
OCCURRENCE OF OBSTRUCTIVE SLEEP APNEA SYNDROME WITH TRANSIENT ISCHEMIC ATTACK .....	109
M.H. Schipper	
ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS ADD RISK TO CIRCADIAN RHYTHM SLEEP PROBLEMS IN DEPRESSION AND ANXIETY.....	110
T.I. Bron	
THE ASSOCIATION BETWEEN METABOLIC SYNDROME, OBESITY-RELATED OUTCOMES, AND ADHD IN ADULTS WITH COMORBID AFFECTIVE DISORDERS.....	111
D. Wynchank	
ADHD, CIRCADIAN RHYTHMS AND SEASONALITY .....	112
D.S. Wynchank	
SOCIAL SUPPORT MODERATES THE EFFECTS OF STRESS ON SLEEP IN ADOLESCENTS .....	113
F.J. van Schalkwijk	
MEMORY TRACES OF LONG-RANGE COORDINATED OSCILLATIONS IN THE SLEEPING HUMAN BRAIN .....	114
G. Piantoni	

THE ROLE OF SLEEP TIMING IN CHILDREN’S OBSERVATIONAL LEARNING .....	115
F.J. van Schalkwijk	
SLEEP TO THE BEAT: A NAP FAVOURS CONSOLIDATION OF TIMING.....	116
I.M. Verweij	
WAKE HIGH-DENSITY ELECTROENCEPHALOGRAPHIC SPATIOSPECTRAL SIGNATURES OF INSOMNIA.....	117
M.A. Colombo	
SLOW DISSOLVING OF EMOTIONAL DISTRESS CONTRIBUTES TO HYPERAROUSAL.....	118
R. Wassing	
DETERMINING the RELATIONSHIP BETWEEN SLEEP ARCHITECTURE, SEIZURE VARIABLES AND MEMORY IN PATIENTS WITH FOCAL EPILEPSY.....	119
L.A. Miller	
CARBON-WIRE LOOP BASED ARTIFACT CORRECTION OUTPERFORMS POST-PROCESSING EEG/FMRI CORRECTIONS – A VALIDATION OF REAL-TIME SIMULTANEOUS EEG/FMRI CORRECTION METHOD.....	120
J.N. van der Meer	
<b>Book Presentations.....</b>	<b>121</b>
SLAPERS .....	122
Bart Heynen	
<b>Members.....</b>	<b>123</b>
HONORARY MEMBERS .....	124
REGULAR MEMBERS.....	125



## PREFACE

During my 10-year presence in the board of the NSWO, I witnessed many important new developments both in the basic science of sleep and in sleep medicine. There has been a huge increase in the knowledge of the functions of sleep, the influence of sleep on memory, behaviour, metabolism and the immune system. Better knowledge of the importance of our chrono-biological system has led to a better understanding of behaviour of adolescents, substance abuse, several types of insomnia and physical performance in top sports. In sleep medicine, the strong relationships between sleep disordered breathing and hypertension, heart rhythm abnormality and cardiovascular disease, have been well established in the past decade. In addition, we learned that some specific neurodegenerative disorders can be preceded for many years by a sleep disorder called REM sleep behaviour disorder (RBD).

The NSWO has become the major institute for questions and answers concerning sleep for the professionals, press and others in the past decade. Amongst other things, the NSWO participated in public seminars, participated in writing a teaching book on sleep medicine and organised yearly web-polls. Many topics such as sleep and sleep disorders in children and the effect these have on their parents, sleep and work, sleep and driving and sleep and learning were amongst the subjects that resulted in a huge amount of media attention for our society. As a result, the NSWO succeeded in increasing the awareness of the general public about the importance of a good night sleep.

The recognition of sleep as a very important health factor has resulted in a growing number of psychologists and medical specialists with interest in sleep and its pathology. Therefore, the NSWO, together with the Belgium and British sleep societies, took the initiative in developing trainings courses on the basic physiology and medical aspects of sleep. This resulted in yearly held 4-day training courses, the “International Sleep Medicine Course (ISMC)” which was first held in The Netherlands in 2008. Several years later the ESRS started an accreditation process for sleep specialists, resulting in a European accreditation for somnologist as technician, medical specialist or psychologist. The 4-day ISMC courses were proven to be extremely helpful for those performing this now yearly held somnologist examination. At present, we count more than 35 somnologists in the Netherlands, working in one of the 15 accredited sleep centres. In the past few years, we aimed to encourage more young scientists to present and publish their studies. Apart from the existing poster prize and financial support for publishing a thesis, the NSWO board recently set the “Kamphuisen award” for the best bi-annual thesis on a topic concerning sleep. Furthermore prominent scientists are invited each year to give the Rudi van den Hoofdakker lecture at the NSWO annual meeting.

When the NSWO was founded 27 years ago, the board comprised of members from basic sciences and those with medical and clinical backgrounds as it is today. Obviously the focus of attention has always been shifting between these two areas of interest.

The knowledge of sleep has gained exponentially in recent years in such a way that NSWO was not able to fully cope with the demand and wishes from all different positions. In the coming years we will have to decide the future direction of the NSWO. A recent survey to discuss the future of the NSWO showed the very diverse opinions amongst our members.

Some like a more basic scientific approach, while others aim for a more clinical goal. This resulted in an up-to-date mission statement, which will be presented during this year's general member meeting. Also ESRS and other international sleep societies have coped with this issue, resulting in a proposal to include the term "sleep medicine" into its name, like our Belgian neighbours did.

The NSWO board has therefore proposed in 2012 to change its name into the Dutch association for Sleep medicine and Sleep research (Nederlandse vereniging voor Slaapgeneeskunde en Wetenschappelijk Onderzoek), without changing its acronym and logo. This is at present still under debate. Furthermore we think it is time to start a "young scientist" committee. Also our website has been upgraded so all members can modify their personal data and institute information. Recently also publications can be published and downloaded as PDF from the member-portal on our website. In the near future we will also add possibilities for uploading news items and other materials such as short videos in a separate continuous channel. However, this development was seemingly not fast enough for all. Some have recently founded medical groups and societies with a more clinical scope. In our aim to eventually create a Dutch Sleep Society in which both scientists and clinicians have their place, the NSWO decided for the first time to have its yearly meeting simultaneously with those representing clinical sleep medicine. We changed from a single into a two-day meeting. This has great advantages and justifies the many topics today in sleep research and sleep medicine, which could not be handled in one day. Also it ensures a multidisciplinary approach of different topics. More time means also a better approach in combining knowledge of so many different directions, which will allow a better understanding of the many functions of sleep, its physiology and pathophysiology. Hopefully, this meeting on November 3-4, 2016 might be the beginning of the new NSWO and new era for our tiny country, which is big in the research of sleep and has a long standing tradition in generating great sleep scientists.

Hans Hamburger, chairman NSWO  
September 2016

## EDITORIAL NOTE

2016 has been eventful for the NSWO. Together with Slaapgeneeskunde Vereniging Nederland (SVNL) we are organizing a brand new Dutch sleep symposium; SLAAP 2016. Not to forget the elaborate discussions on the direction our organisation should take. The details are still to be determined, but at the time of printing, it is clear that NSWO will focus more on research. The Scientific Committee has followed these proceedings with interest and will follow up with their own initiatives to these events; a Young Scientist Session at SLAAP 2016 and the initiation of a young scientist committee for the NSWO, where young scientists (PhD students and postdocs) can work out their own interests and help shape the organisation. We hope to see their contribution also in the yearbooks content in the future.

For this yearbook, we have actively tried to include all research that Dutch sleep scientists presented at conferences or published since the deadline of the preceding yearbook. As usual, past the first deadline there was hardly material enough for a thin booklet, but our efforts have resulted in the inclusion of 76(!) abstracts, where the 2015 yearbook only included 21. We would like to encourage all NSWO members to keep track of their publications and conference presentations throughout the year, to do even better for the 2017 edition!

Besides abstracts, this edition also contains 5 mini-papers on various topics. Last year, we included book reviews for the first time. We are pleased to continue this concept, although with just 1 book review included. The scientific basis of our organisation is broadening even further with the graduation of 2 of Ph.D. members. We are proud to present the summaries of their theses.

Trying to keep up with this digital era, we investigated the possibility of distributing our yearbook in an electronic version. Of our 200+ members 38 completed our little questionnaire on this topic. While more than 75% of the responders prefer reading from paper, the preference for an electronic or a paper version of the yearbook is about 50-50. We will therefore keep both options for now. All your suggestions will be discussed, and potentially incorporated in the next edition. Of course, if you feel you have missed out on our little inquiry, and are sitting with loads of good ideas, you can always let us know!

This yearbook is the result of the joined efforts of the scientific committee. We would like to express our gratitude to Floor, Johan and Peter for their help in the editorial process and as reviewers. Of course, we're very grateful to all contributors for providing the content.

Cathalijn Leenaars (chair scientific committee),  
Els Møst (editor yearbook),

September 2016.



**SLEEP-WAKE  
Research in The Netherlands**

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**PhD Theses**

# SLEEP BENEFIT IN PARKINSON'S DISEASE

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Some patients with Parkinson's disease experience a beneficial effect of sleep. They report improved mobility upon awakening, contrary to what would be expected after a night without medication. This interesting phenomenon is known as 'sleep benefit'. In this thesis sleep benefit was studied and described from several perspectives, and employing diverse methodology.

Chapter 2 presents the results of our first questionnaire study on sleep benefit. In a cohort of 243 Parkinson's patients, 46.9% of patients reported to be familiar with sleep benefit. Among those patients who regularly took a nap, 33.7% experienced sleep benefit after a nap as well. We found no differences in clinical or demographic characteristics between patients with and without subjective sleep benefit. However, the high self-reported prevalence of sleep benefit was reason to renew the research on this intriguing phenomenon.

In chapter 3 we performed a systematic review of the literature on sleep benefit. Most studies used questionnaires to study sleep benefit. There was large variation in the characteristics of sleep benefit found in different studies. Only one study used objective measures (UPDRS III) to assess sleep benefit. Across studies we found large variation in the definition of sleep benefit. This could in part explain the different findings across studies. Therefore, we proposed to combine these definition into one general definition for sleep benefit: *sleep benefit is the experience of a temporary decrease in Parkinson's symptoms upon awakening after a period of sleep (night or daytime), before drug intake; the patient is feeling as good as "on" (or better).*

Several hypotheses for the underlying mechanism of sleep benefit were discussed. Sleep benefit could be caused by replenishment of dopamine in nigral neuronal terminals during sleep. Others proposed that sleep benefit is merely a morning benefit, related to diurnal motor fluctuations rather than an effect of sleep. Even a beneficial effect of sleep deprivation was suggested, however, this hypothesis seemed less likely.

Sleep benefit could have great clinical potential, for example in scheduled afternoon naps as an addition to regular dopaminergic therapy. However, more research on the (objective) effects of sleep benefit is needed.

Chapter 4 studied sleep benefit prospectively using a 7-day symptom diary. Patients completed this diary at bedtime and directly at awakening. They gave an indication of their motor abilities at that specific moment. A positive change in motor function was observed after 267 nights (17.8%) and after 138 daytime naps (23.4%). Based on these results, 75 patients (32%) were classified as having sleep benefit. In response to a subsequent retrospective questionnaire, 73 patients (31%) reported to experience sleep benefit. Interestingly, the groups with sleep benefit according to either the diary or the questionnaire overlapped only partially: outcomes were congruent in 63% of subjects (both negative 49%, both positive 14%). The subjective experience of sleep benefit was not always

related to an actual increase in reported motor function. This showed the need for objective measures of sleep benefit.

Chapter 5 assessed sleep related changes in motor function using quantitative motor tasks. 18 Parkinson's patients with and 20 without subjective sleep benefit and 20 healthy controls participated. The tasks were performed before and after night sleep and a daytime nap. On both the pegboard task and the finger tapping tasks, patients were overall slower than healthy controls (night:  $F_{2,55} = 16.938$ ,  $p = 0.000$ ; nap:  $F_{2,55} = 15.331$ ,  $p = 0.000$ ). On the pegboard task, there was a small main effect of night sleep ( $F_{1,55} = 9.695$ ,  $p = 0.003$ ); both patients and controls were on average slightly slower in the morning. However, on both tasks there was no sleep\*group interaction, neither for nighttime sleep nor for the afternoon nap. We found no correlations in task performance and mood/vigilance or sleep time/efficiency. This study showed that the subjective experience of sleep benefit is not accompanied by an actual improvement in motor functioning. Sleep benefit appeared to be a subjective phenomenon rather than a Parkinson-specific reduction in symptoms.

In chapter 6 we used a grounded theory approach to get more insight in what patients, who report sleep benefit, experience when they wake up. We interview 14 patients that unambiguously reported subjective sleep benefit in a questionnaire. Some, but certainly not all, patients described a temporal decrease in their Parkinson motor symptoms after sleep. However, several patients did not meet the definition of sleep benefit at all. Others experienced beneficial effects of sleep, but not a specific decrease of motor symptoms. There were no general sleep related factors that influenced the presence of sleep benefit. Other factors that were mentioned to influence functioning at awakening were mostly stress related. This study showed that the group of patients convincingly reporting sleep benefit in a questionnaire was very heterogeneous, with only a portion of the patients describing motor sleep benefit. Probably the group of patients actually experiencing motor sleep benefit is far smaller than thought so far, based on previous questionnaire studies.

In chapter 7 we presented a study design for future research on sleep benefit. We introduced a new technique for computerized vision based (video) analyses that can be used to assess motor performance upon awakening in a home environment. 30 Parkinson's patients (15 with and 15 without subjective sleep benefit), will have a video camera installed in their bedroom during a 4 week follow-up period. The camera will record from one hour before until one hour after awakening and register the morning ritual including walking from the bed to the bedroom door. With this technique spatiotemporal and kinematic data (such as walking speed, joint angles, step length, arm swing etc) can be automatically extracted from the video registration. This allows for longitudinal objective assessment of daily life movements without having to wear sensors.

In chapter 8 the main findings of this thesis were discussed. We addressed recurring themes in the different studies, such as the definition of sleep benefit and whether it is a subjective or objective phenomenon. Furthermore, directions and challenges for future research were evaluated, with a focus on the role of qualitative and computer vision methods in clinical research.

# INDIVIDUAL DIFFERENCES IN SHIFT WORK TOLERANCE

H.M. Lammers-van der Holst

February 2016

Shift work is a key feature of our contemporary 24/7 society, employing several successive work teams to sustain around-the-clock operations. Over the last few decades, shift work has increased substantially to meet the demands of industrialization and globalization. Depending on the classification of work hours used, the prevalence of shift work within the Netherlands vary from 17% to 22% of the working population (Kerkhof, 2016 in preparation; Koppes et al., 2013).

Numerous studies present results that imply that frequently shifting the periods of sleep and wakefulness poses a serious threat to the shift worker's physical, mental and psychosocial health (Boivin & Boudreau, 2014) . When working in shifts, the temporal variations of the homeostatic and circadian pressure are desynchronized, resulting in sleep debt and increased sleepiness (Van Dongen, 2006). The misaligned sleep-wake pattern feeds back on to the core processes of the circadian system, thereby disrupting the biological clock (Archer et al., 2014).

In the short term, shift workers suffer from insomnia and/or excessive sleepiness, performance decrements, and mood swings (Drake et al., 2004; Ohayon et al., 2010; Rajaratnam et al., 2013). In the long term, workers may develop shift work disorder, including complaints of either insomnia or excessive sleepiness, and a variety of other physical and mental health-related problems (Roth, 2012; Wright et al., 2013). Sleep-wake disturbances are among the most pertinent and challenging problems of shift work (Åkerstedt, 2003; Åkerstedt & Wright, 2009; Wright et al., 2013). Even in retirement, shift workers report more sleep problems than day workers (Monk et al., 2013).

One of the major issues related to the adverse consequences of shift work concerns the impact of inter-individual differences. Some workers tolerate shift work well, whereas others develop symptoms of chronic illness. Given the central role of sleep deficiencies in shift work, it has been proposed that person-specific characteristics of sleep/wake regulation may be involved in inter-individual differences in shift work tolerance. Trait vulnerability to sleep loss, circadian phase position (chronotype), and flexibility of sleep timing (natural ability to sleep and work at unusual times of day) have been put forward, but conclusive evidence has not yet been presented (Kerkhof, 1985; Van Dongen, 2006; Van Dongen & Belenky, 2009; Kantermann et al., 2010).

The aim of this thesis was to investigate the facets of shift work tolerance, focused on inter-individual variability in response to shift work and the search for potential baseline predictors, using both cross-sectional and longitudinal data. In the first part of this thesis we used an exploratory approach to the concept of shift work tolerance with 2 cross-sectional



studies. In the second part of this thesis, a unique sample of novice police officers was used for three longitudinal studies to provide insight into inter-individual variability in response to shift work over time. Shift work tolerance was operationalized by objective and subjective assessments on sleep, fatigue and stress responses.

In the first cross-sectional study, a large survey was set out to examine how subjective shift work tolerance was related to general health variables, with the expectation of inter-individual differences in the nature of this relation (Lammers-van der Holst & Kerkhof, 2014). A total of 740 employees of the Dutch police force completed a questionnaire, covering seven health-related domains: sleep quality, sleep duration, need for recovery, fatigue, physical health, mental health, and work–life balance. Based on subjective reports of shift work tolerance, participants were classified as intolerant, medium-tolerant, or tolerant workers. Eighteen percent of the shift workers were classified as intolerant. Analysis involved group comparisons, regression, and cluster analysis. The intolerant and medium-tolerant workers expressed more severe complaints than the tolerant workers, for all seven health-related domains. Shift work tolerance was primarily related to sleep quality and subsequently to need for recovery, fatigue and work–life balance. No indications were found for systematic inter-individual differences in the nature of this relationship. For all participants equally, the degree of shift work tolerance was related to the severity of health-related complaints. This study highlights the central role of sleep for tolerance to shift work and underlines the need for occupational medicine to take explicit account of sleep.

In the second cross-sectional study, the aim was to investigate individual factors in relation to subjective health and sleep variables, used as indicators for (in)tolerance of shift work (van der Holst & Kerkhof, 2005). A questionnaire was administered to 315 croupiers working in Dutch casinos. Investigating sleep deficiencies and well-being of croupiers in relation to working hours is unique. Subjective health, emotional exhaustion, sleep quality and sleep duration were used as indicators for shift work tolerance. The set of individual factors included flexibility of sleeping habits, vigorousness, morningness, habitual sleep time, age and shift work exposure. Results of the multiple regression analyses showed that flexibility of sleeping habits and vigorousness were the main factors related to all four indicators of shift work tolerance. Furthermore, age and shift work exposure were associated to subjective health and habitual sleep time was associated to sleep quality and sleep duration.

In these described surveys, the healthy-worker effect may have confounded the results and no causal conclusions could be made due to the cross-sectional design. Therefore, the second part of this thesis focused on a prospective design, with the inclusion of objective assessments to complement the subjective results above.

In the third study, a longitudinal field study of novice police officers was carried out to examine prospectively whether individual nighttime sleep characteristics at baseline (prior to shift work exposure) were related to parameters of daytime sleep after commencing shift work (Lammers-van der Holst et al., 2006). A total of 26 subjects were examined at baseline before they entered shift work and re-examined during follow-up sessions after four and twelve months of shift work exposure.

With the use of wrist actigraphy and sleep diaries, nocturnal sleep at baseline and daytime sleep after night shifts during follow-up sessions were examined. Estimated total sleep time, sleep efficiency, and subjective sleep quality were analyzed as outcome variables. Daytime total sleep time showed a 66 min decline during the first year of shift work exposure. Systematic inter-individual differences were observed for daytime total sleep time and subjective sleep quality (explaining 53% and 38% of the variance, respectively), suggesting potential predictability of these sleep parameters. Although no predictors were found for daytime total sleep time, the subjective quality of nighttime sleep before the onset of shift work predicted 40% of the variance in the subjective quality of daytime sleep after commencing shift work.

The objective of the fourth study was to evaluate the development of individual stress responses to commencing shift work (Lammers-van der Holst & Kerkhof, 2015). Cortisol acts as a critical biological intermediary through which chronic stressors like shift work impact upon multiple physiological, neuro-endocrine and hormonal functions. Therefore, the cortisol awakening response (CAR) was suggested as a prime index of shift work tolerance. A longitudinal field study of young novice police officers (N = 25) was performed, including a baseline session and three follow-up sessions about 4, 14 and 20 months of shift work exposure. Inter-individual differences were measured by repeated assessments of the CAR. Results showed that in the interval between about four and 14 months after transitioning from regular day work to rotating shift work, mean values began to rise from baseline to significantly higher levels at about 14 months after commencing shift work. Visual inspection of the individual trends revealed that a subgroup of 10 subjects followed a monotonically rising trend, whereas another 14 subjects, after an initial rise from about four to 14 months, reverted to a smaller, baseline level cortisol response at about 20 months after the start of shift work. If the initial increase in the cortisol response marks the development of a chronic stress response, the subsequent reversal to baseline levels in the subgroup of 14 participants might be indicative of a process of recovery, possibly the development of shift work tolerance.

In continuation of the third study, the fifth study examined inter-individual differences in sleep responses within the first two years of shift work exposure, using data of all three follow-up sessions (Lammers-van der Holst et al., 2016). Moreover, to search for potential baseline predictors thereof. A total of 42 subjects was assessed at baseline, prior to

commencing shift work. They were re-assessed during three follow-up sessions within the first two years of shift work exposure after approximately 4, 12 and 20 months of rotating shift work.

Wrist actigraphy and sleep diaries were used to investigate nocturnal sleep at baseline and daytime sleep after night shifts during the three follow-up sessions. Actigraphically estimated total sleep time and subjective sleep quality were analyzed as outcome variables, using mixed-effects analysis of variance. Systematic inter-individual differences in the overall response to shift work were observed. In this sample, flexibility of sleeping habits and gender were found to be significant predictors of daytime total sleep time in the first 2 years of shift work exposure. Flexibility of sleeping habits and subjective quality of nighttime sleep prior to shift work were significant predictors of subjective quality of daytime sleep. These results suggest that it may be possible to detect and even predict sleep deficiencies in response to shift work early on, which could be beneficial in terms of productivity and well-being of the shift worker.

In conclusion, this thesis provides a better understanding of shift work tolerance and rudiments for identifying 'vulnerable' shift workers. Sleep was expressed as a significant predictor of shift work tolerance and as a major outcome variable to identify inter-individual variability in the responses to shift work. Occupational medicine should pay more attention to the prominent role of sleep in shift work tolerance.

Early detection of maladaptation to shift work is an essential first step in the targeting of person-directed interventions in order to decrease risks of sleepiness-related accidents and help prevent long-term adverse health outcomes (Herbst et al., 2013). Participation of the individual shift worker in scheduling working times, for instance through self-rostering, offers one potential strategy for mitigating sleep problems and improving shift work tolerance (Ingre et al., 2012; Albertsen et al., 2014).

The second sample, i.e. the novice police officers, were well suited for our research purpose. Police officers work in a high-stress environment and they frequently experience irregular and extended shifts (Vila, 2006; Zimmerman, 2012). However, caution should be made before generalizing the results from police officers to shift workers in other occupations, which might differ in levels of workload and worktime schedules.

In considering the results of our longitudinal studies we do not claim that a period of twenty months suffices to assess short-term as well as long-term effects of commencing shift work. On the contrary, long-term adaptation most likely is a continuous and dynamic process, impacted by effects of changing conditions at work and at home, aging and health alterations.

For the short term, however, our new results add to the existing evidence for inter-individual differences in shift work tolerance. To our knowledge this thesis is the first to present longitudinal data of the effects of shift work exposure both subjectively as well as objectively in novice shift workers.

For future studies it is a challenge to identify intolerant shift workers, before or during the adaptation phase, and to investigate whether additional support may enforce their adaptation.

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## SLEEP AND PERFORMANCE IN ELITE ATHLETES

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Sleep is one of the most important recovery mechanisms of the human body and thus essential for mental and physical performance. Elite athletes train intensive and are required to perform at the peak of their abilities. As such, their improvement and performance are especially dependent on their ability to recover from past exercise. Although the importance of sleep in top-level sport is widely recognized, there is little scientific research to confirm this. How long and how good do elite athletes actually sleep? And if elite athletes do not sleep well, how can sleep be improved? And if sleep is already adequate for top athletes, what can be done to optimize their sleep even further? In our research project "*Optimizing sleep to improve performance in elite athletes*", all these questions are addressed. For the first time this is done in a large scale with Dutch top athletes. Although the project is currently still in progress, the present paper aims to give a background about the importance of sleep for sports performance and aims to sketch the current state of affairs.

Sleep is not so much the absence of activity, but a unique state of the brain where several neural and hormonal processes, contributing in physical recovery as well as in energy supply of the body<sup>1</sup>. In the first half of the night especially *anabolic* hormones, including growth hormone, are released, contributing to growth and tissue production, while in the second half of the night especially *catabolic* hormones, such as cortisol, comes free, preparing the body for daily activities. Understanding these functions of sleep exemplifies that sleep is not only a crucial but also a challenging phenomenon for top athletes. After all, when a maximal effort is demanded from the body, an optimal recovery is extremely important<sup>2</sup>. And sleep produces this recovery! However, the way in which top athletes are living might cause that their sleep cannot always take place under optimal conditions. Often, they have to travel to remote places for games<sup>3</sup>, they cannot always sleep at most desired moments as a result of training and competition times<sup>4</sup>, while they often fight with tension and stress around important games leading to sleep disruptions<sup>5</sup>. The scarce research regarding the quality of sleep of elite athletes outlines an alarming picture: their sleep is too short with many awakenings, and they have in particular trouble with falling asleep<sup>6,7</sup>. Although there are almost no empirical data available, it is assumed that a less long sleep impairs the repair status of the body and affects the performance of elite athletes<sup>4,8</sup>.

### OPTIMIZING SLEEP TO IMPROVE PERFORMANCE IN ELITE ATHLETES

Based on the knowledge of the functions and regulation of sleep and the scarce research into sleep and performing of elite athletes<sup>2,8</sup>, we started in September 2013 the research project: "*Optimizing sleep to improve performance in elite athletes*". We did this with a research consortium consisting of the Radboud University, the Dutch sport-association NOC\*NSF, the companies Philips and Auping, the sport-foundation InnoSportLab Papendal

and different national sports associations. The aim of the project is to study in a large and representative group of Dutch top athletes, the quantitative and qualitative aspects of their sleep together with factors that determine their sleep. Furthermore, we hope to get insight into the common variations of their sleep with the impact on performance. Finally, based on this information, we hope to develop interventions that may improve the sleep of top athletes. Focused on the first two questions a large-scale sleep monitor study was carried out between September 2013 and May 2015. During this study, the sleep of 98 Dutch top athletes (56 women and 42 men, with a mean age of 18.9 years; playing football, volleyball, handball, cycling, mountain bike or triathlon) were accurately examined. In addition, athletes filled out a series of (sub)clinical questionnaires during a standardized 10-day monitoring period. In this way, information on the size and quality of sleep, the evening behavior, their mental and physical load, and their performance was collected. In total, this sleep-monitor study resulted in information on the sleep quality of 89 top athletes, the sleep data of 878 nights, and on 356 performance tests.

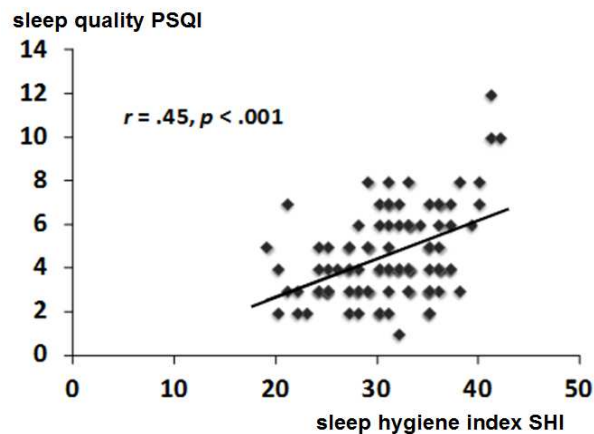
### **HOW LONG AND HOW WELL DO ELITE ATHLETES SLEEP?**

To quantify the sleep of elite athletes, we opted in our monitor study for a mixed-methods approach. Prior to the study, the athletes filled out several (sub)clinical questionnaires measuring their overall sleep quality. During the entire study, the sleep was daily measured by wrist-actigraphy (Actiwatch 2)<sup>9</sup>, by self-reporting (sleep diary), and by a 1-channel EEG recording (Zeo Sleep Manager). Analysis of the (sub)clinical questionnaires showed that the athletes on the average slept well, but that there is a substantial minority of 41% of the athletes, who, based on their score on the Pittsburg Sleep Quality Scale<sup>12</sup>, can be classified as bad sleepers. Objective daily sleep measurements with the actigraph showed a similar picture. During the monitoring period, the total time in bed of the athletes was more than eight hours ('time in bed': M=8.33 h:min, SD=1.10). The athletes slept on average around eight hour ('total sleep time': M=7.51 h:min, SD=1.08), but they had a relatively long time to fall asleep ('sleep onset latency': M=13.67 h:min, SD=0.15), and there were many long-lasting wake times throughout the night ('wake after sleep onset': M=32.68 h:min; SD=0.16). Sleep efficiency score (M=88.64%, SD=5.33) of the athletes was relatively low. While the EEG measurements showed a healthy distribution between the proportion of deep sleep, light sleep and REM sleep, the daily sleep diaries showed that the athletes evaluated their own sleep quality only with a mean of 6.8 (SD=0.9) on a scale of 1 to 10 and by waking up in the morning, they felt only moderately recovered (M=6.1, SD=1.13; on a scale of 1 to 10). Moreover, 40% of the athletes gave themselves, averaged over the entire monitoring period, even an insufficient mark for their recovery status.

All together, the sleep monitor study showed that elite athletes sleep sufficient on the average, but that there is a substantial minority of athletes for whom this does not apply. In addition, values about sleep times and nightly wake moments are relatively high<sup>6, 7</sup>. Moreover, scores with respect to the feeling of recovery are not sufficient for all elite athletes, even if they had slept sometimes for 8 hours<sup>11</sup>. It is important to understand *why* top athletes not always sleep well or experience their objective good sleep not as such. Given this knowledge, it is worth to work towards interventions that aim to improve sleep quality.

### WHAT IS THE IMPORTANCE OF GOOD SLEEP HYGIENE?

As previously mentioned, sleep for elite athletes is not only a crucial, but also a challenging phenomenon. The frequent occurrences of practices and games, sleeping on various locations, and the mental and physical stress associated with top sport, implies that it is difficult for athletes to maintain a good sleep hygiene for optimal sleep. To identify the importance of *Sleep hygiene* for sleep, a careful analysis was made of the behavior in the evenings and the environmental circumstances. This was done based on self-reports before the actual monitor period started, as well as during the whole monitor period. All behavioral and environmental factors regarding sleep hygiene were related to the experienced quality of sleep. An analysis of the questionnaires shows that the Sleep hygiene of elite athletes was generally fair. Nevertheless, scores on the Sleep Hygiene Index<sup>12</sup> verified that in a number of factors, such as bedtimes, stress and tensions, and mental/physical activities in the evening, there is room for improvement. A similar picture emerged for the entire monitor period. In addition, these daily measurements showed that athletes relatively often still take a full meal within 2 hours before they go to sleep (25% of the measured nights), and almost every night take briefly part on brain stimulating activities, which exposes them to blue light of the smart phone, tablet, or laptop (70% of the nights). Although it is difficult for all individual factors to present a robust relationship with the experienced quality of sleep, it appears on a general level that a good sleep hygiene actually matters: the better the sleep hygiene, the better the quality of sleep (Figure 1).



**Figure 1.** Relationship between sleep hygiene (Sleep Hygiene Index, SHI) and the experienced quality of sleep (Pittsburgh Sleep Quality Index, PSQI).

### WHAT IS THE INFLUENCE OF TRAINING LOAD ON SLEEP?

Besides that behavior and circumstances in the evening can impair sleep, it is as well important in understanding the less good sleep of top athletes, to pay attention to the putative negative effects of the training load of athletes. Sleep can be regarded as a reactive process that provides for the recovery needs of the body<sup>1</sup> and data from active individuals show that when the physical load during the day is high, sleep itself will increase in order to meet the increased need of body recovery<sup>13</sup>, but there are also signs that when the load is too high, sleep can be disrupted<sup>14</sup>. Therefore, during the present study, the athletes were daily asked towards their training load and how this was experienced.



The daily training load during the monitoring period was generally average ( $M=5.41$ ,  $SD=1.36$ ; on a scale of 1 to 10), but with ample variation from day to day and between participants. Sometimes the training load was very high, sometimes the training load was very low. The analyses showed that sleep due to an increase in training load slightly deepened with an increase in the percentage deep sleep, but also that falling asleep lasted longer and that total sleep time decreased. Although it is yet not possible to indicate at what level training load affects sleep, the data show that it is important to carefully choose the imposed load during training. The load has to be weight against the recovery capabilities. Additionally, an important question regarding sleep is, when due to a high training load the sleep is deeper but also shorter, whether a sufficient recovery can still take place. The reported recovery experience suggest that this is not always the case.

### FROM UNDERSTANDING TO INTERVENTION

Although not all the results of the sleep-monitoring study are yet known (e.g. whether natural variations in sleep are expressed in performance variations), the above mentioned outcomes reveal a clear picture: the quality of sleep of elite athletes is generally sufficient, but leave, in particular with regard to falling asleep and maintaining sleep, still room for improvement. In addition, there is a substantial minority of athletes (41%), which do not have an optimal sleep. Based on the mentioned areas of improvement, and on the described relationship between sleep hygiene and experienced sleep quality, the focus of the project is currently directed to the development of interventions, favoring the sleep of top athletes. In that sense, we will make a distinction between '*direct*' interventions, which intervene in processes that regulate the sleep directly, such as correct darkness, room temperature, noise and humidity, and '*indirect*' interventions, promoting sleep by specific behavioral and environmental factors, such as taking a pre-sleep snack but not full meals, the prohibition of stimulating drinks or large quantities of alcohol, no activating activities but instead relaxation training, no blue light exposure, and correct bed times, in all thus a perfect sleep hygiene. Extensive studies on the feasibility and the effectiveness of interventions are already initially performed by talented amateur athletes. Based on the results of these studies, and based on consultations with coaches and trainers of the sports programs, large-scale interventions will be carried out under our top athletes in the coming year 2017.

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# NOCTURNAL HYPOVENTILATION DUE TO EXCEPTIONAL NEUROLOGICAL DISORDERS

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## INTRODUCTION

Obstructive sleep apnea syndrome is highly present in the general population and has a clear pathophysiology in most cases. Central sleep apnea syndrome is less common and has different backgrounds. It is probably unnoticed in many cases, as the supervising physician is focused on the primary disorder of which central sleep apnea is a comorbidity. Most prevalent is central sleep apnea syndrome due to heart failure, which is characterized by the so called Cheyne Stokes Respiration (CSR). Its pathophysiology is thought to be related to an aberrant feedback between the two major components of regulation of breathing (namely the brainstem as initiator of cardio-respiratory regulation, and the combination of lungs and the relevant neuromuscular apparatus as effectors). CSR is an example of central sleep apnea with preserved or lowered CO<sub>2</sub> (eucapnic or hypocapnic apneas). Fortunately, there is a growing awareness in cardiologists for this condition in many cardiovascular disorders and the beneficial effects of apnea treatment, in addition to standard cardiac interventions, on quality of life (QoL).

## CASES

Two examples are described and discussed in this paper, one due to an exceptional failure of the neuromuscular system and another one as an example of a disorder in the initiator of respiration which could be exactly visualized in the respiratory nuclei in the brainstem by MRI. In table 1, disorders from the spectrum of hypercapnic central sleep apnea syndromes are summed up.

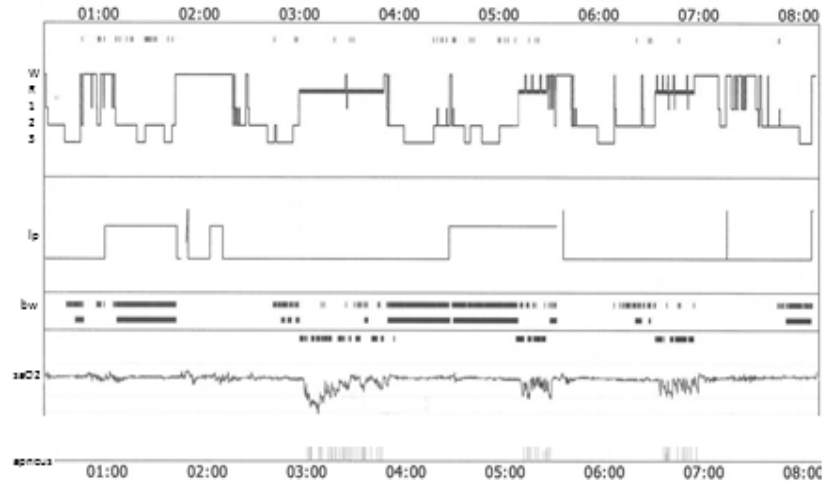
Patient A. is 68 years old and male. In 1999, a bilateral diaphragm paralysis (or eventually severe paresis) was diagnosed at routine X-ray examination, possibly due to protrusion of cervical discs leading to stenosis of the cervical spinal channel. Surgery at that level did not change the dysfunction of the diaphragm. The patient did not complain about his respiration neither before nor after the surgery and was very active during the daytime. Subjective sleep quality was normal. The bed partner did not witness disturbed sleep, i.e. neither restlessness, frequent awakenings or heavy snoring. Some months before his first visit to our center, the condition changed and the patient developed progressively more awakenings at night, together with a feeling of choking. Most episodes took place during the second part of the night, often following a dream. They lasted for 10-20 seconds and could be stopped by

sitting upright. During these episodes, the heart frequency was high, often between 120-150 beats/minute.

**Table 1.** Disorders from the spectrum of hypercapnic central sleep apnea syndrome

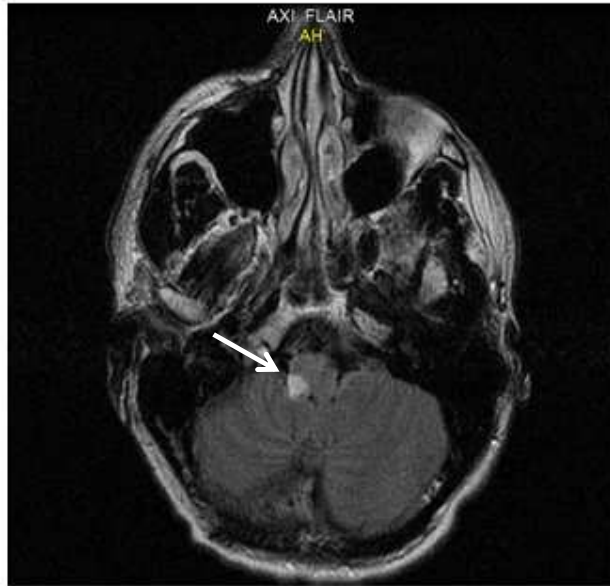
<i>Disorders associated with nocturnal hypoventilation</i>
Disorders of initiation and regulation of respiration: <ul style="list-style-type: none"> <li>• Brainstem dysfunction: infarction, tumor, infection, Arnold-Chiari malformation, infantile encephalopathies</li> <li>• Congenital central alveolar hypoventilation syndrome</li> <li>• Primary alveolar hypoventilation syndrome</li> <li>• Due to medication/substance abuse: for example opiates</li> </ul>
Neuromuscular disorders: <ul style="list-style-type: none"> <li>• Diseases of the motor neurons: ALS, poliomyelitis</li> <li>• Lesion of the cervical spinal cord or lesions of the nerves leaving the cervical spinal cord to the respiratory muscles</li> <li>• Muscular disorders: f. e. dystrophies (Duchenne, myotonias)</li> </ul>
Anatomical disorders of the chest wall: <ul style="list-style-type: none"> <li>• Kyphoscoliosis</li> <li>• Iatrogenic thoracoplastic abnormalities</li> <li>•</li> </ul>
Pulmonological disorders: <ul style="list-style-type: none"> <li>• Chronic obstructive pulmonary disease (COPD)</li> <li>• Obesity hypoventilation syndrome</li> <li>• Cystic fibrosis</li> </ul>

Just before the start of the symptoms, he got a cold with persisting cough, and was less active than before. His family doctor diagnosed an acute bronchitis. Short lasting antibiotic treatment did not change the respiratory problem or other symptoms. Consequently, the patient was referred to a cardiologist (no pathological findings), and finally to our center. Physical examination did not result in any new viewpoints. There were no intoxications or use of relevant medications. Polysomnography (PSG, fig. 1) confirmed the clinical suspicion of frequent awakenings from REM sleep together with hypoventilation, leading to oxygen desaturation as low as 70%. Over the whole night, PaCO<sub>2</sub> increased from 40 to 52 mmHg. Our final diagnosis was chronic nocturnal hypoventilation, particularly during REM sleep, due to severe diaphragmatic dysfunction. As the bronchitis was considered to be the trigger for the clinical deterioration, we decided to treat this disorder more extensively. The patient was informed that CPAP, BiPAP, or eventually non-invasive ventilation at night<sup>1</sup> would be necessary. To our surprise, prolonged treatment of the bronchitis only was sufficient to restore sleep quality to the same level as before the start of the complaints. The patient and his wife were happy with this result and did not want to proceed with additional investigations or treatment. Therefore, a control sleep study was not performed. Nocturnal oximetry showed complete normalization. At follow-up two years later, the patient and his wife were still happy with the result. We did not treat the periodic limb movements that were present (see hypnogram, fig 1), as they did not seem part of the problem (or could simply follow from nocturnal hypoxemia and/or hypercapnie).



**Fig 1** Hypnogram (patient A). W = wake; R = REM sleep; 1 and 2 = light sleep; 3 = deep, slow wave sleep; lp = body position (upper line: supine; lower line: on right side); bw = leg movements (upper line: all leg movements; lower line periodic leg movements); SaO<sub>2</sub> = oxygen saturation (baseline mean 91%; nadir during first REM period: 69%). Sleep is fragmented. Awakenings often occurred during or after REM sleep.

Patient B is a 38 year old male. Two years before referral to our center, he had a small infarction, lateral in the right side of the medulla oblongata, just below the pons (fig. 2). After rehabilitation, only minor sensory disturbances remained (left side from the shoulder downwards for temperature and touch and more global for the right side of his body). Most importantly, there were mild mood changes. A few months after the stroke, his wife witnessed apneas at night, together with restlessness and different sounds, described as snoring. This was the final reason for referral to our center. That moment, his medication was acetylsalicylate, dipyridamol, simvastatine and escitalopram. There were no intoxications. After taking medical history and a physical examination, which did not reveal new signs or symptoms, a PSG was performed. During that night, bradypneic episodes occurred with a frequency of eight/minute, together with a full blown central sleep apnea syndrome (AHI 30-40/hour), leading to a raise of the PaCO<sub>2</sub> of 12 mm Hg above base-line of 40 mmHg in the awake state. The diagnosis set was hypercapnic central sleep apnea syndrome due to a partial lesion of the respiratory nuclei in the brainstem. After a short lasting and not successful try-out with 250 mg acetazolamide, BiPAP therapy (13/8 cm H<sub>2</sub>O) was started. During a control PSG, respiration was normalized with an AHI of 1.5/hour and absence of hypoventilation episodes. The patient reported that sleep was substantially improved and that he was more rested and alert during daytime. His wife confirmed this progression.



**Fig. 2** Axial FLAIR MRI of the brainstem in patient B. In the right dorsolateral part of the medulla oblongata, a small region with hyperdense signal is present, typical for local ischemia.

## DISCUSSION

Chronic hypercapnic central sleep apneas are due to attenuated alveolar gas exchange which is by definition reflected in an increasing  $\text{PaCO}_2 > 10$  mmHg during the course of the night. The three underlying mechanisms are either an insufficient drive from the respiratory nuclei in the brainstem, pulmonary pathology resulting in hyperinflation and altered respiratory mechanics, or ineffective ventilator drive (the bony thoracic cage and neuromuscular failure of the respiratory muscles or their innervation). Even the nuclei in the brainstem are under the influence of the cerebral cortex and (hypo) thalamic nuclei, which explains that also supratentorial brain disorders may introduce (partial) respiratory failure<sup>2</sup>. Even in healthy subjects, respiration is less efficient during sleep, already in laying position<sup>3</sup>. Elements for this phenomenon are less neural output of the brainstem nuclei during sleep, higher upper airway resistance - partially related to altered influence of gravity, lower motor tone and circadian changes in bronchotonus. From these mechanisms, it results that hypoventilation initially develops during sleep. In REM sleep, another problem may arise. The REM related atonia prohibits function of most respiratory muscles, except for the diaphragm muscle. In patient A, the diaphragm muscle did not function properly. However, for a long time, the patient did not experience clinical problems. So, we have to conclude that either his diaphragm was paretic and not completely paralysed, or some function of the other respiratory muscles was preserved in spite of the usual atonia in REM sleep<sup>4</sup>. This equilibrium proved to be fragile, as can be concluded from the deterioration of ventilation during the night, provoked by a simple bronchitis. Recovery after a state of the art antibiotic therapy underlines this hypothesis. Another explanation for the long period of "normal" sleep could be that the hypoventilation during REM sleep provoked short arousals with recovery of the respiratory muscle function in the chest wall and accessory muscles. As we do not have a PSG before the start of the symptoms nor after therapy, this will remain speculative.

Patient B had a lesion exactly in the region of the brainstem where the network of nuclei for respiration is located<sup>5</sup>. During wake supratentorial drive prohibits failure of these nuclei, but during sleep, this higher level system works less efficient. Together with the physiologic phenomena mentioned above, ventilation fails partially during sleep and possibly even when the patient only lies down, <sup>6</sup>. At first, the patient was treated with acetazolamide, a carboanhydrase inhibitor, which induces subtle changes in the acid-base equilibrium, and as a result, activates the respiratory drive<sup>7</sup>. This was not effective (possibly due to a too small dose of this medication), and we had to proceed to CPAP, and during the same titration procedure, to BIPAP. Adapted servo ventilation or continuous non-invasive ventilation at night were not necessary.

## CONCLUSION

This paper gives a concise overview of hypercapnic central sleep apnea syndromes, illustrated with two clinical cases, each with its particular pathophysiology and treatment.

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# ON-THE-ROAD DRIVING PERFORMANCE THE MORNING AFTER BEDTIME USE OF THE OREXIN ANTAGONIST SUVOREXANT

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## INTRODUCTION

Suvorexant (MK-4305, Belsomra®) is a hypnotic drug with a novel mechanism of action, which is approved in the United States since 2014 for the treatment of adults with insomnia, who have difficulty falling asleep and/or staying asleep<sup>1</sup>. Suvorexant acts as a selective antagonist at orexin-1 and orexin-2 receptors. Following oral administration it reaches maximum concentrations in plasma between 1.5 and 4 h, and plasma concentrations decrease thereafter with a half-life of about 12 h. Steady state is reached after 3 days of dosing. Clinical studies have shown that suvorexant in doses of 10 mg or more significantly improves subjective and objective measures of sleep in healthy volunteers and insomnia patients<sup>2-5</sup>. A 1-year multicenter trial showed that suvorexant 40 and 30 mg had sustained effects on subjective total sleep time up to 1 year<sup>4</sup>. Furthermore, suvorexant was well tolerated and did not show rebound or withdrawal effects upon discontinuation. The most common adverse events associated with suvorexant are primarily extensions of the drug's pharmacological activity, i.e., somnolence, fatigue, and dry mouth<sup>4</sup>. The recommended dose in the US for both elderly and non-elderly adults with insomnia is 10 mg, which may be increased to a maximum of 20 mg.

A general concern associated with the use of hypnotics is their potential to impair driving ability the morning after use, due to residual sedative effects<sup>6</sup>. Therefore we conducted two studies in healthy volunteers to evaluate the effects of multiple doses of suvorexant on car driving, after single and repeated bedtime use<sup>7,8</sup>. One study in non-elderly volunteers, and one study in elderly volunteers. The methods were similar in both studies, except for the age ranges of the participants and the doses of suvorexant.

## METHODS

Both studies were conducted using double-blind, randomized, placebo-controlled, 4-period crossover designs in healthy volunteers. In study 1, participants were 28 healthy non-elderly volunteers (13 men, 15 women, aged between 21 and 64 years inclusive). In study 2, participants were 24 healthy elderly volunteers (14 men, 10 women; aged between 65 and 80 years). All participants were required to possess a valid driver's license, and have a driving experience of at least 3000 km/year on average within the last three years.

In both studies, each treatment period lasted for 8 days, and residual effects were assessed in the mornings of day 2 and 9, nine hours after bedtime dosing. Treatments in study 1 were suvorexant 20 mg, suvorexant 40 mg, and placebo on day 1 to 8, and zopiclone 7.5 mg on day 1 and 8 only, with placebo given for the 6 days in between (day 2 to 7). Treatments in study 2 were suvorexant 15 mg, suvorexant 30 mg, and placebo on day 1 to 8, and zopiclone 7.5 mg on day 1 and 8 only, with placebo given for the 6 days in between (day 2 to 7).



Driving performance was assessed using a one-hour standardized highway driving test in normal traffic, measuring Standard Deviation of Lateral Position (SDLP). Drug-placebo differences in SDLP >2.4cm were considered to reflect clinically meaningful driving impairment.

## RESULTS

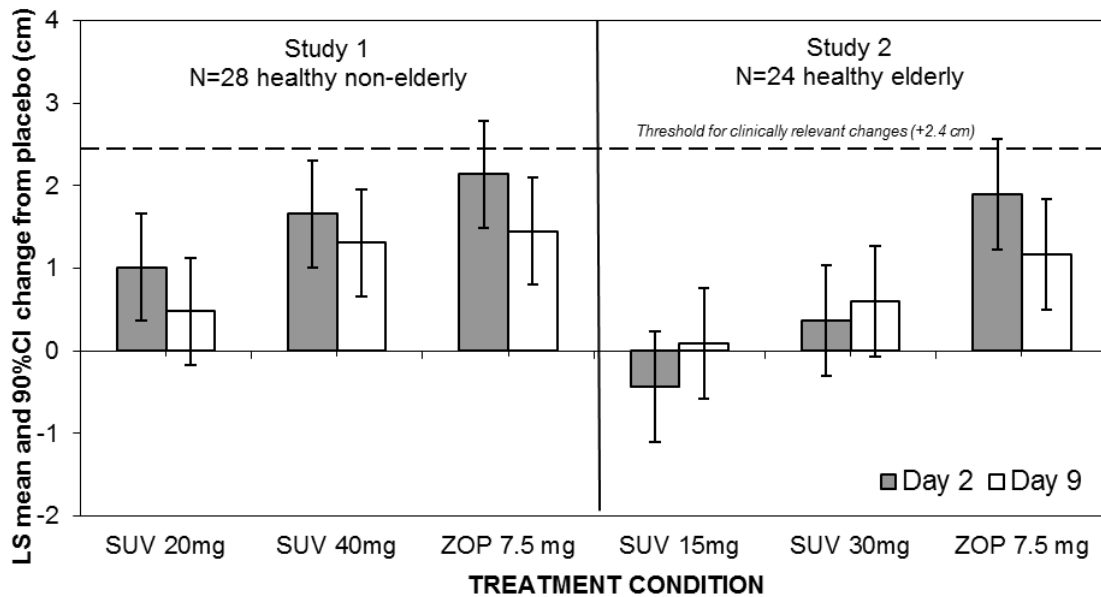


Figure 1.: SDLP changes from placebo (mean and 90% confidence intervals) by treatment and day following bedtime use of suvorexant (SUV) and zopiclone (ZOP).

### Study 1

For one female subject the data on day of placebo treatment were missing because of adverse events: the subject reported severe anxiety and insomnia during the night before testing and withdrew from further testing at that moment. Four female subjects requested that a total of 5 driving tests be stopped prematurely because they felt too drowsy to continue safely: 2 subjects on day 2 after suvorexant 40 mg, 1 subject on day 2 after suvorexant 20 mg, and 1 subject on day 9 after suvorexant 20 mg, and on day 2 after suvorexant 40 mg. SDLP scores for prematurely terminated tests were calculated from the data collected until termination of each ride.

Mean changes from placebo in SDLP for study 1 are shown in the left panel of figure 1. On day 2, mean changes from placebo in SDLP scores were 1.01 and 1.66 cm after suvorexant 20 mg and 40 mg, respectively. On day 9, the differences were 0.48 and 1.31 cm after suvorexant 20 mg and 40 mg, respectively. The upper limits of the 90%CI of these changes all fell below the criterion of 2.4 cm, indicating that the residual effects of suvorexant on driving were not clinically relevant. The lower limits of the 90% CI, however, fell above 0 cm on both days after suvorexant 40 mg, and on day 2 after suvorexant 20 mg, indicating that the mean change was statistically significantly different from placebo. After zopiclone mean SDLP was increased by 2.14 cm and 1.45 cm on day 2 and 9, respectively. These results confirm assay sensitivity, and show effects of zopiclone on driving were clinically relevant on day 2, but not on day 9.

## Study 2

One driving test, of a 72-year old female subject, was terminated prematurely by the driving instructor, because he judged the subject too drowsy to continue safely. The test was stopped after 45 minutes on day 2 of placebo treatment. None of the tests were stopped after suvorexant and zopiclone treatment.

Mean changes from placebo in SDLP for study 2 are shown in the right panel of figure 1. Mean changes from placebo in SDLP scores in after suvorexant 15 and 30 mg were very small on both test days: they ranged from -0.43 to +0.60. None of these changes were statistically significant, or clinically meaningful, as determined by the lower limits of the 90% CI of these changes which all fell below 0 cm, and the upper limits of the 90%CI which all fell below the criterion of 2.4 cm, respectively. After use of zopiclone 7.5 mg mean SDLP was increased by 1.89 cm on day 2, and by 1.17 cm on day 9. These results show that effects of zopiclone on driving were statistically significant on both days (demonstrating assay sensitivity), and clinically relevant on day 2, but not on day9.

## **DISCUSSION**

Results showed that measurable impairment occurred in non-elderly drivers after suvorexant 20 and 40 mg as compared to placebo, but the mean effects on SDLP were less severe than previously found for alcohol in blood concentrations of 0.5 g/L, which is the legal limit for driving in most countries. The effects were therefore not considered to be clinically meaningful. Nonetheless, four non-elderly subjects requested that a total of 5 driving tests be stopped before scheduled completion, because they felt too drowsy to continue safely. Results of study 2 showed that driving performance of elderly, as measured by SDLP, was not impaired following suvorexant 15 and 30 mg. Mean drug-placebo differences in SDLP following suvorexant 15 and 30 mg on Day 2 and 9 were small, and not clinically meaningful or statistically significant.

It can be concluded that the residual effects of suvorexant 15 to 40 mg are on average not clinically meaningful, but there may be some individuals who experience next-day effects. Use of the recommended dose of 10 mg is likely to be safe for patients who have to drive to morning after bedtime administration.

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# IMPACT OF SLEEP DEPRIVATION AND CAFFEINE ON WORKING MEMORY MANAGEMENT

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## INTRODUCTION

Sleep deprivation adversely affects cognition and task performance in a wide range of contexts.<sup>1,2</sup> However, the ability to maintain information in the focus of attention, i.e., in working memory (WM), is largely preserved during sleep deprivation, even as the flow of information into WM is compromised.<sup>3</sup> Less clear is how processes involved in the *management* of WM are affected by sleep deprivation or how these processes are affected by caffeine, a commonly used sleep deprivation countermeasure.<sup>4,5</sup> Here we explored the effects of sleep deprivation on the ability to manage the contents of WM by deactivating and reactivating information in response to changing response requirements and to what extent caffeine could decrease the detrimental effects of sleep deprivation on task performance.

## METHODS

Data were available for 11 healthy subjects (ages 19–39, 5 females) who participated in an 18-day (17-night) study inside a strictly controlled laboratory setting. After 3 baseline days with 10 h sleep opportunities (21:00–07:00), subjects were kept awake for 48 h. The 48 h total sleep deprivation (TSD) period was followed by a 5 h nap (07:00–12:00) and 3 recovery days with 10 h sleep opportunities (21:00–07:00). The pattern of 48 h TSD followed by a nap and 3 recovery days was repeated two more times – that is, subjects were exposed to TSD three times in total. The last TSD period was followed by 2 instead of 3 recovery days.

During each of the TSD periods, caffeine or placebo was administered after 6, 18, 30 and 42 h of scheduled wakefulness (at 13:00, 01:00, 13:00 and 01:00, respectively). At each time point, subjects were provided with 3 pieces of chewing gum that each could contain either 100 mg caffeine or placebo. During one TSD period, the total dose of caffeine at each time point was 0 mg; during another TSD period, the total dose at each time point was 200 mg; and during the remaining TSD period, the total dose at each time point was 300 mg. The three caffeine dose conditions occurred in double-blind, randomized order.

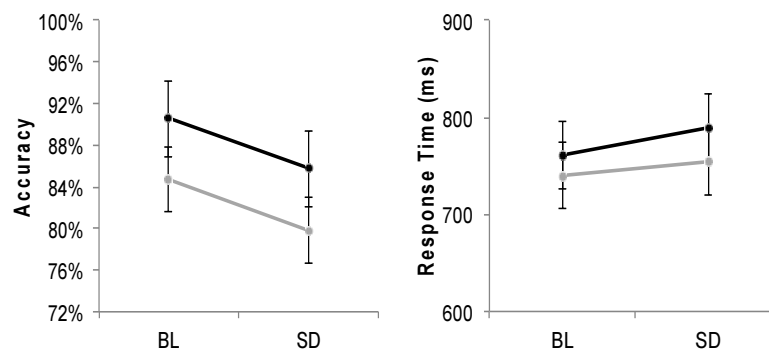
During each TSD period, subjects performed a computerized WM task 30 min post gum administration, after 6.5 h of scheduled wakefulness (baseline) and again 24 h later after 30.5 h of scheduled wakefulness (sleep-deprived). In the WM task, subjects were presented two memory sets, labeled 1 and 2, with each set containing three random letters. A cue was presented indicating which set was the active set to use as the basis for responding. Subjects were then presented with a probe letter (probe 1) and asked to identify whether the probe was in the cued memory set with a speeded “yes” or “no” response on a computer keyboard. Then, another cue was presented indicating the active set to use in responding to

a second probe. On half of the trials the active set was the same for both probes, and on the other half the active set switched. Subjects were then presented with the second probe letter (probe 2) and asked to identify whether the probe was in the cued memory set with a speeded "yes" or "no" response. Half of the probe stimuli were in the active set, requiring a "yes" response, and half the stimuli were not in the active set, requiring a "no" response. On the "no" trials half of the stimuli were from the non-cued memory set and half the stimuli were in neither memory set. Each test session contained 128 trials.

Overall response time and accuracy were measured for each test session, in the baseline and sleep deprivation conditions and across all three caffeine doses. Furthermore, the amount of interference produced by having to respond "no" to a probe from the non-cued memory set was assessed relative to when the probe was in neither memory set. This interference effect represents the ability to "deactivate" the non-cued set in favor of the cued set. Finally, the cost to performance of switching between memory sets in preparation for probe 2 was assessed relative to not switching. The switch cost provides an index of the ability to manage WM by returning the non-cued set to the active focus of attention.<sup>6</sup> Response time and accuracy data were analyzed with mixed-effects analysis of variance (ANOVA) with fixed effects for condition (baseline or sleep-deprived), caffeine dose (0 mg, 200 mg, or 300 mg), probe context (probe in cued, non-cued or neither memory set), and switch trial type (switching or no switching), and a random effect over subjects on the intercept.

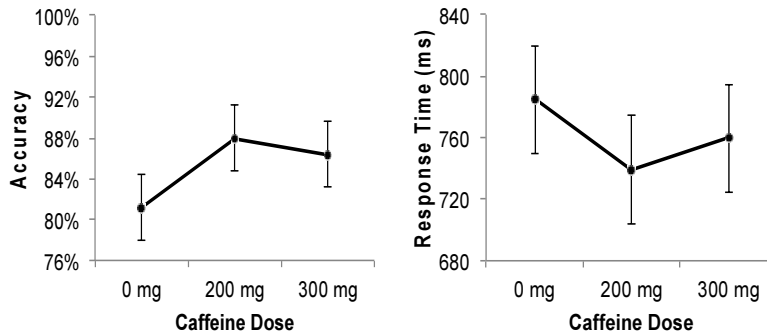
## RESULTS AND DISCUSSION

Overall performance was impaired in the sleep deprivation condition compared to the baseline condition as measured by probe 1 accuracy ( $F_{1,8416}=46.93, P<0.001$ ) and response time ( $F_{1,8416}=19.95, P<0.001$ ) and probe 2 accuracy ( $F_{1,8398}=35.33, P<0.001$ ) and response time ( $F_{1,8398}=4.85, P=0.028$ ), as shown in figure 1.



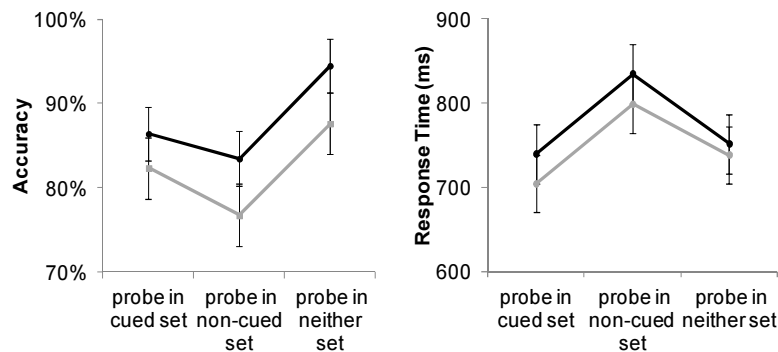
**Figure 1.** Responses as a function of condition. The left panel shows accuracy (mean  $\pm$  standard error) and the right panel shows response time (mean  $\pm$  standard error) for probe 1 (black) and probe 2 (grey). BL: baseline; SD: sleep-deprived.

When subjects received caffeine, there was a significant improvement in probe 1 accuracy ( $F_{2,8416}=19.96, P<0.001$ ) and response time ( $F_{2,8416}=16.83, P<0.001$ ) regardless of condition (baseline or sleep-deprived), as shown in figure 2. This pattern held true across baseline and sleep deprivation conditions for probe 2 accuracy ( $F_{2,8398}=8.32, P<0.001$ ) but did not reach significance for probe 2 response time ( $F_{2,8398}=2.24, P=0.106$ ).

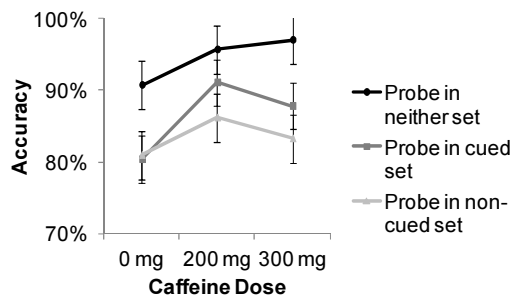


**Figure 2.** Probe 1 responses as a function of caffeine dose. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error).

We obtained the expected effects by probe type, as shown in figure 3. Probes from the non-cued memory sets produced significant interference for probe 1 accuracy ( $F_{2,8416}=75.82$ ,  $P<0.001$ ) and response time ( $F_{2,8416}=89.30$ ,  $P<0.001$ ) as well as probe 2 accuracy ( $F_{2,8398}=48.33$ ,  $P<0.001$ ) and response time ( $F_{2,8398}=83.43$ ,  $P<0.001$ ). The effect of probe type did not interact significantly with condition (baseline or sleep-deprived).



**Figure 3.** Responses as a function of probe context. The left panel shows accuracy (mean ± standard error) and the right panel shows response time (mean ± standard error) for probe 1 (black) and probe 2 (grey).



**Figure 4.** Probe 1 accuracy level (mean ± standard error) by probe 1 context as a function of caffeine dose.

Probe 2 context did not have a statistically significant interaction with caffeine dose for accuracy ( $F_{4,8398}=1.35$ ,  $P=0.249$ ) or response time ( $F_{4,8398}=0.19$ ,  $P=0.946$ ). Likewise probe 1 context did not have a significant interaction with caffeine dose for response time

( $F_{4,8416}=0.91$ ,  $P=0.458$ ). However, probe 1 context did interact significantly with caffeine dosage for accuracy ( $F_{4,8416}=4.03$ ,  $P=0.003$ ), as shown in figure 4.

Overall switch effects were significant for accuracy ( $F_{1,8398}=10.19$ ,  $P=0.001$ ), with subjects responding 3.4% less accurately after a switch versus no switch. Switch effects were not statistically significant for probe 2 response time ( $F_{1,8398}=1.51$ ,  $P=0.220$ ). Furthermore, switch effects did not exhibit significant interaction with condition for accuracy ( $F_{1,8398}=0.02$ ,  $P=0.894$ ) or response time ( $F_{1,8398}=0.53$ ,  $P=0.465$ ) or with caffeine dose for accuracy ( $F_{2,8398}=0.09$ ,  $P=0.916$ ) or response time ( $F_{2,8398}=0.43$ ,  $P=0.653$ ). Finally, switch effects did not have a significant interaction with probe 2 context for accuracy ( $F_{2,8398}=1.79$ ,  $P=0.167$ ) or response time ( $F_{2,8398}=1.12$ ,  $P=0.327$ ).

These observations of impaired cognitive performance in sleep-deprived individuals are consistent with previous findings of a general decline in speed and accuracy of responding.<sup>1,2</sup> Our result of improved overall performance on the task when subjects received caffeine is also consistent with previous studies.<sup>4,5</sup> However, there was little evidence for effects of sleep deprivation or caffeine on specific components of the management of WM.

## CONCLUSIONS

Our findings are consistent with previous examinations of WM performance under sleep deprivation showing that while non-executive task elements such as stimulus encoding and response execution may be impaired by sleep deprivation, WM processes of maintenance and updating remain intact.<sup>3</sup> Our findings are also consistent with the observation that caffeine may not mitigate all aspects of performance impairment during sleep deprivation.<sup>5</sup>

## ACKNOWLEDGMENTS

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# SOMNAMBULISM AND MILITARY SERVICE

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## INTRODUCTION

A medical and psychological screening is a standard procedure for everybody willing to join the army. This procedure is designed to select healthy recruits who have no medical or psychological conditions which can obstruct military service. Recruits are medically examined, followed by an interview protocol in which one of the issues assessed is the nature of their sleep. One of the items discussed is the occurrence of sleepwalking, since dangerous situations may arise when a soldier, having access to weapons, displays episodes of sleepwalking. In the last years, the item has become more relevant since it became clear that several cases of aggressive acts were carried out by apparently sleepwalking persons<sup>1</sup>. The question is how to deal with recruits with somnambulism who would like to join the military forces.

## SOMNAMBULISM

Sleepwalking, or somnambulism, is a sleep disturbance that belongs to the group of sleep disorders called 'parasomnias', referring to abnormal behaviours that can occur while asleep. Examples are nightmares, bedwetting, sleep talking and sleepwalking. The latter is a behavioural disorder that starts in arousal from sleep and results in sitting in bed, walking or in performing other complex behaviours. The brain condition of a sleepwalker is between sleeping and waking, in a sort of confusional arousal or twilight state. Somnambulism is often indicated as an 'incomplete arousal' response<sup>2,3</sup>.

Sleepwalking is much more common in children than in adults. The prevalence of sleepwalking in children is up to 15%. It is not regarded as an abnormal phenomenon in children; it is usually benign and rarely needs treatment<sup>2,3</sup>. Typically, at the first onset of a sleepwalking episode, the child obeys to an internal trigger like a full bladder. The child stands up to go to the toilet, is confused and loses the way. Generally, sleepwalking decreases with the onset of puberty to a prevalence of approximately 2.5% in adulthood. Somnambulism has a genetic component, with 10 to 20% of the family members of the sleepwalker that also present with this parasomnia.

Symptoms of sleepwalking range from simply sitting up in bed and shortly looking around (the 'abortive form' of sleepwalking) to an execution of series of complex behaviours (the 'manifest' form of sleepwalking). Episodes commonly last 5 to 10 minutes. The prevalence of abortive sleepwalking is about 2%, while 0.5% for the manifest form. When we discuss sleepwalking, the manifest form is usually implied, as the abortive form is often not regarded as genuine sleepwalking.

The most obvious behavioural pattern of the manifest form is walking, mostly around the room or the house, but also routine behaviours such as eating, dressing and cleaning can occur. Walking behaviour ranges from quiet walking to agitated running, and may even involve complex behavioural patterns, looking like 'escaping from a frightening situation'<sup>3,4</sup>. Sometimes the person leaves the house and even moves over a considerable distance.

Typically, the eyes of a sleepwalker are open with a blank, staring appearance. On questioning, subjects answer mostly unclear and vague; just like spontaneous utterances. If returned to bed, the subject usually does not remember the sleepwalking incident the next morning. This is probably due to the fact that the sleepwalker does not fully awake. A sleepwalker can be fully aroused, but is commonly confused after waking. Attempts to wake the subject can lengthen the sleepwalking episode and can induce resistance or violence<sup>2, 3, 4</sup>. Before, sleepwalking was considered to be an acting out of dreams, although sleepwalking usually takes place mostly during slow wave sleep, and only rarely during REM sleep when dreams occur<sup>4, 5</sup>. This implies that sleepwalking episodes tend to appear in the first half of the night. Bouts of sleepwalking can be triggered by stress, fever, anxiety, alcohol consumption and different medications. Sleep deprivation can also act as a precipitating factor. Sleepwalking is frequently associated with obstructive sleep apnea syndrome, which is not surprising, since patients are repeatedly aroused during their sleep. Another condition that frequently co-exists with somnambulism is epilepsy. Many epileptic attacks are difficult to distinguish from sleepwalking bouts. Sleep disorders such as narcolepsy and restless legs with periodic limb movements are also identified as co-morbidities.

The causes of sleepwalking are not exactly known, but various factors can contribute to its pathophysiology. Sleepwalking often has emotional origins. Subjects with mental disorders, such as depressions, anxiety disorders, and obsessive compulsive disorders, are found to have episodes of sleepwalking more frequently<sup>6</sup>, although discussions on this point are still ongoing<sup>7</sup>. Also suffering from stress and emotional situations, is associated with higher incidence of sleepwalking. This is also true for the post-traumatic stress syndrome<sup>8</sup>. All these disorders and conditions are associated with night terrors (pavor nocturnus) and nightmares, with or without sleepwalking episodes. Sleepwalking, night terrors and nightmares are considered to be manifestations of the same disease continuum.

A difference between night terrors and nightmares is, that night terrors mainly occur during non-REM sleep, taking place early in the night without dream recall, while nightmares are frightening dreams appearing in REM sleep. Both conditions often lead to an abrupt arousal in a confused terrified state. These arousals can trigger bouts of sleepwalking, and it is not exceptional that this type of sleepwalking has aggressive features. The enactment of the nightmare dream can consist of kicking, punching, flailing limbs, grabbing and shouting. Normally, the muscle paralysis in REM sleep prevents the dreamer to move, but sometimes this safety mechanism fails, giving room to the person to act out his dream. 'REM sleep behavior disorder' becomes more and more<sup>5</sup>. Several cases have been described in which persons while sleeping went out of bed and became engaged in activities such as walking and cleaning, but also in hazardous activities such as driving, violent gestures, sexual acts and even homicide. The case of the Canadian Kenneth Parks is notorious in this respect. Parks rose from bed and drove in the middle of the night to his wife's parents. He attacked them with a knife, killed the mother and seriously injured the father. Following this attack, Parks went to a police station and turned himself in. Afterwardshe drove back home and continued his sleep. At the trial, Parks argued that he was sleepwalking at the time of the incident, and acted in a non-insane automatic way. He was suffering from a sleep disorder rather than from a psychiatric illness. Neurological experts confirmed that he was effectively sleepwalking and was not responsible for his acts. The jury acquitted Parks. Several other examples of severe violent behaviours due to REM sleep behaviour disorder are known, and



lawyers and sleep experts are disputing the degree of guilt of the offender in many cases. REM sleep behaviour disorder is usually noticed when it causes danger to the sleeping person, to the bed partner, or to other encountered people. It is often associated with neurodegenerative disorders, blocking the REM sleep paralysis. It may occur chronically or acutely, often precipitated by alcohol or medicine withdrawal.

## **DISCUSSION AND CONCLUSION**

Several European armies have no strict rules on dealing with somnambulism. Whether a person with somnambulism can enter the army depends on an individual evaluation of the problem. Mild sleepwalking does mostly not lead to restrictions, whereas in severe cases, comprising aggressive, violent or self-harming activities, the person will not be allowed to enter service. The disadvantage of this policy is the arbitrary decision with respect to the gravity of the sleep problem. Moreover, manifested sleepwalking in adults has a low prevalence and most often, somnambulism co-exists with other disorders, such as sleep apnea, epilepsy, narcolepsy or restless legs. People with mental disorders such as anxiety and depression are also more vulnerable for sleepwalking than others. These accompanying disorders make sleepwalkers less suitable for military service. In addition, the small but unpredictable risk of developing violent acts makes it undesirable that armed forces take up young adults with a sleepwalking history. Nevertheless, the probability of rejecting suitable recruits is small. The benign form of isolated manifest sleepwalking, without co-morbidities, is seen in maximally 10% of all sleepwalkers and is often not recognised. The policy of excluding recruits with manifest somnambulism from the army is standard in the United States. Weighing all pros and cons regarding somnambulism and military service the same would be recommended for the Netherlands.

## **ACKNOWLEDGMENT**

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**SLEEP-WAKE**  
**Research in the Netherlands**

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**Abstracts**

## A GROUNDED THEORY STUDY ON THE INFLUENCE OF SLEEP ON PARKINSON'S SYMPTOMS

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**Background:** Upon awakening, many Parkinson's patients experience an improved mobility, a phenomenon known as 'sleep benefit'. Despite the potential clinical relevance, no objective correlates of sleep benefit exist. The discrepancy between the patients' subjective experience of improvement in absence of objective changes is striking, and raises questions about the nature of sleep benefit. We aimed to clarify what patients reporting subjective sleep benefit, actually experience when waking up. Furthermore, we searched for factors associated with subjective sleep benefit.

**Methods:** Using a standardized topic list, we interviewed 14 Parkinson patients with unambiguous subjective sleep benefit, selected from a larger questionnaire-based cohort. A grounded theory approach was used to analyse the data.

**Results:** A subset of the participants described a temporary decrease in their Parkinson motor symptoms after sleep. Others did experience beneficial effects which were, however, non-specific for Parkinson's disease (e.g. feeling 'rested'). The last group misinterpreted the selection questionnaire and did not meet the definition of sleep benefit for various reasons. There were no general sleep-related factors that influenced the presence of sleep benefit. Factors mentioned to influence functioning at awakening were mostly stress related.

**Conclusion:** The group of participants convincingly reporting sleep benefit in the selection questionnaire appeared to be very heterogeneous, with only a portion of them describing sleep benefit on motor symptoms. The group of participants actually experiencing motor sleep benefit may be much smaller than reported in the literature so far. Future studies should employ careful inclusion criteria, which could be based on our reported data.

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## SLEEP AND FOOD CHOICE IN A DUTCH STUDENT POPULATION

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**Background:** The increased risk of obesity among short sleepers is most likely explained by increased energy intake. However, food intake could not only be altered quantitatively but also qualitatively. Therefore, we performed a correlational analysis on self-reported food intake and sleep in 51 students from Maastricht and surroundings.

**Results:** Students that slept longer had a lower caloric intake:  $\rho = -0.378$ ,  $p = 0.006$ , the amount of calories consumed per minute awake remaining relatively stable. However, sleep duration did not correlate with intake of percentage fat, saturated fat, carbohydrates or protein. Average energy intake during the reported breakfasts, lunches, dinners or snacks separately did also not correlate with total sleep time.

**Conclusion:** It seems that shorter sleep correlates with absolute caloric intake, but not with the intake of specific dietary components.

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## THE LEEDS FOOD PREFERENCE QUESTIONNAIRE AFTER MILD SLEEP RESTRICTION – A SMALL FEASIBILITY STUDY

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**Introduction:** Besides the increased sedentary lifestyle and increased caloric intake, changes in dietary composition may play an important role in the increased prevalence of obesity. Because inadequate sleep could be a risk factor in the aetiology of obesity, reliable methods for assessing food intake and food choice after sleep restriction are needed.

**Methods:** We translated the Leeds food preference questionnaire (LFPQ), addressing preferences for sweet/savoury tastes and low-fat/high-fat foods, into Dutch, and tested it in 15 mildly sleep-restricted psychology students. The participants completed the LFPQ in our laboratory on two separate occasions, with approximately one week in between. Sleep on the preceding night was not controlled, but mild sleep-restriction was confirmed by a short sleep latency test (sSLT) or a short maintenance of wakefulness test (sMWT). Each participant completed the sSLT and sMWT once, just before the LFPQ, in a cross-over design randomised for the first test.

**Results:** Differences were present in preferences for food items from different categories (sweet/savoury and low-fat/ high-fat;  $p < 0.001$ ). The choice frequencies for various food categories were comparable on both occasions ( $p = 0.27$ ). The choice frequencies for individual items were also comparable on both occasions ( $p = 0.27$ ).

**Conclusion:** The LFPQ is easily implemented under mild sleep-restricted conditions, and translation is straightforward. Future studies using the LFPQ after sleep restriction could elucidate if restricting sleep or longer periods affects food choice, which could underlie increases in obesity risk.

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## TIME DELAY BETWEEN CARDIAC AND BRAIN ACTIVITY DURING SLEEP

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Human sleep consists of wake, rapid-eye-movement (REM) sleep, and non-REM (NREM) sleep that includes light and deep sleep stages. This work investigated the time delay between changes of cardiac and brain activity for sleep transitions. Here, the brain activity was quantified by electroencephalographic (EEG) mean frequency and the cardiac parameters included heart rate, standard deviation of heartbeat intervals, and their low- and high-frequency spectral powers. Using a cross-correlation analysis, we found that the cardiac variations during wake-sleep and NREM sleep transitions preceded the EEG changes by 1–3 min but this was not the case for REM sleep transitions. These important findings can be further used to predict the onset and ending of some sleep stages in an early manner.

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# EFFECTS OF BETWEEN- AND WITHIN-SUBJECT VARIABILITY ON AUTONOMIC CARDIORESPIRATORY ACTIVITY DURING SLEEP AND THEIR LIMITATION ON SLEEP STAGING: A MULTILEVEL ANALYSIS

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Autonomic cardiorespiratory activity changes across sleep stages. However, it is unknown to what extent it is affected by between- and within-subject variability during sleep. As it is hypothesized that the variability is caused by differences in subject demographics (age, gender, and body mass index), time, and physiology, we quantified these effects and investigated how they limit reliable cardiorespiratory-based sleep staging. Six representative parameters obtained from 165 overnight heartbeat and respiration recordings were analyzed. Multilevel models were used to evaluate the effects evoked by differences in sleep stages, demographics, time, and physiology between and within subjects. Results show that the between- and within-subject effects were found to be significant for each parameter. When adjusted by sleep stages, the effects in physiology between and within subjects explained more than 80% of total variance but the time and demographic effects explained less. If these effects are corrected, profound improvements in sleep staging can be observed. These results indicate that the differences in subject demographics, time, and physiology present significant effects on cardiorespiratory activity during sleep. The primary effects come from the physiological variability between and within subjects, markedly limiting the sleep staging performance. Efforts to diminish these effects will be the main challenge.

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## DETECTION OF NOCTURNAL SLOW WAVE SLEEP BASED ON CARDIORESPIRATORY ACTIVITY IN HEALTHY ADULTS

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Abstract: Human slow wave sleep (SWS) during bedtime is paramount for energy conservation and memory consolidation. This work aims at automatically detecting SWS from nocturnal sleep using cardiorespiratory signals that can be acquired with unobtrusive sensors in a home-based scenario. From the signals, time-dependent features are extracted for continuous 30-s epochs. To reduce the measuring noise, body motion artifacts, and/or within-subject variability in physiology conveyed by the features and thus enhance the detection performance, we propose to smooth the features over each night using a spline fitting method. In addition, it was found that the changes in cardiorespiratory activity precede the transitions between SWS and the other sleep stages (non-SWS). To this matter, a novel scheme is proposed that performs the SWS detection for each epoch using the feature values prior to that epoch. Experiments were conducted with a large data set of 325 overnight polysomnography (PSG) recordings using a linear discriminant classifier and ten-fold cross validation. Features were selected with a correlation-based method. Results show that the performance in classifying SWS and non-SWS can be significantly improved when smoothing the features and using the preceding feature values of 5-min earlier. We achieved a Cohen's Kappa coefficient of 0.57 (at an accuracy of 88.8%) using only six selected features for 257 recordings with a minimum of 30-min overnight SWS that were considered representative of their habitual sleeping pattern at home. These features included the standard deviation, low-frequency spectral power, and detrended fluctuation of heartbeat intervals as well as the variations of respiratory frequency and upper and lower respiratory envelopes. A marked drop in Kappa to 0.21 was observed for the other nights with SWS time of less than 30 min which were found to more likely occur in elderly. This will be the future challenge in cardiorespiratory-based SWS detection.

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## ESTIMATING ACTIGRAPHY FROM MOTION ARTIFACTS IN ECG AND RESPIRATORY EFFORT SIGNALS

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Recent work in unobtrusive sleep/wake classification has shown that cardiac and respiratory features can help improve classification performance. Nevertheless, actigraphy remains the single most discriminative modality for this task. Unfortunately, it requires the use of dedicated devices in addition to the sensors used to measure electrocardiogram (ECG) or respiratory effort. This paper proposes a method to estimate actigraphy from the body movement artifacts present in the ECG and respiratory inductance plethysmography (RIP) based on the time-frequency analysis of those signals. Using a continuous wavelet transform to analyze RIP, and ECG and RIP combined, it provides a surrogate measure of actigraphy with moderate correlation (for ECG+RIP,  $\rho = 0.74$ ,  $p < 0.001$ ) and agreement (mean bias ratio of 0.94 and 95% agreement ratios of 0.11 and 8.45) with reference actigraphy. More important, it can be used as a replacement of actigraphy in sleep/wake classification: after cross-validation with a data set comprising polysomnographic (PSG) recordings of 15 healthy subjects and 25 insomniacs annotated by an external sleep technician, it achieves a statistically non-inferior classification performance when used together with respiratory features (average  $\kappa$  of 0.64 for 15 healthy subjects, and 0.50 for a dataset with 40 healthy and insomniac subjects), and when used together with respiratory and cardiac features (average  $\kappa$  of 0.66 for 15 healthy subjects, and 0.56 for 40 healthy and insomniac subjects). Since this method eliminates the need for a dedicated actigraphy device, it reduces the number of sensors needed for sleep/wake classification to a single sensor when using respiratory features, and to two sensors when using respiratory and cardiac features without any loss in performance. It offers a major benefit in terms of comfort for long-term home monitoring and is immediately applicable for legacy ECG and RIP monitoring devices already used in clinical practice and which do not have an accelerometer built-in.

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## SLEEP STAGE CLASSIFICATION WITH ECG AND RESPIRATORY EFFORT

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Automatic sleep stage classification with cardiorespiratory signals has attracted increasing attention. In contrast to the traditional manual scoring based on polysomnography, these signals can be measured using advanced unobtrusive techniques that are currently available, promising the application for personal and continuous home sleep monitoring. This paper describes a methodology for classifying wake, rapid-eye-movement (REM) sleep, and non-REM (NREM) light and deep sleep on a 30 s epoch basis. A total of 142 features were extracted from electrocardiogram and thoracic respiratory effort measured with respiratory inductance plethysmography. To improve the quality of these features, subject-specific Z-score normalization and spline smoothing were used to reduce between-subject and within-subject variability. A modified sequential forward selection feature selector procedure was applied, yielding 80 features while preventing the introduction of bias in the estimation of cross-validation performance. PSG data from 48 healthy adults were used to validate our methods. Using a linear discriminant classifier and a ten-fold cross-validation, we achieved a Cohen's kappa coefficient of 0.49 and an accuracy of 69% in the classification of wake, REM, light, and deep sleep. These values increased to kappa = 0.56 and accuracy = 80% when the classification problem was reduced to three classes, wake, REM sleep, and NREM sleep.

*Physiological Measurement* 36(10): 2027-2040, 2015.

## CARDIORESPIRATORY SLEEP STAGE DETECTION USING CONDITIONAL RANDOM FIELDS

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**Abstract:** This manuscript explores the probabilistic properties of sleep stage sequences and transitions to improve the performance of sleep stage detection using cardiorespiratory features. A new classifier, based on Conditional Random Fields, is used in different sleep stage detection tasks (N3, NREM, REM and wake) in night-time recordings of ECG and RIP of healthy subjects. Using a dataset of 342 PSG recordings of healthy subjects, amongst which 135 with regular sleep architecture, it outperforms Hidden Markov Models and Bayesian Linear Discriminants in all tasks, achieving an average accuracy of 87.38% and kappa of 0.41 (87.27% and 0.49 for regular subjects) for N3 detection, 78.71% and 0.55 (80.34% and 0.56 for regular subjects) for NREM detection, 88.49% and 0.51 (87.35% and 0.57 for regular subjects) for REM, and 85.69% and 0.51 (90.42% and 0.52 for regular subjects) for wake. In comparison with the state-of-the-art, and having been tested on a much larger data set, the classifier was found to outperform most of the work reported in the literature for some of the tasks, in particular for subjects with regular sleep architecture. It achieves a comparable accuracy for N3, higher accuracy and kappa for REM, and higher accuracy and comparable kappa for NREM than the best performing classifiers described in literature.

*IEEE Journal of Biomedical and Health Informatics, 2016.*

## DETERMINANTS OF PERCEIVED SLEEP QUALITY IN NORMAL SLEEPERS, INCLUDING NIGHT-TO-NIGHT VARIABILITY

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**Introduction:** The aim of this study was to establish the determinants of perceived sleep quality over a longer period of time and whether these are mainly driven by subjective or actigraphy-defined sleep measures.

**Methods:** Fifty participants (52 ± 6.6 years; 27 females) completed two consecutive weeks of home monitoring, during which people kept a sleep-wake diary while their sleep was monitored using a wrist-worn actigraph. The diary included questions on perceived sleep quality, sleep-wake information and additional factors such as well-being and stress. The data was analyzed using marginal linear mixed models to compare a model that included only objective, actigraphy-based sleep measures (Model O) to a model that included the same subjective, diary-based sleep measures (Model S) to explain perceived sleep quality. Secondly, an extended model was analyzed that included the additional, non-sleep related factors (Model Z).

**Results:** Model S explained 49% of the variance while Model O explained 18%. In Model S sleep onset latency, wake time after sleep onset and number of wake-ups were the strongest predictors of sleep quality. The analysis of model Z showed that extending model S with additional factors did not improve the model (45% explained variance).

**Conclusion:** Perceived sleep quality is mainly induced by subjective sleep measures and not actigraphy-based sleep measures. Moreover, the strongest determinants were related to wake time during the night.

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## SUBJECTIVE RATINGS AND PERFORMANCE IN THE HEAT AFTER SLEEP DEPRIVATION

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**Background:** It has been shown that endurance performance after one night of sleep deprivation is not compromised despite the feeling of fatigue and that, in contrast, performance in the heat deteriorates even though people may feel good. However, it is essentially unknown how the estimation of performance capabilities relate to actual performance. We hypothesized that endurance performance in the heat would be overestimated and performance after sleep deprivation would be underestimated. We also hypothesized that jumping performance will be underestimated in the heat.

**Methods:** There were 11 fit (VO<sub>2peak</sub> 52.0 ± 3.7 ml · kg<sup>-1</sup> · min<sup>-1</sup>) men, familiar with cycling, who performed a 20-min all-out cycling test (AO) and a vertical jump test (VJ) under four different conditions: a test trial at 24°C, at 11°C ambient temperature without (C) and with one night of sleep deprivation (CS), and at 31°C (H). The subjects estimated the performance prior to exercise in CS, C, and H.

**Results:** AO performance was less for H (6.95 ± 0.36 km) than for C (7.68 ± 0.29 km) and CS (7.62 ± 0.33 km). The subjects underestimated AO performance for CS by 1.11 km and C by 0.42 km, but not for H. VJ was higher in the H condition, in contrast with subjects' assessment.

**Discussion:** We conclude that subjective estimates of performance are not in line with actual performance for endurance exercise after sleep deprivation and for explosive exercise in the heat.

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## SPATIALLY SPECIFIC CHANGES IN EEG SPECTRAL POWER IN POST TRAUMATIC STRESS DISORDER DURING REM AND NREM SLEEP

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**Introduction:** Sleep problems are a core feature in PTSD. However, a robust objective measure for the sleep disturbance has yet to be found. The current study assessed whether the spatial distribution of EEG spectral power in PTSD would provide such a measure.

**Methods:** EEG power in F3, F4, C4 and O2 was calculated (FFT) for non-REM and REM sleep, in PTSD patients and trauma-exposed controls. In addition, a full polysomnographical evaluation was performed, including sleep staging, assessment of respiratory function, limb movements and heart rate.

**Results:** A large power shift was observed in NREM sleep of PTSD patients relative to controls, with a reduction in slow oscillation power and increased activity in higher frequency bands (delta to gamma). REM sleep showed a substantial power shift in the opposite direction. There was a distinct spatial pattern, with NREM sleep abnormalities being most prominent in the right frontal region and REM sleep-related changes most eminent occipitally. These pronounced power spectral changes occurred in the context of severe subjective sleep problems, as well as changes in sleep macrostructure, including reduced sleep efficiency, increased awakening, trends towards increased N1 and decreased SWS, and increased REM latency. Furthermore, patients showed increased leg movements.

**Conclusion:** Large changes were found in EEG spectral topography during both major sleep states in PTSD. Less pronounced changes were shown in sleep macrostructure. Spectral analysis thus appears much more powerful in revealing PTSD-related sleep abnormalities than traditional sleep staging. The observed abnormalities provide a candidate biomarker for sleep disturbances in PTSD.

*23<sup>rd</sup> Congress of the European Sleep Research Society, 13-16 september 2016, Bologna, Italy*

# SIGMA FLUCTUATIONS IN POLICE OFFICERS AND COMBAT VETERANS WITH PTSD

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**Introduction:** Post Traumatic Stress Disorder (PTSD) is a significant health problem with as key symptoms aversive memory intrusions and overgeneralization of the traumatic event, as well as sleep disturbances. Interestingly, sleep has an important role in memory consolidation. In particular, sleep spindles in different cortical areas reflect reprocessing and consolidation of specific memory traces. Given their strong relationship with memory reprocessing during sleep and reported memory and sleep alterations in PTSD, sleep spindles may play a role in the aetiology of PTSD. The current study assesses sigma fluctuations in PTSD patients.

**Methods:** Several parameters of sigma fluctuations were analysed and compared between traumatized police officers and combat veterans with (N=13) and without (N=14) PTSD. An automated detection method, free of a-priori assumptions regarding spindle characteristic, was used to obtain an unbiased representation of all sigma fluctuations. The standard deviation of the filtered sleep EEG (11-16 Hz) was computed (moving window: 0.2s), and all waxing/waning couplets with an amplitude over 5 microvolt were detected. For each detected sigma fluctuation, several variables were computed (e.g. duration, amplitude etc).

**Results:** Increased spindling activity was found in PTSD patients compared to trauma controls. This despite SSRI use in a small subsample of patients, which decreased spindling. The assumption free analyses revealed details regarding spindle abnormalities in PTSD that would have been missed by analysing only heuristically detected spindles.

**Conclusion:** The spindle abnormalities in PTSD may reflect excessive reprocessing and consolidation of trauma-related memories and may in this way contribute to the emotional memory problems.

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# HITTING THE RIGHT SPOT: A NEW CLOSED-LOOP STIMULATION PROCEDURE FOR OSCILLATORY PHASE TARGETING

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**Introduction:** Closed-loop stimulation is a hot topic in sleep research. It enables presentation of stimuli in alignment with specific patterns in ongoing biophysical signals. We have previously developed a closed-loop procedure for targeting stimuli to selected phases of EEG oscillations, which we used to demonstrate differential processing of stimuli presented in slow oscillation up- and down-states (Cox et al., 2014, PLoS One). We have now developed a new procedure for oscillatory phase targeting, in combination with hd-EEG recording, that is more accurate, faster and more convenient to implement.

**Methods:** The procedure involves a new oscillatory phase prediction algorithm, based on non-linear fitting on very short data segments of unfiltered EEG signal. The criteria for stimulus release are 1) the fitted sine is in a predefined frequency range of interest, 2) reaching a fitting error threshold, 3) reaching a relative power threshold in the frequency range of interest (the last criterion is to prevent stimulation when the frequency of interest is not sufficiently present in the EEG). The method was validated for the slow oscillation and alpha frequency range, in off-line simulations and on-line recordings.

**Results:** Results show that this method is faster and more accurate than any previously reported methods and performs well for both slow oscillations and alpha.

**Conclusion:** The new method shows superior performance compared to previous validated methods and broad applicability. The full set-up, with one amplifier and two PCs, performing hd-recording, real-time analysis and stimulus presentation, is convenient and can be run on any EEG set-up.

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## A NEW MINIMAL ASSUMPTION, SPINDLE ANALYSIS METHOD, APPLIED TO PTSD SLEEP

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**Introduction:** Neurophysiological mechanisms underlying spindling involve interactions between inhibitory cells in the thalamic reticular nucleus (RE) and bursting thalamocortical (TC) relay neurons. Gradual cell recruitment in RE-TC-RE loops is linked to the waxing of spindles. The cause of spindle waning is less clear, but a depolarizing action by the thalamic IH current may be involved. The influence of these neurophysiological mechanisms on spindle morphology in the scalp EEG is still to be clarified.

Given the transient nature of spindling and incomplete knowledge of precise underlying mechanisms the analysis of scalp EEG spindles may best be performed with a minimum of assumptions and high temporal resolution. We have recently implemented these requirements in a statistical approach to determine the dynamics of sigma power in the scalp EEG.<sup>1</sup> Here, we apply this automated procedure to an analysis of spindling in post-traumatic stress disorder (PTSD).

**Methods:** The algorithm entails EEG band-pass filtering (11.0-16.0 Hz) using a FIR-filter. The standard deviation of the signal is computed with a moving window of 0.2 second. The resulting power has a time resolution of the sample rate of the signal. Waxing and waning characteristics of sigma fluctuations are represented by the time-variant characteristics of the power. A pattern recognition algorithm detects all waxing/waning couplets. Various characteristics like peak power, total intensity, duration, symmetry, polarization / depolarization speed, etc., are calculated for each waxing and waning couplet. In addition, power dynamics in different spindle bands are calculated.

**Results:** Preliminary findings indicate increased spindles in PTSD patients compared to traumatised control subjects without PTSD, possibly reflecting excessive reprocessing and consolidation of trauma-related memories. The statistical analyses without prior assumptions revealed details regarding spindle abnormalities in PTSD that would likely have been missed by analysing only heuristically detected spindles.

**Conclusion:** In conclusion, analysing waxing/waning patterns in the sigma band, without prior criteria like amplitude, duration etc. appears useful. The spindle abnormalities in PTSD may form part of the mechanism through which the profound sleep disturbance in this disorder contributes to emotional memory problems.

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## THE IMPACT OF TRAINING LOAD ON SLEEP PARAMETERS IN ELITE ATHLETES

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**Purpose.** While it is assumed that regular exercise benefits sleep, it is also plausible that high exercise load, such as encountered by elite athletes, jeopardizes sleep and hence limits adequate recovery. To test this hypothesis, the current study investigated the impact of training load on sleep parameters, such as latency, quantity, efficiency and stage distributions, in a large cohort of elite athletes.

**Method.** Self-reported training load, actigraphy and one-channel EEG recordings were obtained among 98 elite athletes during 7 consecutive days of habitual training.

**Results.** Training load was moderate with large individual and daily variability ( $5.41 \pm 2.56$ ; scale 1-10). Actigraphy revealed healthy sleep quantity for the majority of athletes, showing total sleep durations of  $7:51 \pm 1:08$  hours, sleep onset latencies of  $00:13 \pm 0:15$  hours, and sleep efficiency scores of  $88.64 \pm 5.33$  %, but slightly elevated wake after sleep onset (WASO;  $00:32 \pm 0:16$  hrs). Distribution of sleep stages falls within healthy ranges. Multilevel analysis revealed significant associations between training load and all sleep quantity estimates except for WASO. In particular, high training load negatively affected sleep duration, sleep onset latency, and sleep efficiency ( $.08 < \beta > .17$ ). For sleep stage distributions, high training load was associated with higher percentages deep sleep and fewer percentages REM sleep ( $.09 < \beta > .15$ ). No significant associations were observed for light sleep.

**Conclusion.** In a field study employing robust and objective sleep parameters among elite athletes, the current study indicates deteriorated sleep latency, quantity and efficiency as a function of training load. However, the increase in deep sleep, although at the cost of REM sleep, contributes presumably to bodily recovery after stressors induced by strenuous exercise. Future research should aim to detect the transition point from beneficial to deteriorating effects of exercise on sleep.

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*Submitted*

## PREVALANCE OF PHYSICIAN-DIAGNOSED ASTHMA IN PATIENTS WITH SUSPECTED OBSTRUCTIVE SLEEP APNEA SYNDROME: A CROSS-SECTIONAL ANALYSIS OF THE ESADA DATABASE

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On behalf of the ESADA Study Group

**Introduction:** It has been reported that bronchial asthma is often associated with obstructive sleep apnea (OSA) and daytime sleepiness. We analyzed the prevalence of physician-diagnosed asthma in 4929 subjects with suspected OSA in the European Sleep Apnea Database (ESADA) cohort.

**Methods:** Patients were studied by respiratory polygraphy (PG: n=1624, 66.6% males) or full polysomnography (PSG: n=3305, 70.4% males), and the clinical characteristics of asthmatic (A) and non-asthmatic (non-A) patients were analyzed according to OSA severity. Significance was at p<0.05.

**Results:** Prevalence of physician-diagnosed asthma was 6.8% (n=111) in the PG Group, and 7.0% (n=231) in the PSG Group, with a higher frequency in females (F: 10.2%, M: 5.3%, p<0.0001). Compared to non-A patients, A patients were slightly heavier (mean BMI±SD: 32.8±7.6 vs 31.2±7.8 kg/m<sup>2</sup>, p=0.0004) and showed more severe daytime sleepiness (Epworth score: 10.4±5.6 vs 9.5±5.3, p=0.0015) and a trend for worse nocturnal lowest SaO<sub>2</sub> (p=0.053). Asthmatic patients showed normal AHI (<5, n=1009) more often than non-A patients (9.0 vs 6.4%, p=0.003). As for sleep structure in PSG Group, SWS was significantly less represented in A than non-A patients (21.9±15.5 vs 25.8±17.2%, p=0.0009).

**Conclusion:** among patients undergoing sleep studies for suspected OSA, prevalence of physician-diagnosed asthma was not high. In asthmatic patients, sleep was disturbed even in the absence of OSA, suggesting a referral bias of asthmatic patients to the sleep clinic, possibly due to nocturnal symptoms of asthma.

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## REM REBOUND DURING CPAP TITRATION AS A PREDICTOR OF CHRONIC CPAP COMPLIANCE

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**Introduction:** Brillante et al (Respirology 2012;17: 547-553) defined Rapid-Eye Movement sleep (REM) rebound as an increase of  $\geq 20\%$  of REM sleep during the first exposure to CPAP therapy, compared to the diagnostic night, with the presence of at least one REM episode of  $\geq 30$  min. However, few studies have tried to examine the extent and clinical relevance of this phenomenon. Therefore, our study was aimed at describing the prevalence of REM rebound during CPAP titration in patients with obstructive sleep apnea (OSA), and the characteristics of these patients. Also, the correlation with short-term and long-term CPAP compliance was studied.

**Methods:** 665 OSA patients were included (apnea-hypopnea index (AHI)  $> 20$ /h during the diagnostic night). Subjects underwent polysomnography (PSG) during the diagnostic as well as during the CPAP titration night. Classification of REM rebound was based on the definition of Brillante et al. CPAP compliance was assessed at 1 month, at 1 year, and at 2 years follow-up. CPAP compliance was defined as a minimal use for  $\geq 3$  hours a night.

**Results:** 34 Subjects out of 665 presented with REM rebound during CPAP titration, resulting in a prevalence of 5%. Patients with REM rebound were more obese, had less Stage REM sleep, a longer REM sleep latency, and a higher AHI compared to the No REM rebound group. The REM rebound group used CPAP significantly more during the first month of treatment compared to the No REM rebound group. However, this effect disappeared on the long-term.

**Table 1:** Baseline characteristics

	<b>Overall (n = 665)</b>	<b>REM rebound (n = 34)</b>	<b>No REM rebound (n = 631)</b>
BMI (kg/m <sup>2</sup> )	30,7 ± 6	35,3 ± 1 <sup>a</sup>	30,5 ± 1
Stage REM sleep (%TST)	18 ± 7	10 ± 1 <sup>a</sup>	19 ± 1
REM sleep latency (min)	112 ± 97	200 ± 22 <sup>a</sup>	107 ± 4
AHI (#/h)	40 ± 19	56 ± 8 <sup>a</sup>	34 ± 1
Short-term CPAP compliance (h/night)	5,1 ± 3	6,2 ± 1 <sup>a</sup>	5,1 ± 1

<sup>a</sup> p<0,05, statistically significant difference compared to No REM rebound group

**Conclusion:** REM rebound has a low prevalence in OSA patients during CPAP titration. These patients often have a significantly higher BMI and demonstrate more impairment of their sleep architecture at baseline conditions. Presence of REM rebound on initial CPAP exposure is associated with a higher short-term CPAP compliance.

*Presented at the 25<sup>th</sup> International Congress of the European Respiratory Society 2015 (Amsterdam)*

## UPPER AIRWAY STIMULATION FOR OBSTRUCTIVE SLEEP APNEA: QUALITY OF LIFE OUTCOME AFTER 30 MONTHS OF FOLLOW UP

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**Introduction:** Upper airway stimulation has been shown to be safe and effective in participants with moderate-to-severe OSA in a large cohort study after 12 months of follow-up. This study was aimed to summarize self-report outcome of quality of life measures after 30 months of follow-up.

**Methods:** A total of 126 participants received an implanted upper airway stimulation system (Inspire Medical Systems, Minnesota, USA) in a prospective phase III trial. The primary outcome at 12 months included AHI and ODI. The secondary outcome measures included sleep-related quality of life (Epworth Sleepiness Scale, Functional Outcomes of Sleep Questionnaire) at 12 months, and repeated again at 30 months post-implant.

**Results:** A total of 124 completed follow up at 12 and 111 participants at 30 months. ESS reduced significantly from 11.6 (5.0), mean (SD), at baseline to 7.0 (4.3) at 12 months ( $p < 0.001$ ) and 6.7 (4.0) at 30 months ( $p < 0.0001$ ). Similarly, FOSQ improved significantly from 14.3 (3.2) at baseline to 17.3 (2.9) at 12 months ( $p < 0.001$ ) and 17.6 (2.7) at 30 months ( $p < 0.001$ ).

**Conclusion:** Upper airway stimulation via hypoglossal nerve maintained sustained benefit on self-report quality of life measures (ESS and FOSQ) after 2.5 years of follow-up.

*Presented at the 25<sup>th</sup> International Congress of the European Respiratory Society 2015 (Amsterdam)*

# SLEEP DISTURBANCES ARE ASSOCIATED WITH REDUCED HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SUBSTANCE USE DISORDER

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## BACKGROUND AND OBJECTIVES:

Sleep problems and substance use are strongly linked. Sleep problems play a role in the etiology of substance use, but also may be a result of it. After detoxification, sleep problems may worsen leading to relapse. Nowadays, most substance dependence treatment programs aim at recovery rather than total abstinence, and in that view health-related quality of life (HRQL) is a relevant construct. This article describes the association between self-perceived sleep problems and HRQL in a naturalistic population of polydrug-using inpatients.

## METHODS:

At the start of treatment, 388 polydrug-using inpatients completed questionnaires concerning their sleep quality and HRQL. Three categories were established based on reported sleep problems: patients without sleep problems (21.6%), those with clinically relevant sleep problems (34.5%), and patients with sleep disorders (43.8%).

## RESULTS:

Mean grades for quality of sleep were  $M = 7.3$  (sd 1.7),  $M = 6.6$  (sd 1.7) and  $M = 5.3$  (sd 1.9) for the three categories, respectively. In addition, patients in the disorder category perceived a lower HRQL than those in the other categories. In the explanation of HRQL, both sleep problems and sleep disorders added significantly to the model when controlling for baseline characteristics.

## DISCUSSION AND CONCLUSIONS:

Our findings stress the need for clinicians to pay attention to the quality of sleep of recovering polydrug users, since this may play an important role in the recovery process. Monitoring sleep during treatment is advocated. This study adds to the knowledge about the way HRQL and sleep are related in a naturalistic sample of substance-dependent patients.

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## **SLEEP DEPRIVATION AND HIPPOCAMPAL VULNERABILITY: CHANGES IN NEURONAL PLASTICITY, NEUROGENESIS AND COGNITIVE FUNCTION**

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Despite the ongoing fundamental controversy about the physiological function of sleep, there is general consensus that sleep benefits neuronal plasticity, which ultimately supports brain function and cognition. In agreement with this are numerous studies showing that sleep deprivation results in learning and memory impairments. Interestingly, such impairments appear to occur particularly when these learning and memory processes require the hippocampus, suggesting that this brain region may be particularly sensitive to the consequences of sleep loss. Although the molecular mechanisms underlying sleep and memory formation remain to be investigated, available evidence suggests that sleep deprivation may impair hippocampal neuronal plasticity and memory processes by attenuating intracellular cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling which may lead to alterations in cAMP response element binding protein (CREB) mediated gene transcription, neurotrophic signaling, and glutamate receptor expression. When restricted sleep becomes a chronic condition, it causes a reduction of hippocampal cell proliferation and neurogenesis, which may eventually lead to a reduction in hippocampal volume. Ultimately, by impairing hippocampal plasticity and function, chronically restricted and disrupted sleep contributes to cognitive disorders and psychiatric diseases.

*Kreutzmann JC, Havekes R, Abel T, Meerlo P. Sleep Deprivation and Hippocampal Vulnerability: Changes in Neuronal Plasticity, Neurogenesis and Cognitive Function. Neuroscienc, 309: 173-190, 2015.*



## EARLY-LIFE ORIGIN OF ADULT INSOMNIA: DOES PRENATAL EARLY-LIFE STRESS PLAY A ROLE?

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Insomnia is very common in the adult population and it includes a wide spectrum of sequelae, that is, neuroendocrine and cardiovascular alterations as well as psychiatric and neurodegenerative disorders. According to the conceptualization of insomnia in the context of the 3-P model, the importance of predisposing, precipitating, and perpetuating factors has been stressed. Predisposing factors are present before insomnia is manifested and they are hypothesized to interact with precipitating factors, such as environmental stressful events, contributing to the onset of insomnia. Understanding the early-life origins of insomnia may be particularly useful in order to prevent and treat this costly phenomenon. Based on recent evidence, prenatal–early-life stress exposure results in a series of responses that involve the stress system in the child and could persist into adulthood. This may encompass an activation of the hypothalamic-pituitary-adrenal axis accompanied by long-lasting modifications in stress reactivity. Furthermore, early life stress exposure might play an important role in predisposing to a vulnerability to hyperarousal reactions to negative life events in the adult contributing to the development of chronic insomnia. Epigenetic mechanisms may also be involved in the development of maladaptive stress responses in the newborn, ultimately predisposing to develop a variety of (psycho-) pathological states in adult life.

*Palagini L, Drake CL, Gehrman P, Meerlo P, Riemann D. Early life origin of adult insomnia: does prenatal-postnatal stress play a role? Sleep Medicine 16: 446-456, 2015.*

## SLEEP DEPRIVATION CAUSES MEMORY DEFICITS BY NEGATIVELY IMPACTING NEURONAL CONNECTIVITY IN HIPPOCAMPAL AREA CA1

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Brief periods of sleep loss have long-lasting consequences such as impaired memory consolidation. Structural changes in synaptic connectivity have been proposed as a substrate of memory storage. Here, we examine the impact of brief periods of sleep deprivation on dendritic structure. In mice, we find that five hours of sleep deprivation decreases dendritic spine numbers selectively in hippocampal area CA1 and increased activity of the filamentous actin severing protein cofilin. Recovery sleep normalizes these structural alterations. Suppression of cofilin function prevents spine loss, deficits in hippocampal synaptic plasticity, and impairments in long-term memory caused by sleep deprivation. The elevated cofilin activity is caused by cAMP-degrading phosphodiesterase-4A5 (PDE4A5), which hampers cAMP-PKA-LIMK signaling. Attenuating PDE4A5 function prevents changes in cAMP-PKA-LIMK-cofilin signaling and cognitive deficits associated with sleep deprivation. Our work demonstrates the necessity of an intact cAMP-PDE4-PKA-LIMK-cofilin activation-signaling pathway for sleep deprivation-induced memory disruption and reduction in hippocampal spine density.

*Havekes R, Park AJ, Ferri SL, Tudor JC, Bruinenberg VM, Poplawski SG, Day JP, Aton SJ, Radwańska K, Meerlo P, Houslay MD, Baillie GS, Abel T. Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. eLIFE, in press, 2016.*

## TIMING OF EXAMS AFFECTS SCHOOL PERFORMANCE DIFFERENTLY IN EARLY AND LATE CHRONOTYPES

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Circadian clocks of adolescents typically run late – including sleep times – while adolescents generally are expected at school early in the morning. Due to this mismatch between internal (circadian) and external (social) times, they suffer from chronic sleep deprivation, which, in turn, affects academic performance negatively. This constellation impacts students' future career prospects. Our study correlates chronotype and exam performance. In total, 4,734 grades were collected from 741 Dutch high school students (ages 11-18 yrs) that had completed the Munich ChronoType Questionnaire (MCTQ) to estimate their internal time. Overall, the lowest grades were obtained by students who were very late chronotypes ( $MSF_{sc} > 5.31$  h) or slept very short on schooldays ( $SD_w < 7.03$  h). The effect of chronotype on exam performance depended on the time of day that exams were taken. Opposed to late types, early chronotypes obtained significantly higher grades during the early (8:15-9:45) and late (10:00-12:15) morning. This group difference in grades disappeared in the early afternoon (12:45-15:00). Late types also obtained lower grades than early types when tested at the same internal time (hours after  $MSF_{sc}$ ), which may reflect general attention and learning disadvantages of late chronotypes during the early morning. Our results support delaying high school starting times as well as scheduling exams in the early afternoon to avoid discrimination of late chronotypes, and to give all high school students equal academic opportunities.

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*van der Vinne V, Zerbini G, Siersema A, Pieper A, Merrow M, Hut RA, Roenneberg T, Kantermann T (2015). Timing of examinations affects school performance differently in early and late chronotypes. J Biol Rhythms. 30(1):53-60.*

## **SLEEP RESTRICTION IN RATS LEADS TO CHANGES IN OPERANT BEHAVIOR INDICATIVE OF REDUCED PREFRONTAL CORTEX FUNCTION**

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Sleep deprivation has profound effects on cognitive performance and some of these effects may be mediated by impaired prefrontal cortex function. In search of an animal model to investigate this relationship we studied the influence of restricted sleep on operant conditioning in rats, particularly the performance in a differential reinforcement of low rate responding (DRL) task, which is highly dependent on an intact prefrontal cortex. Animals were trained to withhold a lever press until an imposed delay of 30 seconds after the last press had passed in order to achieve a food reward. Once the animals had mastered the task, they were sleep restricted for seven days with 20h of sleep deprivation per day. At the end of each daily sleep deprivation session, performance on the DRL task was assessed. The results show that sleep restricted animals were less able to correctly time their responses, started pressing the lever more randomly and showed signs of behavioral disinhibition, the latter possibly reflecting enhanced impulsivity. Our data support the hypothesis that a sleep debt has disruptive consequences for the functioning of the prefrontal cortex. This model offers possibilities for future studies investigating the underlying biochemical and molecular mechanisms of this relationship.

*Kamphuis J, Baichel S, Lancel M, De Boer SF, Koolhaas JM, Meerlo P. Sleep deprivation in rats leads to changes in operant behavior indicative of reduced prefrontal cortex function. Journal of Sleep Research, in press, 2016.*

## THE TWO-PROCESS MODEL OF SLEEP REGULATION: A REAPPRAISAL

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In the last three decades the two-process model of sleep regulation has served as a major conceptual framework in sleep research. It has been applied widely in studies on fatigue and performance and to dissect individual differences in sleep regulation. The model posits that a homeostatic process (Process S) interacts with a process controlled by the circadian pacemaker (Process C), with time-courses derived from physiological and behavioural variables. The model simulates successfully the timing and intensity of sleep in diverse experimental protocols. Electrophysiological recordings from the suprachiasmatic nuclei (SCN) suggest that S and C interact continuously. Oscillators outside the SCN that are linked to energy metabolism are evident in SCN-lesioned arrhythmic animals subjected to restricted feeding or methamphetamine administration, as well as in human subjects during internal desynchronization. In intact animals these peripheral oscillators may dissociate from the central pacemaker rhythm. A sleep/fast and wake/feed phase segregate antagonistic anabolic and catabolic metabolic processes in peripheral tissues. A deficiency of Process S was proposed to account for both depressive sleep disturbances and the antidepressant effect of sleep deprivation. The model supported the development of novel non-pharmacological treatment paradigms in psychiatry, based on manipulating circadian phase, sleep and light exposure. In conclusion, the model remains conceptually useful for promoting the integration of sleep and circadian rhythm research. Sleep appears to have not only a short-term, use-dependent function; it also serves to enforce rest and fasting, thereby supporting the optimization of metabolic processes at the appropriate phase of the 24-h cycle.

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## **MODELING SLEEP ALTERATIONS IN PARKINSON'S DISEASE: HOW CLOSE ARE WE TO VALID TRANSLATIONAL MODELS?**

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Parkinson disease is one of the neurodegenerative diseases that benefited the most from the use of non-human models. Consequently, significant advances have been made in the symptomatic treatments of the motor aspects of the disease. Unfortunately, this translational success has been tempered by the recognition of the debilitating aspect of multiple non-motor symptoms of the illness. Alterations of the sleep/wakefulness behavior experienced as insomnia, excessive daytime sleepiness, sleep/wake cycle fragmentation and REM sleep behavior disorder are among the non-motor symptoms that predate motor alterations and inevitably worsen over disease progression. The absence of adequate humanized animal models with the perfect phenocopy of these sleep alterations contribute undoubtedly to the lack of efficient therapies for these non-motor complications. In the context of developing efficient translational therapies, we provide an overview of the strengths and limitations of the various currently available models to replicate sleep alterations of Parkinson's disease. Our investigation reveals that although these models replicate dopaminergic deficiency and related parkinsonism, they rarely display a combination of sleep fragmentation and excessive daytime sleepiness and never REM sleep behavior disorder. In this light, we critically discuss the construct, face and predictive validities of both rodent and non-human primate animals to model the main sleep abnormalities experienced by patients with PD. We conclude by highlighting the need of integrating a network-based perspective in our modeling approach of such complex syndrome in order to celebrate valid translational models.

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## PLASTICITY OF CIRCADIAN CLOCKS AND CONSEQUENCES FOR METABOLISM

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The increased prevalence of metabolic disorders and obesity in modern society, together with the widespread use of artificial light at night, have led researchers to investigate whether altered patterns of light exposure contribute to metabolic disorders. This article discusses the experimental evidence that perturbed environmental cycles induce rhythm disorders in the circadian system, thus leading to metabolic disorders. This notion is generally supported by animal studies. Distorted environmental cycles, including continuous exposure to light, affect the neuronal organization of the central circadian pacemaker in the suprachiasmatic nucleus (SCN), its waveform and amplitude of the rhythm in electrical activity. Moreover, repeated exposure to a shifted light cycle or the application of dim light at night are environmental cues that cause a change in SCN function. The effects on the SCN waveform are the result of changes in synchronization among the SCN's neuronal cell population, which lead consistently to metabolic disturbances. Furthermore, we discuss the effects of sleep deprivation and the time of feeding on metabolism, as these factors are associated with exposure to disturbed environmental cycles. Finally, we suggest that these experimental studies reveal a causal relationship between the rhythm disorders and the metabolic disorders observed in epidemiological studies performed in humans.

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## THERMOREGULATION IN SLEEP AND HIBERNATION

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The human sleep-wake cycle is tightly coupled to the circadian time course of core body temperature. The evening increase in heat loss through distal skin regions and reduction in heat production is associated with sleepiness and the ease to fall asleep, whereas the homeostatic increase in sleep pressure does not influence the thermoregulatory system. After sleep initiation, ultradian NREM-REM sleep cycle fluctuations seem to have minor thermoregulatory functions, especially in humans. From experimental data it can be concluded that mild warming can increase sleep propensity, sleep consolidation, and the duration of SWS. More reproducible systematic investigations applying temperature levels within the thermoneutral zone on different skin regions are needed to develop applicable thermal therapeutic strategies for sleep disturbances. The preoptic anterior hypothalamus integrates input from brain areas involved in circadian, temperature, and sleep-wake regulation and in turn influences vigilance states and body temperature in response to that input. In animals, the torpid state may be a valuable model to investigate the relationship between thermoregulation and sleep. During daily torpor, similar physiologic processes occur as during normal entrance into sleep, but this is observed in a more extreme way, providing an excellent opportunity to investigate these processes in more detail.

*Principles and Practice of Sleep Medicine, pp220-228*



## CAFFEINE INCREASED LIGHT RESPONSIVENESS OF THE MOUSE CIRCADIAN PACEMAKER

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Caffeine is the most commonly used psychoactive stimulant worldwide. It reduces sleep and sleepiness by blocking access to the adenosine receptors. The level of adenosine is known to increase during sleep deprivation, and is thought to promote entrance into sleep. Another important player in sleep timing is the circadian clock. In mammals this clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus. Light-induced phase shifts of the circadian rest–activity rhythm are mediated by light-responsive neurons of the SCN. Previously it was shown that sleep deprivation reduces circadian clock phase-shifting capacity, and decreases SCN neuronal activity. Adenosine agonists and antagonists mimicked or blocked the effect of sleep deprivation on light-induced phase shifts, suggesting a role for adenosine. With *in vivo* electrical activity recordings of the SCN in freely moving mice, we showed that the sustained response to light of SCN neuronal activity was attenuated after a 6-h sleep deprivation. Application of caffeine was able to restore the response to light. Remarkably, behavioural recordings showed that the endogenous period lengthened during chronic caffeine treatment in the drinking water in constant light conditions, but not in constant darkness. The data suggest that increased homeostatic sleep pressure changes circadian pacemaker functioning by reducing SCN neuronal responsiveness to light. The electrophysiological and behavioural data together provide evidence that caffeine enhances clock sensitivity to light. The results may have consequences for our view on the role of caffeine on how it influences sleep and waking.

*ESRS Bologna 2016*

## **DIM LIGHT AT NIGHT CHANGES SLEEP PATTERNS IN MICE**

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Exposure to dim light at night (DLAN) can disrupt circadian rhythms and alter behavioral and sleep patterns as well as influence the metabolic and immune system in humans. However, in mice no effects of DLAN on sleep were observed until now. In this study, we investigated the effect of DLAN on the daily sleep-wake cycle in male C57BL/6 mice. The mice were exposed to either a normal 12L:12D cycle (50-100 lux during the light period, n=8) or a 12L:12Dim (5 lux DLAN, n=7) for three months. We recorded the electroencephalogram (EEG) and electromyogram for 48h and conducted a sleep deprivation during the first 6h of the second day. Mice exposed to DLAN showed increased Waking and decreased NREM sleep at the beginning of the light period and decreased Waking and increased NREM and REM sleep in the first part of the Dim period. Thus, compared to controls, a lower daily amplitude in vigilance states was observed under DLAN (t-tests,  $p < 0.05$  after significant ANOVAs). The NREM sleep EEG power density of the fast slow-waves (2.5-4Hz) was decreased in the DLAN mice compared to controls, whereas no difference was found in the slow slow-waves (0.5-2.5Hz) (t-tests,  $p < 0.05$  after significant ANOVAs). The data show a general disturbance of the daily rhythm due to DLAN. Since EEG alterations in slow wave activity were only apparent in the fast slow-waves, the data suggest that DLAN may primarily affect thalamocortical network properties.

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## AGING IS ASSOCIATED WITH ALTERED NON-RAPID-EYE MOVEMENT SLEEP SLOW-WAVE CHARACTERISTICS IN MICE

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Aging in humans is accompanied by reduced sleep and slow-wave activity (SWA, EEG power density between 0.5-4 Hz) in NREM sleep, and the slow waves are characterized by lower amplitude, slope and density. Since mice sleep more when they age, we investigated sleep parameters and NREM sleep slow-wave morphology in aged (18-24 months, n=24) mice and compared it to young (6 months, n=9) male C57BL/6 mice. EEG and the electromyogram were recorded for 48h in a 12:12 L:D cycle beginning at lights on. Aged mice demonstrated an increase in NREM sleep during the dark period and an overall elevated SWA level compared to the young group (t-tests,  $p < 0.05$  after significant ANOVAs). The aged mice had less multiple peak slow waves and steeper slow-wave slopes (t-tests,  $p < 0.05$  after significant ANOVAs). Multiplex waves showed a significant negative correlation with the absolute SWA in both groups ( $R^2$  in young: 0.885; old: 0.952), however, the groups formed two different clusters where the slope (young:  $-0.39 \pm 0.05$ ; old:  $-0.22 \pm 0.02$ ;  $p=0.007$ ), and intercept (young:  $60.8 \pm 3.0$ ; old:  $54.7 \pm 2.8$ ;  $p=0.034$ ) of the regressions differed significantly. During the down state of the slow wave, sigma activity was lower in the aged mice compared to the young mice (t-tests,  $p < 0.05$  after significant ANOVAs). The data suggest an increased sleep pressure in the older mice which can explain the increased amount of sleep. The slow-wave morphology data point towards altered properties of the underlying cortical neuronal network in aged mice.

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## LONG TERM EFFECTS OF SLEEP DEPRIVATION ON HYPOTHALAMIC NUCLEI

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Electroencephalogram (EEG) slow wave activity (EEG power density between 0.5-4.0 Hz) during NREM sleep is a well characterized marker for the homeostatic regulation of sleep. Whether this EEG marker also reflects homeostatic regulation of deeper brain structures is unknown. By combining EEG recordings with electrical activity in several hypothalamic nuclei in the rat, we found that cortical SWA does not reflect the homeostatic changes in electrophysiological activity of hypothalamic structures after sleep deprivation (SD). Following a 6h SD, while cortical SWA recovered to normal values after 7h, neuronal activity in the Lateral hypothalamus (n=20) was decreased for up to 21h. In the Mammillary bodies (n=6) the decrease in the activity lasted 36h while in the Arcuate nucleus (n=5) a decrease was evident during the first half of the subjective night following SD. Interestingly, the Paraventricular nucleus (n=7) showed an opposite response with a sustained increase lasting 42h following SD. These results show that sleep deprivation has severe and long term effects on hypothalamic structures that regulate several physiological and behavioural functions (i.e. food intake, sleep, cognitive function and fear). The duration of these effects extends beyond the period of after-effects of sleep deprivation observed in the EEG SWA, which is the common marker to define the duration of recovery from sleep deprivation. Our data provide also a possible neuronal mechanisms of the many adverse health issues associated with sleep deprivation.

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## CORTICAL NETWORK DYNAMICS DIFFER AFTER TORPOR AND SLEEP DEPRIVATION IN DJUNGARIAN HAMSTERS

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**Objectives:** It has been shown previously in Djungarian hamsters that the initial EEG slow-wave activity (power in the 0.5-4.0 Hz band; SWA) in NREM sleep following an episode of daily torpor (T) is consistently enhanced, similar to the SWA increase after sleep deprivation (SD). However, it is unknown whether the network mechanisms underlying the SWA increase after T and SD are similar.

**Methods:** Adult male Djungarian hamsters (*Phodopus sungorus*) were used (n=6). EEG (parietal, P and frontal, F) and EMG were recorded continuously. Individual NREM sleep slow waves were analysed during 1-h interval after SD or T and corresponding BSL.

**Results:** We found that in both T and SD the SWA increased significantly in both derivations (SD: P, 165.1±6.2, F, 174.8±4.9 % of BSL, T: P, 134.1±9.2, F, 158.5±12.1% of BSL). After SD slow-wave slopes increased significantly in the parietal and in the frontal derivation (p< 0.01). The increase in the frontal derivation was significantly greater than in the parietal derivation for the 1st slope (113.1±2.0 vs 107.5±1.9%, p=0.01), and somewhat higher for the 2nd slope (114.1±1.5 vs 110.9±1.1%, p=0.1). In contrast, in neither derivation a change in slopes was found after T (all effects< 5%, n.s.).

**Conclusions:** We found that slopes of single slow waves during NREM sleep were steeper after SD but not after torpor. The data suggest that prolonged waking and torpor result in a similar homeostatic sleep response, but have different effects on cortical network dynamics.

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## **CIRCADIAN AND HOMEOSTATIC MODULATION OF MULTI-UNIT ACTIVITY IN DOPAMINERGIC AND STRIATAL STRUCTURES**

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Several neurological disorders associated with Basal Ganglia dysfunctioning, like Parkinson's and Huntington's diseases, are characterised by seriously debilitating sleep abnormalities. The involvement of Basal Ganglia in sleep modulation has been recently documented. However, the reciprocal modulation of Basal Ganglia activity by sleep-wake dependent processes is unknown. We combined Electroencephalogram (EEG) recordings with electrical multi-unit activity (MUA) in different subdivisions of both Midbrain Dopaminergic structures [Substantia nigra lateral (SNL, n=6), Substantia nigra Medial (SNM, n=5), Ventral Tegmental area (VTA, n=6)] and striatal structures [Striatum Latero-dorsal (STR-LD, n=4), Striatum Medio-dorsal (STR-MD, n=4), Ventral striatum (STR-V, n=4)] under 12:12 light/dark (LD) and constant darkness (DD) conditions. We also investigated the effects of a 6h sleep deprivation on MUA in these areas. Both under LD and DD conditions, the MUA in the areas examined showed a vigilance state dependency with the highest firing rates during wakefulness and REM sleep compared to NREM sleep ( $p < 0.001$ , t-test). Interestingly, striatal subdivisions displayed different sensitivities towards changes in homeostatic sleep pressure as evidenced by EEG Slow Wave Activity. Our results indicate that circadian and homeostatic processes influence the activity of midbrain dopaminergic and striatal structures. These influences may contribute to behavioural changes observed in neurological disorders related to dysfunctioning in the Basal Ganglia.

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## DIM LIGHT AT NIGHT DISTURBS THE DAILY SLEEP-WAKE CYCLE AND SLEEP ARCHITECTURE IN RATS

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**Study Objectives:** Exposure to artificial light during the dark phase of the circadian cycle is common in present society. Light provides the main input to the suprachiasmatic nucleus (SCN) which regulates sleep-wake behavior and energy metabolism. In humans, exposure to light at night has been correlated to insomnia and obesity. Here we aimed to develop a rat model to study the effects of dim light at night on sleep-wake behavior and energy metabolism. **Methods:** Male Wistar rats were exposed to either a 12-h light (150-200lux):12-h dark (LD) schedule or a 12-h light (150 lux):12-h dim white light (5 lux) (LDim) schedule. Sleep-wake rhythms were assessed with EEG/EMG recordings, homecage locomotor activity, and in situ hybridizations of clock genes in the SCN. Energy metabolism was assessed with calorimetric measurements and intravenous glucose tolerance tests. **Results:** LDim decreased the amplitude of the daily rhythms in waking, NREM sleep and REM sleep. Within NREM sleep, LDim induced a pronounced loss of rhythm in slow wave activity (0.75-4 Hz) and the circadian (16-19 Hz) frequency domain. LDim induced a free running rhythm in locomotor activity with a period of  $25.1 \pm 0.0$  h that interfered with the remaining 24 h rhythm. In the SCN, LDim reduced the amplitude in the daily rhythm of *Per1* and *Arntl* (*Bmal1*) expression. LDim also decreased the amplitude of the daily rhythms in food intake and energy expenditure, but despite this it did not affect body weight, adiposity or glucose tolerance. **Conclusion:** In the Wistar rat, LDim disturbs the daily rhythm in sleep-wake behavior by a direct sleep promoting effect of dim light, as well as by introducing an endogenous free running rhythm with a period of ~25-h that reduces SCN output amplitude. **Significance:** We introduce the first rodent model showing decreased sleep-wake rhythms due to dim light at night. Dim light disturbances in sleep/wake rhythms were caused by the induction of a second rhythmic components in locomotor activity with a period of ~25 hours. Our data show for the first time that behavioral desynchronization can be induced despite adherence of the main L/D Zeitgeber to a 12h:12h cycle. This rat model may help to identify the causal mechanism underlying the associations between light at night and insomnia in humans. Future studies with transgenic clock-gene luciferase rats are needed to elucidate the anatomical representation of the endogenous free running rhythm.

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SRBR Conference, Palm Harbor FL, May 2016

## THE EFFECT OF AGING ON NREM SLEEP EEG SLOW WAVES IN MICE

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In the course of aging an overall decline in circadian drive, associated with circadian amplitude decrements, is observed. In addition, sleep-wake impairments emerge, predominantly sleep fragmentation. In this study, we want to investigate the effect of age on sleep and electroencephalogram (EEG) parameters, and NREM sleep slow wave morphology in young (6 months, n=9) and aged (18-24months, n=24) male C57BL/6 mice. EEG and the electromyogram were recorded for 48 h in a 12:12 L:D cycle beginning at lights on. On the second day a 6-h sleep deprivation (SD) was performed starting at light onset. Aged mice had increased total NREM sleep during darkness and more long NREM sleep episodes (32-256s) (t-tests,  $p < 0.0001$  after significant ANOVAs). In addition, older animals exhibited significantly higher levels of absolute EEG slow-wave activity (SWA, 0.5-4.0 Hz) in NREM sleep as compared to younger animals (t-tests,  $p < 0.0001$  after significant ANOVA). In both age groups more large amplitude slow waves, less multipeak waves and steeper slopes of the slow waves were found at the beginning of the light period as compared to the end of the light period (t-tests,  $p < 0.0001$  after significant ANOVAs). However, the incidence of multipeak waves was lower in aged mice and the changes in slopes during baseline and after SD were less pronounced as compared to the young mice (t-tests,  $p < 0.0001$  after significant ANOVAs). The increased sleep, the longer NREM sleep episodes, the higher SWA together with the lower number of multipeak slow-waves suggest an increased sleep pressure in the older mice. The differences observed in the shape and incidence of individual slow waves may arise from changes in connectivity and altered cortical network properties, such as local and global neuronal synchronization.

*Worldsleep 2015 Istanbul*



## CHRONIC HIGH FAT DIET INCREASES RAPID EYE MOVEMENT SLEEP IN MICE

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Consumption of high caloric food has increased in societies around the world and part of this increase has been attributed to a decrease in amount and quality of sleep. Many studies have investigated the influence of disturbed sleep on food intake and development of weight and metabolic syndrome. However, not many studies have investigated the influence of increased caloric intake on sleep. In this study we investigated the effect of chronic high fat diet on sleep and electroencephalogram (EEG) characteristics in mice. Male C57BL/6 mice were kept under 12h:12h light-dark conditions with normal chow (Control, n=8) or high fat chow (HF, n=9) for at least 3 months. At the age of six months (Control: 28.7±0.7 g, HF: 47.6 ±0.8 g, mean ±SEM) EEG and the electromyogram were recorded for 48 hours. On the second day a 6h sleep deprivation (SD) was performed starting at light onset. Rapid eye movement (REM) sleep in the light period was increased from 6.8 ±1.1% in control to 13.7 ±1.3% in the HF group ( $p < 0.005$ , unpaired t-test). This was mainly caused by an increase in the episode frequency (Control 5.3 ±1.4/h, HF 12.5 ±1.4/h,  $p < 0.005$ ) while episode duration remained unchanged. No large changes were seen in the amount of NonREM sleep and waking. EEG activity between 8-11 Hz was significantly increased in both sleep states in the HF group ( $p < 0.05$ , unpaired t-test) and during the sleep deprivation this frequency range was increased more in the HF group in waking. The increase in REM sleep frequency in the HF group may be caused by changes in mono-amine balance and are in accordance with reduced serotonin plasma levels published previously. The data show that changes in food consumption and caloric intake can influence sleep architecture and the sleep EEG.

*Worldsleep 2015, Istanbul*

## TIRED OF BLUNT TOOLS? SHARPENING THE CLINICAL ASSESSMENT OF FATIGUE AND SLEEPINESS

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Fatigue and sleepiness are ubiquitous symptoms in various conditions and are frequently associated to impaired sleep quality. While separate fatigue and sleepiness scales exist, both constructs are often confused. Unraveling this issue requires estimating the instruments' measurement properties, potential scale recalibration and re-evaluation of symptom intensities on a comparable basis. This study aims at improving the assessment of these symptoms and quantifying their degree of overlap using common-person-equating (CPE). One hundred fifty-nine patients, either with complaints of fatigue, sleepiness and/or non-restorative sleep, addressed to an academic sleep unit for a full-night polysomnography (PSG), enrolled in the study. Symptom levels were measured with the Fatigue Severity (FSS) and Epworth Sleepiness (ESS) scales. Sleep quality was assessed by the Pittsburgh Sleep Quality Index, defining 'good' and 'poor' sleeper groups. Good and poor sleepers did not differ statistically regarding demographics and PSG parameters. Rasch analysis revealed that, considering proper calibration, the ESS and FSS generate reliable and valid, unidimensional linear measures and to be invariant to perceived sleep quality. CPE showed predominantly fatigued, rather than sleepy patients, being more likely to present as poor sleepers. A concordance diagram based on scale scores is provided, in order to improve the differentiation of both symptoms.

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## EMOTION REGULATION MEDIATES THE RELATIONSHIP BETWEEN PERSONALITY AND SLEEP QUALITY

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**OBJECTIVE:** Despite a long history of interest in personality as well as in the mechanisms that regulate sleep, the relationship between personality and sleep is not yet well understood. The purpose of this study was to explore how personality affects sleep.

**DESIGN:** The present cross-sectional study, based on a sample of 1291 participants with a mean age of 31.16 years (SD = 12.77), investigates the impact of personality styles, assessed by the Personality Adjectives Checklist (PACL), on subjective sleep quality, as well as the possible mediation of this relationship by dispositional emotion regulation (ER) styles.

**RESULTS:** The dispositional use of suppression was a quite consistent predictor of poor subjective sleep quality for individuals scoring high on Confident, Cooperative or Introversive personality traits, but low on Respectful personality traits. Although a positive relationship between reappraisal and subjective sleep quality was found, there was only little evidence for a relationship between the assessed personality styles and the use of cognitive reappraisal.

**CONCLUSION:** The present results indicate that in the evaluation of subjective sleep, the impact of personality and ER processes, such as emotion suppression, should be taken into account.

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## EXERCISE DURING SHORT-TERM AND LONG-TERM CONTINUOUS EXPOSURE TO HYPOXIA EXACERBATES SLEEP-RELATED PERIODIC BREATHING

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**STUDY OBJECTIVES:** Exposure to hypoxia elevates chemosensitivity, which can lead to periodic breathing. Exercise impacts gas exchange, altering chemosensitivity; however, interactions between sleep, exercise and chronic hypoxic exposure have not been examined. This study investigated whether exercise exacerbates sleep-related periodic breathing in hypoxia.

**METHODS:** Two experimental phases. Short-Term Phase: a laboratory controlled, group-design study in which 16 active, healthy men (age:  $25 \pm 3$  y, height:  $1.79 \pm 0.06$  m, mass:  $74 \pm 8$  kg) were confined to a normobaric hypoxic environment ( $FIO_2 = 0.139 \pm 0.003$ , 4,000 m) for 10 days, after random assignment to a sedentary (control, CON) or cycle-exercise group (EX). Long-Term Phase: conducted at the Concordia Antarctic Research Station (3,800 m equivalent at the Equator) where 14 men (age:  $36 \pm 9$  y, height:  $1.77 \pm 0.09$  m, mass:  $75 \pm 10$  kg) lived for 12-14 months, continuously confined. Participants were stratified post hoc based on self-reported physical activity levels. We quantified apnea-hypopnea index (AHI) and physical activity variables.

**RESULTS:** Short-Term Phase: mean AHI scores were significantly elevated in the EX group compared to CON (Night1 = CON:  $39 \pm 51$ , EX:  $91 \pm 59$ ; Night10 = CON:  $32 \pm 32$ , EX:  $92 \pm 48$ ;  $P = 0.046$ ). Long-Term Phase: AHI was correlated to mean exercise time ( $R(2) = 0.4857$ ;  $P = 0.008$ ) and the coefficient of variation in night oxyhemoglobin saturation ( $SpO_2$ ;  $R(2) = 0.3062$ ;  $P = 0.049$ ).

**CONCLUSIONS:** Data indicate that exercise (physical activity) per se affects night  $SpO_2$  concentrations and AHI after a minimum of two bouts of moderate-intensity hypoxic exercise, while habitual physical activity in hypobaric hypoxic confinement affects breathing during sleep, up to 13+ months' duration.

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## INDIVIDUAL DIFFERENCES IN SUBJECTIVE CIRCADIAN FLEXIBILITY

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The aim of this study was to evaluate individual differences in the subjective flexibility of the circadian system in a community sample, with respect to age, gender, chronotype, and sleepiness perceptions. An online questionnaire containing the Circadian Type Inventory, the Composite Scale of Morningness, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale was administered. In addition, participants performed a visuo-verbal judgment task to determine time-of-day variations in estimated sleepiness. We analyzed data of 752 participants, aged between 18 and 83 years, who reported good sleep quality, no sleep disturbances, no excessive daytime sleepiness, and no engagement in shiftwork. Our results suggest gender- and chronotype-related differences in the subjective flexibility of the circadian system. Subjective circadian flexibility was higher in men in comparison with women and was positively related to evening preference. Age was not associated with flexibility scores. Additionally, the subjective flexibility of the circadian system had an influence on estimated sleepiness profiles: individuals with a high flexibility displayed lower sleepiness estimations during the biological night in comparison to individuals with a low flexibility. These findings suggests that, next to known chronotype and other dispositional differences, subjective circadian flexibility should be taken into account when evaluating tolerance to activities associated with nighttime functioning (e.g. night shifts).

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## COMPLEX SLEEP APNEA AT AUTO TITRATING CPAP INITIATION: PREVELANCE, SIGNIFICANCE AND PREDICTIVE FACTORS

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**INTRODUCTION:** Obstructive sleep apnea (OSA) patients may develop central respiratory events under continuous positive airway pressure (CPAP), referred to as complex sleep apnea (CompSA).

**OBJECTIVE:** We aimed to assess prevalence and predictive factors of complex apnea and to evaluate treatment response to CPAP.

**METHODS:** Within a retrospective cohort study, we assessed clinical data of OSA patients, attending the sleep lab during a 15-months period. Included participants underwent two consecutive polysomnographies; baseline diagnosis and treatment trial. Complex apnea patients, defined by a central apnea index  $\geq 5$  per hour during pressure auto-titration, were compared to remainders.

**RESULTS:** Among 263 included patients, the prevalence of complex apnea was 9.1%. The mean apnea hypopnea index only dropped from 52.7 to 39.9 per hour in CompSA patients, while it improved from 40.9 to 7.3 in patients without CompSA. Although a decreased sleep-fragmentation under CPAP was observable in both groups, the enhancement of Non-REM sleep was superior in patients without CompSA. The CompSA patients showed higher median apnea-hypopnea, mixed apnea and central apnea indices at baseline and displayed higher rates of comorbid heart failure and obstructive pulmonary disease, but no higher severity of associated daytime fatigue and sleepiness symptoms.

**CONCLUSION:** Despite evidenced partial improvement of obstructive events, nocturnal hypoxemia and sleep fragmentation, the occurrence of complex apnea presented here as a clear therapeutic failure of auto-titrating CPAP and was associated with heart failure, COPD and higher central and mixed apnea indices at baseline.

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## ALTITUDE AND SEASONALITY IMPACT ON SLEEP IN ANTARTICA

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**BACKGROUND:** This study investigates the effects of seasonality and altitude on sleep in extreme Antarctic conditions.

**METHODS:** During summer and winter periods, 24 h of actimetric recordings were obtained at two different research stations, Dumont d'Urville (sea level altitude) and Concordia (corrected altitude 12,467 ft or 3800 m).

**RESULTS:** During daytime, there were no altitude- or season-related differences in time spent at work, energy expenditure, or number of walking steps. During the nighttime however, total sleep time was longer ( $m = 427.4$ ;  $SD = 42.4$ ), sleep efficiency higher ( $m = 90$ ;  $SD = 4.8$ ), and wake after sleep onset shorter ( $m = 42.2$ ;  $SD = 28.7$ ) at sea level. Additionally, sleep fragmentation episodes and energy expenditure were higher during summer than winter periods.

**DISCUSSION:** Our results show that dramatic variations in light exposure are not the only main factor affecting sleep quality in Antarctica, as altitude also markedly impacted sleep in these conditions. The effect of altitude-induced hypoxia should be taken into account in future investigations of sleep in extreme environments.

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## DOES MORE SLEEP MATTER? DIFFERENTIAL EFFECTS OF NREM- AND REM-DOMINANT SLEEP ON SLEEPINESS AND VIGILANCE

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We investigated effects of NREM and REM predominant sleep periods on sleepiness and psychomotor performances measured with visual analog scales and the psychomotor vigilance task, respectively. After one week of stable sleep-wake rhythms, 18 healthy sleepers slept 3hours of early sleep and 3hours of late sleep, under polysomnographic control, spaced by two hours of sustained wakefulness between sleep periods in a within subjects split-night, sleep interruption protocol. Power spectra analysis was applied for sleep EEG recordings and sleep phase-relative power proportions were computed for six different frequency bands (delta, theta, alpha, sigma, beta and gamma). Both sleep periods presented with similar sleep duration and efficiency. As expected, phasic NREM and REM predominances were obtained for early and late sleep conditions, respectively. Albeit revealing additive effects of total sleep duration, our results showed a systematic discrepancy between psychomotor performances and sleepiness levels. In addition, sleepiness remained stable throughout sustained wakefulness during both conditions, whereas psychomotor performances even decreased after the second sleep period. Disregarding exchanges for frequency bands in NREM or stability in REM, correlations between outcome measures and EEG power proportions further evidenced directional divergence with respect to sleepiness and psychomotor performances, respectively. Showing that the functional correlation pattern changed with respect to early and late sleep condition, the relationships between EEG power and subjective or behavioral outcomes might however essentially be related to total sleep duration rather than to the phasic predominance of REM or NREM sleep.

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## WHOSE CLOCK MAKES YOURS TICK? HOW MATERNAL CARDIORESPIRATORY PHYSIOLOGY INFLUENCES NEWBORN'S HEART RATE VARIABILITY

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This study examined the existence of direct maternal-infant physiological relatedness in respiratory sinus arrhythmia (RSA) when the infant was age 1, 2, 4, 8, and 12 weeks. We instructed mothers to breathe at 6, 12, 15, 20, and 6 cycles per minute while their infants lay on their body. The mother-infant ECG and respiration were registered and video recordings were made. RR-interval (RRI), respiration rate (fR) and RSA were calculated and mother-infant RSA response-patterns were analyzed. The results revealed that infants adjusted their RSA levels to their mothers' levels during the first 2 months of life, but not at 3 months of age, which could be interpreted as a continuing intra-uterine effect. The attenuation between 2 and 3 months could be a reflection of the 2-month developmental shift of social orientation.

*Biological Psychology* 2015 108, 132-141.

# **SLOW WAVE SLEEP IN THE CHRONICALLY FATIGUED: POWER SPECTRA DISTRIBUTION PATTERNS IN CHRONIC FATIGUE SYNDROME AND PRIMARY INSOMNIA**

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**OBJECTIVES:** To investigate slow wave sleep (SWS) spectral power proportions in distinct clinical conditions sharing non-restorative sleep and fatigue complaints without excessive daytime sleepiness (EDS), namely the chronic fatigue syndrome (CFS) and primary insomnia (PI). Impaired sleep homeostasis has been suspected in both CFS and PI.

**METHODS:** We compared perceived sleep quality, fatigue and sleepiness symptom-intensities, polysomnography (PSG) and SWS spectral power distributions of drug-free CFS and PI patients without comorbid sleep or mental disorders, with a good sleeper control group.

**RESULTS:** Higher fatigue without EDS and impaired perceived sleep quality were confirmed in both patient groups. PSG mainly differed in sleep fragmentation and SWS durations. Spectral analysis revealed a similar decrease in central ultra slow power (0.3-0.79Hz) proportion during SWS for both CFS and PI and an increase in frontal power proportions of faster frequencies during SWS in PI only. The latter was correlated to affective symptoms whereas lower central ultra slow power proportions were related to fatigue severity and sleep quality impairment.

**CONCLUSIONS:** In combination with normal (PI) or even increased SWS durations (CFS), we found consistent evidence for lower proportions of slow oscillations during SWS in PI and CFS.

**SIGNIFICANCE:** Observing normal or increased SWS durations but lower proportions of ultra slow power, our findings suggest a possible quantitative compensation of altered homeostatic regulation.

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## EAMI: A QUALITATIVE QUANTIFICATION OF PERIODIC BREATHING BASED ON AMPLITUDE OF OSCILLATIONS

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**STUDY OBJECTIVES:** Periodic breathing is sleep disordered breathing characterized by instability in the respiratory pattern that exhibits an oscillatory behavior. Periodic breathing is associated with increased mortality, and it is observed in a variety of situations, such as acute hypoxia, chronic heart failure, and damage to respiratory centers. The standard quantification for the diagnosis of sleep related breathing disorders is the apnea-hypopnea index (AHI), which measures the proportion of apneic/ hypopneic events during polysomnography. Determining the AHI is labor-intensive and requires the simultaneous recording of airflow and oxygen saturation. In this paper, we propose an automated, simple, and novel methodology for the detection and qualification of periodic breathing: the estimated amplitude modulation index (eAMI).

**PARTICIPANTS:** Antarctic Cohort (3800 meters): 13 normal individuals. Sleep Clinic Cohort: 39 different patients suffering from diverse sleep-related pathologies.

**MEASUREMENTS AND RESULTS:** When tested in a population with high levels of periodic breathing (Antarctic Cohort), eAMI was closely correlated with AHI ( $r = 0.95$ ,  $P < 0.001$ ). When tested in the clinical setting, the proposed method was able to detect portions of the signal in which subclinical periodic breathing was validated by an expert ( $n = 93$ ; accuracy = 0.85). Average eAMI was also correlated with the loop gain for the combined clinical and Antarctica cohorts ( $r = 0.58$ ,  $P < 0.001$ ).

**CONCLUSIONS:** In terms of quantification and temporal resolution, the eAMI is able to estimate the strength of periodic breathing and the underlying loop gain at any given time within a record. The impaired prognosis associated with periodic breathing makes its automated detection and early diagnosis of clinical relevance.

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## RUMINATION IS ASSOCIATED WITH A REDUCED EFFICIENCY IN COGNITIVE CONTROL AND PERCEIVED SLEEP QUALITY

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Ruminative thought is a characterizing feature of insomnia disorder. Despite its clinical relevance, research on the underlying cognitive mechanisms of rumination remains scarce. According to the processing efficiency hypothesis rumination interferes with normal cognition by taking up valuable working memory resources. Consequently, individuals with a tendency to ruminate will have to engage more effort to maintain effective task performance at the expense of cognitive efficiency. In the present study, we specifically investigated whether rumination was associated with a reduced cognitive control ability. In order to do this, we administered the continuous performance task (AX-CPT) to a group of undergraduates ( $n = 83$ ). From this sample, low-ruminators ( $n = 25$ ), moderate ruminators ( $n = 23$ ) and high-ruminators ( $n = 23$ ) were selected. In the AX-CPT task, subjects have to provide a certain response to target trials (i.e., AX) and a different response to non-target trials (i.e., BX, AY and BY), while target trials are presented with a high frequency (70%) and therefore creating an expectancy bias. The main results showed that although the three groups made a similar amount of errors on the task, high-ruminators were significantly slower than moderate- and low-ruminators on target trials. Furthermore, a significant interaction was found between the type of non-target trial and ruminator group, showing that moderate ruminators made more errors on AY trials compared to high ruminators, which indicated that moderate ruminators make use of a proactive strategy. Additionally, rumination was found to be significantly associated with poor subjective sleep quality and prolonged subjective sleep onset latency. The results lend further support that, given an equal performance between groups (similar error rates), rumination is associated with reduced efficiency in cognitive control (increased reaction time). Furthermore, these findings suggest that rumination is important for understanding sleep disturbances. In a follow-up study, we will examine whether this impairment in processing efficiency associated with a tendency to ruminate, also holds true in patients with insomnia disorder. Investigating the potential contribution of rumination to cognitive efficiency in patients with insomnia disorder may possibly elucidate reported difficulties in cognitive functioning in these patients.

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## VALIDATION AND PSYCHOMETRIC PROPERTIES OF THE 'BRUGMANN FATIGUE SCALE' (BFS): A NEW INSTRUMENT FOR THE CLINICAL ASSESSMENT OF PERCEIVED FATIGUE

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**Introduction:** While often confused, fatigue, in contrast to sleepiness, mostly requires rest, not sleep to recover from. Likewise for pain, unidimensional single-variable-based objective measures of fatigue seem elusive to develop. Yet more than for sleepiness, clinical routine evaluations of fatigue therefore mainly rely on available instruments for symptom-intensity. The 'Brugmann Fatigue Scale' (BFS), assessing both mental and physical fatigue has been developed with a similar conceptual background than the Epworth Sleepiness Scale (ESS) (focusing on behavioural change or response).

The present study evaluates the psychometric properties of the BFS and compares the BFS with the ESS and the Fatigue Severity Scale (FSS).

**Methods:** The BFS is an 8-item 4-point Likert scale (scoring from 0 to 24). The sample comprised 295 hypnotic-free patients (173 males, mean age 48.4±13.4), addressed to an academic sleep unit. Inclusion criteria comprised referral for clinical complaints of either fatigue, sleepiness or non-restorative sleep, or combinations of the aforementioned. Perceived sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI).

**Results:** Convergent validity between the BFS and FSS was satisfactory ( $r=.517$ ;  $p<.001$ ). Discriminant validity of the BFS and FSS (with respect to the ESS) were similar ( $r=.279$  and  $r=.256$  respectively;  $p<.001$ ). The BFS showed higher internal consistency than the FSS (Cronbach's alpha:  $.923$  and  $.787$  respectively). In contrast to the ESS, the PSQI was positively correlated to the BFS ( $r=.336$ ,  $p<.001$ ). The proposed cut-off for clinically significant fatigue was 12.

**Conclusion:** The BFS (and its subscales) shows to be a reliable and precise instrument for the assessment of fatigue symptom-levels.

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## PRELIMINARY DATA ON THE EFFECTIVENESS AND COMPLIANCE OF A SLEEP POSITIONING PILLOW IN THE TREATMENT OF POSITIONAL SLEEP RELATED BREATHING DISORDERS

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**Objective:** Continuous positive airway pressure (CPAP) remains a first choice treatment for both moderate and severe obstructive sleep apnea (OSA). Till present, there is however no clear consensus on optimal treatment interventions for milder sleep-related breathing disorders (SRBD) in general or for positional SRBD (pSRBD) in particular. While several therapeutic options are either relatively invasive and/or expensive, positional therapy (PT) may still present as a valuable and affordable first-line intervention for pSRBD.

**Methods:** 13 patients, free from any sleep interfering drug treatment, without any major physical or mental co-morbid condition, presenting with pSRBD, underwent three nights of full polysomnographic (PSG) recording in an academic sleep lab. Inclusion criteria were based on the first night's PSG. During the second (consecutive) night, a sleep positioning pillow (Posiform®) was administered. A third PSG was performed after one month of usage of the pillow at home.

**Results:** Significant immediate treatment effects ( $p < .05$ ) after one night and significantly sustained effects after one month were observed in our sample. Significant reductions of sleep time in supine position, sleep fragmentation, apnea-hypopnea index, respiratory distress index (RDI) and oxygen desaturation index were observed. In addition, we obtained remitted sleep quality impairment as measured by the Pittsburgh Sleep Quality Index. Daytime sleepiness (Epworth Sleepiness Scale) and the Function Outcomes of Sleep Questionnaire also showed significant improvements after PT.,

**Conclusions:** The combined and significant improvement on both sleep-related respiratory variables and symptom-scales were observed after treatment initiation and one month of follow-up.

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## EFFECTS OF LIGHT AND TEMPERATURE ON ALERTNESS AND THERMOPHYSIOLOGICAL RESPONSES

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Light and ambient temperature both influence alertness and productivity of building occupants. Effects of the light condition vary over the time of the day. In the evening and night, alerting effects of light go along with a change in physiology, as reflected in skin temperatures, core body temperature and melatonin. The aim of this experiment is to study the effect of light intensity and temperature in the morning on thermophysiology and how this relates to alertness.

A randomized crossover design was performed in which 19 healthy female subjects participated. The study consisted of two sessions: a bright (1200 lux) and dim (5 lux) light session, both with a correlated colour temperature of 4000K. During each session three different room temperatures were offered: cool (26°C), neutral (29°C) and warm (32°C). Subjects were in semi-supine position and wore underwear. Skin temperatures, core temperature, cortisol and alertness are the main outcome variables. Statistics are performed using a random intercept model in SPSS 23.

Self-assessed alertness was influenced by both light intensity and room temperature. Bright light resulted in a higher self-assessed alertness ( $p=0.038$ ) compared to dim light, irrespective of the ambient temperature. Subjects indicated to feel most alert in the cool temperature ( $p<0.01$ ). Reaction time was only influenced by ambient temperature, not by light, and was slowest during the warm condition ( $p<0.01$ ). Physiological data shows a higher core temperature ( $p=0.013$ ) and proximal skin temperature ( $p<0.01$ ) during dim light session. There was no interaction between light and room temperature. Proximal-distal temperature gradient was larger during dim light ( $p=0.01$ ). Cortisol level was higher at the end of the dim session compared to bright ( $p=0.04$ ) and preliminary results indicate a larger increase of adrenaline during dim light ( $p=0.04$ ).

The three different ambient temperatures result in similar effects of morning light intensity on thermophysiology. However, these effects were opposite to thermo physiological effects reported in literature for evening/nighttime light exposure. At all ambient temperatures studied here, morning bright light increased self-assessed alertness as compared to dim light. This indicates that the relation between thermophysiology and alertness in the morning and evening are of a different nature, warranting further studies.

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

*Society for Light Treatment and Biological Rhythms Abstracts 2016;28:69*

## CIRCADIAN RHYTHMS IN GLUCOSE AND LIPID METABOLISM IN NOCTURNAL AND DIURNAL MAMMALS

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Most aspects of energy metabolism display clear variations during day and night. This daily rhythmicity of metabolic functions, including hormone release, is governed by a circadian system that consists of the master clock in the suprachiasmatic nuclei of the hypothalamus (SCN) and many secondary clocks in the brain and peripheral organs. The SCN control peripheral timing via the autonomic and neuroendocrine system, as well as via behavioral outputs. The sleep–wake cycle, the feeding/fasting rhythm and most hormonal rhythms, including that of leptin, ghrelin and glucocorticoids, usually show an opposite phase (relative to the light–dark cycle) in diurnal and nocturnal species. By contrast, the SCN clock is most active at the same astronomical times in these two categories of mammals. Moreover, in both species, pineal melatonin is secreted only at night. In this review we describe the current knowledge on the regulation of glucose and lipid metabolism by central and peripheral clock mechanisms. Most experimental knowledge comes from studies in nocturnal laboratory rodents. Nevertheless, we will also mention some relevant findings in diurnal mammals, including humans. It will become clear that as a consequence of the tight connections between the circadian clock system and energy metabolism, circadian clock impairments (e.g., mutations or knock-out of clock genes) and circadian clock misalignments (such as during shift work and chronic jet-lag) have an adverse effect on energy metabolism, that may trigger or enhancing obese and diabetic symptoms.

*Mol Cell Endocrinol 418(2015)74-88*



## SEROTONIN, A POSSIBLE INTERMEDIATE BETWEEN DISTURBED CIRCADIAN RHYTHMS AND METABOLIC DISEASE

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It is evident that eating in misalignment with the biological clock (such as in shift work, eating late at night and skipping breakfast) is associated with increased risk for obesity and diabetes. The biological clock located in the suprachiasmatic nucleus dictates energy balance including feeding behavior and glucose metabolism. Besides eating and sleeping patterns, glucose metabolism also exhibits clear diurnal variations with higher blood glucose concentrations, glucose tolerance and insulin sensitivity prior to waking up. The daily variation in plasma glucose concentrations in rats, is independent of the rhythm in feeding behavior. On the other hand, feeding itself has profound effects on glucose metabolism, but differential effects occur depending on the time of the day. We here review data showing that a disturbed diurnal eating pattern results in alterations in glucose metabolism induced by a disrupted circadian clock. We first describe the role of central serotonin on feeding behavior and glucose metabolism and subsequently describe the effects of central serotonin on the circadian system. We next explore the interaction between the serotonergic system and the circadian clock in conditions of disrupted diurnal rhythms in feeding and how this might be involved in the metabolic dysregulation that occurs with chronodisruption.

*Neuroscience 301(2015)155-167*

## EFFECTS OF CENTRAL GASTRIN-RELEASING PEPTIDE ON GLUCOSE METABOLISM

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Gastrin-releasing peptide (GRP) mediated signals in the central nervous system (CNS) influence many functions associated with energy metabolism. The purpose of the present study was to investigate the central effect of GRP on glucose metabolism in the male rat. Intracerebroventricular (icv) administration of GRP caused an immediate hyperglycaemia which was sustained till the end of the infusion. The rise in plasma glucose levels was accompanied by an increase in endogenous glucose production (EGP), as well as increases in plasma glucagon and insulin concentrations. Furthermore, no differences in plasma corticosterone levels were noted between control and GRP treated rats. These results demonstrate that central GRP increases plasma glucose levels, probably by stimulating pancreatic glucagon release and concomitantly or subsequently endogenous glucose production.

*Brain Res, 1625(2015)135-141*

## THE ROLE OF FEEDING RHYTHM, ADRENAL HORMONES AND NEURONAL INPUTS IN SYNCHRONIZING DAILY CLOCK GENE RHYTHMS IN THE LIVER

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The master clock in the hypothalamic suprachiasmatic nucleus (SCN) is assumed to distribute rhythmic information to the periphery via neural, humoral and/or behavioral connections. Until now, feeding, corticosterone and neural inputs are considered important signals for synchronizing daily rhythms in the liver. In this study, we investigated the necessity of neural inputs as well as of the feeding and adrenal hormone rhythms for maintaining daily hepatic clock gene rhythms. Clock genes kept their daily rhythm when only one of these three signals was disrupted, or when we disrupted hepatic neuronal inputs together with the adrenal hormone rhythm or with the daily feeding rhythm. However, all clock genes studied lost their daily expression rhythm after simultaneous disruption of the feeding and adrenal hormone rhythm. These data indicate that either a daily rhythm of feeding or adrenal hormones should be present to synchronize clock gene rhythms in the liver with the SCN.

*Mol Cell Endocrinol*, 422(2016)125-131

# EFFECTS OF 6-MEALS-A-DAY FEEDING AND 6-MEALS-A-DAY FEEDING COMBINED WITH ADRENALECTOMY ON DAILY GENE EXPRESSION RHYTHMS IN RAT EPIDIDYMAL WHITE ADIPOSE TISSUE

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The master clock in the hypothalamic suprachiasmatic nucleus (SCN) is assumed to synchronize the tissue-specific rhythms of the peripheral clocks with the environmental day/night changes via neural, humoral and/or behavioral connections. The feeding rhythm is considered an important Zeitgeber for peripheral clocks, as daytime feeding reverses (clock) gene rhythms in the periphery, but not in the SCN. In this study, we investigated the necessity of a daily feeding rhythm for maintaining gene expression rhythms in epididymal white adipose tissue (eWAT). We showed that 7 of 9 rhythmic metabolic/adipokine genes, but not clock genes, lost their rhythmicity upon exposure to 6-meals-a-day feeding. Previously, we showed comparable effects of adrenalectomy on eWAT; therefore, subsequently we investigated the effect of simultaneous disruption of these humoral and behavioral signaling pathways, by exposing adrenalectomized animals to 6-meals-a-day feeding. Interestingly, under these conditions, all the clock genes and 10 of 11 rhythmic metabolic/adipokine genes lost their rhythmicity. These data indicate that adrenal hormones and feeding rhythm are indispensable for maintaining daily rhythms in metabolic/adipokine gene, but not clock gene, expression in eWAT. In contrast, at least one of these two signals should be present in order for eWAT clock gene rhythms to be maintained.

*Genes to Cells*, 21(2016)6-24

## **SUPRACHIASMATIC NUCLEUS NEUROPEPTIDES AND THEIR CONTROL OF ENDOGENOUS GLUCOSE PRODUCTION**

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Defective control of endogenous glucose production is an important factor responsible for hyperglycaemia in the diabetic individual. During the past decade, progressively more evidence has appeared indicating a strong and potentially causal relationship between disturbances of the circadian system and defects of metabolic regulation, including glucose metabolism. The detrimental effects of disturbed circadian rhythms may have their origin in disturbances of the molecular clock mechanisms in peripheral organs, such as the pancreas and liver, or in the central brain clock in the hypothalamic suprachiasmatic nuclei (SCN). To assess the role of SCN output per se on glucose metabolism, we investigated (i) the effect of several SCN neurotransmitters on endogenous glucose production and (ii) the effect of SCN neuronal activity on hepatic and systemic insulin sensitivity. We show that silencing of SCN neuronal activity results in decreased hepatic insulin sensitivity and increased peripheral insulin sensitivity. Furthermore, both oxytocin neurones in the paraventricular nucleus of the hypothalamus (PVN) and orexin neurones in the lateral hypothalamus may be important targets for the SCN control of glucose metabolism. These data further highlight the role of the central clock in the pathophysiology of insulin resistance.

*J Neuroendocrinol, 2016(In Press).*

## ABSENCE OF DIURNAL VARIATION IN VISCEROMOTOR RESPONSE TO COLORECTAL DISTENTION IN NORMAL LONG EVANS RATS

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**Background:** Enhanced colorectal sensitivity (i.e. visceral hypersensitivity) is thought to be a pathophysiological mechanism in irritable bowel syndrome (IBS). In healthy men a circadian variation in rectal perception to colonic distention was described. Disturbed day and night rhythms, which occur in shift work and trans meridian flights, are associated with the prevalence of IBS. This raises the question whether disruptions of circadian control are responsible for the observed pathology in IBS. Prior to investigating altered rhythmicity in relation to visceral hypersensitivity in a rat model for IBS, it is relevant to establish whether normal rats display circadian variation similar to healthy men.

**Methodology and findings:** In rodents colorectal distension leads to reproducible contractions of abdominal musculature. We used quantification of this so called visceromotor response (VMR) by electromyography (EMG) to assess visceral sensitivity in rats. We assessed the VMR in normal male Long Evans rats at different time points of the light/dark cycle. Although a control experiment with male maternal separated rats confirmed that intentionally inflicted (i.e. stress induced) changes in VMR can be detected, normal male Long Evans rats showed no variation in VMR along the light/dark cycle in response to colorectal distension.

**Conclusions:** In the absence of a daily rhythm of colorectal sensitivity in normal control rats it is not possible to investigate possible aberrancies in our rat model for IBS.

*F1000 Research, 5(2016)98*

## INDIVIDUAL DIFFERENCES IN SLEEP TIMING RELATE TO MELANOPsin-BASED PHOTOTRANSDUCTION IN HEALTHY ADOLESCENTS AND YOUNG ADULTS

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**Study Objectives:** Individual differences in sleep timing have been widely recognized and are of particular relevance in adolescents and young adults who often show mild to severely delayed sleep. The biological mechanisms underlying the between-subject variance remain to be determined. Recent human genetics studies showed an association between sleep timing and melanopsin gene variation, but support for functional effects on downstream pathways and behavior was not demonstrated before. We therefore investigated the association between the autonomic (i.e., pupil diameter) and behavioral (i.e., sleep timing) readouts of two different downstream brain areas, both affected by the same melanopsin-dependent retinal phototransduction: the olivary pretectal nucleus (OPN) and the suprachiasmatic nucleus (SCN).

**Methods:** Our study population included 71 healthy individuals within an age range with known vulnerability to a delayed sleep phase (16.8–35.7 y, 37 males, 34 females). Pupillometry was performed to estimate functionality of the intrinsic melanopsin-signaling circuitry based on the OPN-mediated post-illumination pupil response (PIPR) to blue light. Sleep timing was quantified by estimating the SCN-mediated mid-sleep timing in three different ways in parallel: using a chronotype questionnaire, a sleep diary, and actigraphy.

**Results:** All three measures consistently showed that those individuals with a later mid-sleep timing had a more pronounced PIPR ( $0.03 < P < 0.05$ ), indicating a stronger blue-light responsiveness of the intrinsic melanopsin-based phototransduction circuitry.

**Conclusions:** Trait-like individual differences in the melanopsin phototransduction circuitry contribute to individual differences in sleep timing. Blue lightsensitive young individuals are more prone to delayed sleep.

*Sleep, 39(2016)1305-1310.*

## SLEEP RESTRICTION ACUTELY IMPAIRS GLUCOSE TOLERANCE IN RATS

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Chronic sleep curtailment in humans has been related to impairment of glucose metabolism. To better understand the underlying mechanisms, the purpose of the present study was to investigate the effect of acute sleep deprivation on glucose tolerance in rats. A group of rats was challenged by 4-h sleep deprivation in the early rest period, leading to prolonged (16 h) wakefulness. Another group of rats was allowed to sleep during the first 4 h of the light period and sleep deprived in the next 4 h. During treatment, food was withdrawn to avoid a postmeal rise in plasma glucose. An intravenous glucose tolerance test (IVGTT) was performed immediately after the sleep deprivation period. Sleep deprivation at both times of the day similarly impaired glucose tolerance and reduced the early-phase insulin responses to a glucose challenge. Basal concentrations of plasma glucose, insulin, and corticosterone remained unchanged after sleep deprivation. Throughout IVGTTs, plasma corticosterone concentrations were not different between the control and sleep-deprived group. Together, these results demonstrate that independent of time of day and sleep pressure, short sleep deprivation during the resting phase favors glucose intolerance in rats by attenuating the first-phase insulin response to a glucose load. In conclusion, this study highlights the acute adverse effects of only a short sleep restriction on glucose homeostasis.

*Physiol Rep*, 2016(In Press).



## **NUTRITION IN THE SPOTLIGHT: METABOLIC EFFECTS OF ENVIRONMENTAL LIGHT**

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Use of artificial light resulted in relative independence from the natural light–dark (LD) cycle, allowing human subjects to shift the timing of food intake and work to convenient times. However, the increase in artificial light exposure parallels the increase in obesity prevalence. Light is the dominant Zeitgeber for the central circadian clock, which resides within the hypothalamic suprachiasmatic nucleus, and coordinates daily rhythm in feeding behaviour and metabolism. Eating during inappropriate light conditions may result in metabolic disease via changes in the biological clock. In this review, we describe the physiological role of light in the circadian timing system and explore the interaction between the circadian timing system and metabolism. Furthermore, we discuss the acute and chronic effects of artificial light exposure on food intake and energy metabolism in animals and human subjects. We propose that living in synchrony with the natural daily LD cycle promotes metabolic health and increased exposure to artificial light at inappropriate times of day has adverse effects on metabolism, feeding behaviour and body weight regulation. Reducing the negative side effects of the extensive use of artificial light in human subjects might be useful in the prevention of metabolic disease.

*Proc Nutr Soc, 2016(In Press)*

## SLEEPINESS AND MELATONIN SUPPRESSION DURING EVENING EXPOSURE TO BLUE-DEPLETED AND VIOLET-ENRICHED WHITE LIGHT

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**Introduction:** Selective filtering of short wavelengths can reduce melatonin suppression by evening/nighttime light exposure and make such light exposure less sleep disruptive. However, this filtering also impacts the quality of light: it changes color appearance, lowers the correlated color temperature (CCT) and makes the light more yellow. We tested whether it is possible to define a blue-depleted white light spectrum that maintains CCT but reduces melatonin suppression at a given light intensity/illuminance.

**Methods:** Sixteen volunteers participated in three evening laboratory sessions, separated by one week. During each session, salivary melatonin, subjective sleepiness (KSS) and reaction time performance (PVT) were measured while participants received a 3-hour light exposure. Each participant received three lighting conditions: dim light (< 5 lux), bright white light (3600 K, 250 lux), and bright white light that is band-stop filtered between 460 and 480 nm and enriched with extra violet light (410 nm) to maintain CCT (3600 K, 250 lux).

**Results:** The two bright light conditions did not differ significantly in any of the outcomes. In both bright light conditions, participants felt less sleepy and melatonin suppression was significantly higher as compared to the dim light condition. No significant effects on PVT reaction time performance were observed between the three light conditions.

**Conclusions:** Melatonin suppression and sleepiness during evening light exposure to 250 lux are not significantly different between normal 3600 K white light or special 3600 K white light that is enriched in violet (410 nm) while blocking wavelengths between 460 - 480 nm.

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*Conference abstract P 037, 23<sup>rd</sup> ESRS, Bologna, September 2016*

## CIRCADIAN RHYTHM DISRUPTION AS A LINK BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY?

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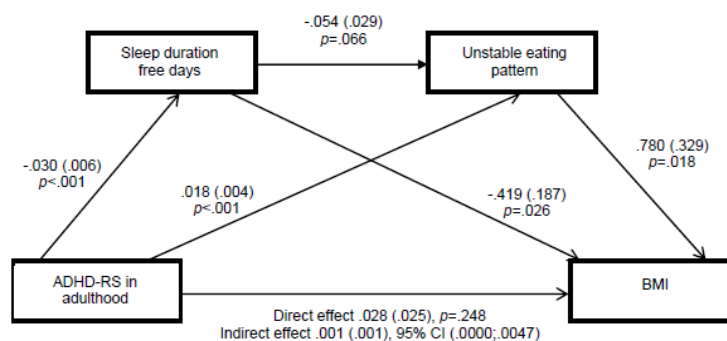
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**Introduction** – Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) have a high prevalence of obesity. This is the first study to investigate whether circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity.

**Methods** – ADHD symptoms and two manifestations of circadian rhythm disruption: sleep problems and an unstable eating pattern (skipping breakfast and binge eating later in the day) were assessed in participants with obesity (n=114), controls (n=154), and adult ADHD patients (n=202).

**Results** – Participants with obesity had a higher prevalence of ADHD symptoms and short sleep on free days as compared to controls, but a lower prevalence of ADHD symptoms, short sleep on free days, and an unstable eating pattern as compared to ADHD patients. We found that participants with obesity had a similar prevalence rate of an unstable eating pattern when compared to controls. Moreover, mediation analyses showed that both sleep duration and an unstable eating pattern mediated the association between ADHD symptoms and body mass index (BMI).

**Conclusion** – Our study supports the hypothesis that circadian rhythm disruption is a mechanism linking ADHD symptoms to obesity. Further research is needed to determine if treatment of ADHD and circadian rhythm disruption is effective in the prevention and treatment of obesity in patients with obesity and/or ADHD.



**Figure 1.** Effect of ADHD symptoms, as measured by the ADHD-Rating Scale, in adulthood on body mass index (BMI), mediated through sleep duration on free days (in hours) and an unstable eating pattern, N=384 ( $R^2 = .615$ ).

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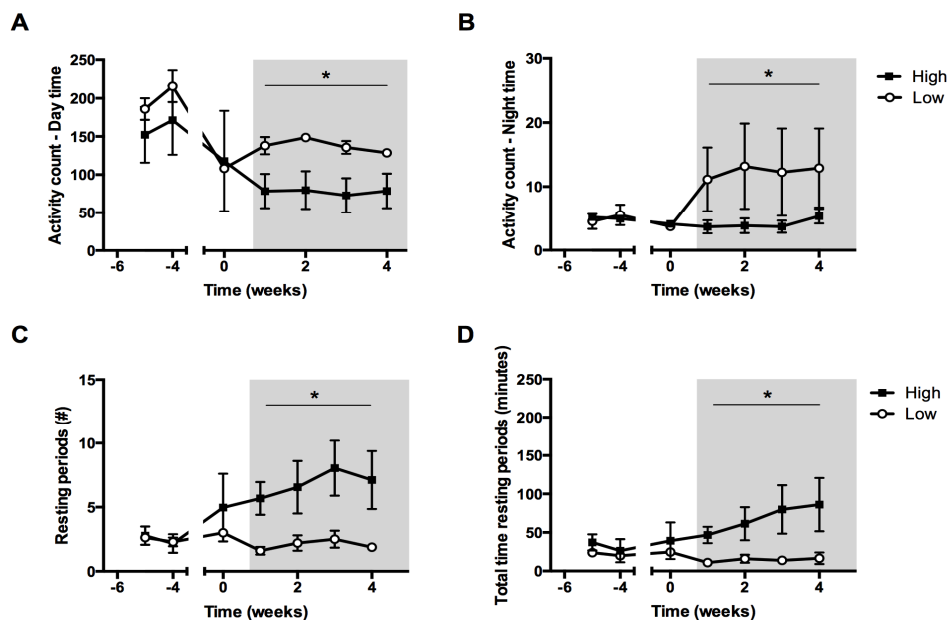
## INDIVIDUAL AND FAMILIAL SUSCEPTIBILITY TO MPTP IN A COMMON MARMOSSET MODEL FOR PARKINSON'S DISEASE

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Insight into susceptibility mechanisms underlying Parkinson's disease (PD) would aid the understanding of disease aetiology, enable target finding and benefit the development of more refined disease-modifying strategies. PD was induced by intermittent low-dose MPTP (0.5 mg/kg/week) injections in twelve marmoset monkeys. Disease progression was monitored by behavioural and neurochemical parameters. Genetically diverse monkeys from different breeding families were selected to investigate inter- and intra-family differences in susceptibility to MPTP treatment. We show that such differences exist in clinical signs, and non-motor behaviours such as number and duration of daytime naps (Fig. 1), that was conversely related to noradrenalin levels in the striatum. In line with the contribution of a genetic component, different susceptibility phenotypes (low responders vs high responders) could be traced back through genealogy to individuals of the different families. Our findings show that low-dose MPTP treatment in marmosets represents a clinically relevant PD model, with a window of opportunity to examine the onset of the disease, allowing the detection of individual variability in disease susceptibility, which may be of relevance for the diagnosis and treatment of PD in humans.



**Figure 1:** Homecage activity and power naps in parkinsonian monkeys measured by actimeters (mean±SE; n=6/group). Shaded area indicates MPTP exposure. High: high responders for PD (closed squares). Low: low responders for PD (open circles). \* Significant difference between the slope of both curves (p<0.05).

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## OCCURRENCE OF OBSTRUCTIVE SLEEP APNEA SYNDROME WITH TRANSIENT ISCHEMIC ATTACK

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is a sleep breathing disorder with episodes of upper airway obstructions. Patients with cardiovascular diseases such as myocardial infarction and stroke show a high prevalence of OSAS. Several studies focus on stroke and not on transient ischemic attack (TIA), suggesting it could be a symptom after stroke. We analyzed the occurrence of OSAS in high-risk patients with TIA.

**Methods:** There were 555 patients suspected for TIA by the general practitioner who were referred to our TIA daycare clinic. They were screened for OSAS using three screening factors: snoring (yes/no), Body Mass Index  $\geq 30$  and Epworth Sleepiness Score  $> 10$ . When 2 out of 3 were positive, patients received a polysomnography. An apnea/ hypopnea index (AHI) of 5-15 is defined as mild OSAS, AHI 15-30 as moderate OSAS and AHI  $>30$  as severe OSAS.

**Results:** 77 patients received a polysomnography. 25 patients had a diagnosis of TIA, 18 of cerebral ischemia and 34 had other diagnoses. 20 of the 25 (80%) TIA patients had OSAS, compared to 16 of the 34 (47%) patients without a vascular diagnosis ( $p=0.010$ ). When excluding patients with a cardiovascular history, we found 15 of the 20 patients with OSAS, compared to 14 out of 30 patients ( $p=0.047$ ).

**Conclusions:** There is a significant higher occurrence of OSAS in TIA patients compared to patients without a vascular diagnosis, even after excluding patients with a history of cardiovascular events.

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## ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS ADD RISK TO CIRCADIAN RHYTHM SLEEP PROBLEMS IN DEPRESSION AND ANXIETY

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**Introduction:** Comorbid ADHD symptoms may partly account for circadian rhythm disturbances in depression and anxiety disorders.

**Methods:** Self-reported sleep characteristics of 2,090 participants in the Netherlands Study of Depression and Anxiety were assessed using the Munich Chronotype Questionnaire. We defined 3 groups: healthy controls (HC), persons with lifetime depression and/or anxiety disorders (LDA), and those with both LDA and high ADHD symptoms (LDA+ADHD), using the Conner's Adult ADHD Rating Scale.

**Results:** Sleep characteristics were least favorable in the LDA+ADHD group. Important group differences between LDA+ADHD, LDA and HC were found for extremely late chronotype (12% vs. 5% vs. 3%;  $p < .001$ ), sleep duration <6 hours (15% vs. 5% vs. 4%;  $p < .001$ ), and for an indication of the Delayed Sleep Phase Syndrome (DSPS; 16% vs. 8% vs. 5%;  $p < .001$ ). After adjustment for covariates, including depression and anxiety, presence of ADHD symptoms increased the odds ratio for late chronotype (OR=2.6;  $p = .003$ ), indication of DSPS (OR=2.4;  $p = .002$ ), and sleep duration <6 hours (OR=2.7;  $p = .007$ ).

**Conclusion:** High ADHD symptoms were associated with an increased rate of circadian rhythm sleep disturbances in an already at-risk population of people with depression and/or anxiety disorders. Circadian rhythm sleep disorders, as often seen in ADHD are not entirely due to any comorbid depression and/or anxiety disorder. Adequate treatment of such sleep problems is needed and may prevent serious health conditions in the long term.

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# THE ASSOCIATION BETWEEN METABOLIC SYNDROME, OBESITY-RELATED OUTCOMES, AND ADHD IN ADULTS WITH COMORBID AFFECTIVE DISORDERS

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**Introduction:** ADHD may predispose to obesity, a metabolic syndrome component. Affective disorders are also associated with MetSyn and ADHD. This study examined whether ADHD confers any added risk of MetSyn and obesity-related associations in a large sample with varying stages of affective disorders.

**Method:** Participants included 2,303 adults from the Netherlands Study of Depression and Anxiety. Three groups were compared (controls, those with depressive/anxiety disorders without ADHD; and those with depressive/anxiety disorders and ADHD) for presence of MetSyn risk factors, body mass index, and waist-hip ratio. ADHD symptoms were identified by using a T-score > 65 (Conners Adult ADHD Rating Scale).

**Result:** Multivariable analyses were additionally adjusted for sociodemographic, lifestyle, health factors, and affective disorders. Analyses showed no significant association between MetSyn, obesity-related variables, and comorbid ADHD. High Inattention and Hyperactivity/Impulsivity symptoms were not associated with MetSyn.

**Conclusion:** This study did not confirm that MetSyn and obesity-related parameters are increased in comorbid ADHD.

*The infrastructure for the NESDA study ([www.nesda.nl](http://www.nesda.nl)) is funded through the Geestkracht Program of the Netherlands Organization for Health Research and Development (Zon-Mw, grant number 10-000-1002). This organization had no further role in study design, collection, analysis and interpretation of data, writing of the report, and in the decision to submit the paper for publication. NESDA is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).*

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## ADHD, CIRCADIAN RHYTHMS AND SEASONALITY

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**Introduction:** We evaluated whether the association between Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Seasonal Affective Disorder (SAD) was mediated by the circadian rhythm.

**Method:** Data of 2239 persons from the Netherlands Study of Depression and Anxiety (NESDA) were used. Two groups were compared: with clinically significant ADHD symptoms (N = 175) and with No ADHD symptoms (N = 2064). Sleep parameters were sleep-onset and offset times, mid sleep and sleep duration from the Munich Chronotype Questionnaire. We identified the prevalence of probable SAD and subsyndromal SAD using the Seasonal Pattern Assessment Questionnaire (SPAQ). Clinically significant ADHD symptoms were identified by using a T score > 65 on the Conners Adult ADHD Rating Scale.

**Result:** The prevalence of probable SAD was estimated at 9.9% in the ADHD group (vs. 3.3% in the No ADHD group) and of probable s-SAD at 12.5% in the ADHD group (vs 4.6% in the No ADHD group). Regression analyses showed consistently significant associations between ADHD symptoms and probable SAD, even after adjustment for current depression and anxiety, age, sex, education, use of antidepressants and benzodiazepines (B = 1.81, p < 0.001). Late self-reported sleep onset was an important mediator in the significant relationship between ADHD symptoms and probable SAD, even after correction for confounders (total model effects: B = 0.14, p ≤ 0.001).

**Conclusion:** Both seasonal and circadian rhythm disturbances are significantly associated with ADHD symptoms. Delayed sleep onset time in ADHD may explain the increase in SAD symptoms. Treating patients with SAD for possible ADHD and delayed sleep onset time may reduce symptom severity in these complex patients.

*The infrastructure for the NESDA study ([www.nesda.nl](http://www.nesda.nl)) is funded through the Geestkracht Program of the Netherlands Organization for Health Research and Development (Zon-Mw, grant number 10-000-1002). This organization had no further role in study design, collection, analysis and interpretation of data, writing of the report, and in the decision to submit the paper for publication. NESDA is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos Institute).*

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## SOCIAL SUPPORT MODERATES THE EFFECTS OF STRESS ON SLEEP IN ADOLESCENTS

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Academic expectations and demands become primary sources of stress during adolescence, negatively affecting sleep. To cope with stress, adolescents may turn to social support figures. The present study tested the extent of main and moderating effects of various sources of social support on the association between stress and sleep. Adolescents ( $n = 202$ , mean age 14.6 years, standard deviation = 0.71) reported on academic stress, sleep, and support using questionnaires during a low- and high-stress period, defined by the absence or presence of examinations, respectively. Inquiries were made regarding social support from parents, friends, and class supervisor. During both stress periods, academic stress was associated negatively with sleep quality and positively with sleep reduction. Social support increased sleep quality and lowered sleep reduction. In addition, social support moderated the effects of academic stress on sleep, thus improving sleep quality and lowering sleep reduction. Moderating effects were stronger during a period of high stress. The present study showed that adolescents can benefit from stress moderation through social support by improvements of sleep quality and sleep reduction. Such moderating effects should be taken into account when studying stress and sleep. Implications and recommendations based on these findings are discussed.

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## MEMORY TRACES OF LONG-RANGE COORDINATED OSCILLATIONS IN THE SLEEPING HUMAN BRAIN

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Cognition involves coordinated activity across distributed neuronal networks. Neuronal activity during learning triggers cortical plasticity that allows for reorganization of the neuronal network and integration of new information. Animal studies have shown post-learning reactivation of learning-elicited neuronal network activity during subsequent sleep, supporting consolidation of the reorganization. However, no previous studies, to our knowledge, have demonstrated reactivation of specific learning-elicited long-range functional connectivity during sleep in humans. We here show reactivation of learning-induced long-range synchronization of magnetoencephalography power fluctuations in human sleep. Visuomotor learning elicited a specific profile of long-range cortico-cortical synchronization of slow (0.1 Hz) fluctuations in beta band (12-30 Hz) power. The parieto-occipital part of this synchronization profile reappeared in delta band (1-3.5 Hz) power fluctuations during subsequent sleep, but not during the intervening wakefulness period. Individual differences in the reactivated synchronization predicted postsleep performance improvement. The presleep resting-state synchronization profile was not reactivated during sleep. The findings demonstrate reactivation of long-range coordination of neuronal activity in humans, more specifically of reactivation of coupling of infra-slow fluctuations in oscillatory power. The spatiotemporal profile of delta power fluctuations during sleep may subserve memory consolidation by echoing coordinated activation elicited by prior learning.

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## THE ROLE OF SLEEP TIMING IN CHILDREN'S OBSERVATIONAL LEARNING

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Acquisition of information can be facilitated through different learning strategies, classically associated with either declarative or procedural memory modalities. The consolidation of the acquired information has been positively associated with sleep. In addition, subsequent performance was better when acquisition was quickly followed by sleep, rather than daytime wakefulness. Prior studies with adults have indicated the viability of the alternative learning strategy of observational learning for motor skill acquisition, as well as the importance of sleep and sleep timing. However, relatively little research has been dedicated to studying the importance of sleep for the consolidation of procedural memory in children. Therefore, this study investigated whether children could encode procedural information through observational learning, and whether sleep timing could affect subsequent consolidation and performance. School-aged children aged 9-12 years ( $N=86$ , 43% male,  $M_{age}=10.64$  years,  $SD=.85$ ) were trained on a procedural fingertapping task through observation, either in the morning or evening; creating immediate wake and immediate sleep groups, respectively. Performance was evaluated the subsequent evening or morning on either a congruent or incongruent task version. Observation and task execution was conducted using an online interface, allowing for remote participation. Performance of the immediate wake group was lower for a congruent version, expressed by a higher error rate, opposed to an incongruent version; an effect not observed in the immediate sleep group. This finding showed that observational learning did not improve performance in children. Yet, immediate sleep prevented performance reduction on the previously observed task. These results support a benefit of sleep in observational learning in children, but in a way different from that seen in adults, where sleep enhanced performance after learning by observation.

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## SLEEP TO THE BEAT: A NAP FAVOURS CONSOLIDATION OF TIMING

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Growing evidence suggests that sleep is important for procedural learning, but few studies have investigated the effect of sleep on the temporal aspects of motor skill learning. We assessed the effect of a 90-min day-time nap on learning a motor timing task, using 2 adaptations of a serial interception sequence learning (SISL) task. Forty-two right-handed participants performed the task before and after a 90-min period of sleep or wake. Electroencephalography (EEG) was recorded throughout. The motor task consisted of a sequential spatial pattern and was performed according to 2 different timing conditions, that is, either following a sequential or a random temporal pattern. The increase in accuracy was compared between groups using a mixed linear regression model. Within the sleep group, performance improvement was modeled based on sleep characteristics, including spindle- and slow-wave density. The sleep group, but not the wake group, showed improvement in the random temporal, but especially and significantly more strongly in the sequential temporal condition. None of the sleep characteristics predicted improvement on either general of the timing conditions. In conclusion, a daytime nap improves performance on a timing task. We show that performance on the task with a sequential timing sequence benefits more from sleep than motor timing. More important, the temporal sequence did not benefit initial learning, because differences arose only after an offline period and specifically when this period contained sleep. Sleep appears to aid in the extraction of regularities for optimal subsequent performance.

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## WAKE HIGH-DENSITY ELECTROENCEPHALOGRAPHIC SPATIOSPECTRAL SIGNATURES OF INSOMNIA

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**STUDY OBJECTIVES:** Although daytime complaints are a defining characteristic of insomnia, most EEG studies evaluated sleep only. We used high-density electroencephalography to investigate wake resting state oscillations characteristic of insomnia disorder (ID) at a fine-grained spatio-spectral resolution.

**METHODS:** A case-control assessment during eyes open (EO) and eyes closed (EC) was performed in a laboratory for human physiology. Participants (n = 94, 74 female, 21-70 y) were recruited through [www.sleepregistry.nl](http://www.sleepregistry.nl): 51 with ID, according to DSM-5 and 43 matched controls. Exclusion criteria were any somatic, neurological or psychiatric condition. Group differences in the spectral power topographies across multiple frequencies (1.5 to 40 Hz) were evaluated using permutation-based inference with Threshold-Free Cluster-Enhancement, to correct for multiple comparisons.

**RESULTS:** As compared to controls, participants with ID showed less power in a narrow upper alpha band (11-12.7 Hz, peak: 11.7 Hz) over bilateral frontal and left temporal regions during EO, and more power in a broad beta frequency range (16.3-40 Hz, peak: 19 Hz) globally during EC. Source estimates suggested global rather than cortically localized group differences.

**CONCLUSIONS:** The widespread high power in a broad beta band reported previously during sleep in insomnia is present as well during eyes closed wakefulness, suggestive of a round-the-clock hyperarousal. Low power in the upper alpha band during eyes open is consistent with low cortical inhibition and attentional filtering. The fine-grained HD-EEG findings suggest that, while more feasible than PSG, wake EEG of short duration with a few well-chosen electrodes and frequency bands, can provide valuable features of insomnia.

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## SLOW DISSOLVING OF EMOTIONAL DISTRESS CONTRIBUTES TO HYPERAROUSAL

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The mechanisms underlying hyperarousal, the key symptom of insomnia, have remained elusive, hampering cause-targeted treatment. Recently, restless rapid-eye-movement (REM) sleep emerged as a robust signature of sleep in insomnia. Given the role of REM sleep in emotion regulation, we hypothesized that restless REM sleep could interfere with the overnight resolution of emotional distress, thus contributing to accumulation of arousal. Participants ( $n = 1,199$ ) completed questionnaires on insomnia severity, hyperarousal, self-conscious emotional distress, and thought-like nocturnal mentation that was validated to be a specific proxy for restless REM sleep (selective fragmentation:  $R = 0.57$ ,  $P < 0.001$ ; eye movement density:  $R = 0.46$ ,  $P < 0.01$ ) in 32 polysomnographically assessed participants. The experience of distress lasting overnight increased with insomnia severity ( $\beta = 0.29$ ,  $P < 10(-23)$ ), whereas short-lasting distress did not ( $\beta = -0.02$ ,  $P = 0.41$ ). Insomnia severity was associated with hyperarousal ( $\beta = 0.47$ ,  $P < 10(-63)$ ) and with the thought-like nocturnal mentation that is specifically associated with restless REM sleep ( $\beta = 0.31$ ,  $P < 10(-26)$ ). Structural equation modeling showed that 62.4% of the association between these key characteristics of insomnia was mediated specifically by reduced overnight resolution of emotional distress. The model outperformed all alternative mediation pathways. The findings suggest that restless REM sleep reflects a process that interferes with the overnight resolution of distress. Its accumulation may promote the development of chronic hyperarousal, giving clinical relevance to the role of REM sleep in emotion regulation in insomnia, depression, and posttraumatic stress disorder.

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## DETERMINING THE RELATIONSHIP BETWEEN SLEEP ARCHITECTURE, SEIZURE VARIABLES AND MEMORY IN PATIENTS WITH FOCAL EPILEPSY

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Sleep has been shown to be important to memory. Both sleep and memory have been found to be abnormal in patients with epilepsy. In this study, we explored the effects that nocturnal epileptiform discharges and the presence of a hippocampal lesion have on sleep patterns and memory. Twenty-five patients with focal epilepsy who underwent a 24-hr ambulatory EEG also completed the Everyday Memory Questionnaire (EMQ). The EEG record was scored for length of time spent in the various sleep stages, time spent awake after sleep onset, and rapid eye movement (REM) latency. Of these sleep variables, only REM latency differed when the epilepsy patients were divided on the bases of either presence/absence of nocturnal discharges or presence/absence of a hippocampal lesion. In both cases, presence of the abnormality was associated with longer latency. Furthermore, longer REM latency was found to be a better predictor of EMQ score than either number of discharges or presence of a hippocampal lesion. Longer REM latency was associated with a smaller percentage of time spent in slow-wave sleep in the early part of the night and may serve as a particularly sensitive marker to disturbances in sleep architecture.

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# CARBON-WIRE LOOP BASED ARTIFACT CORRECTION OUTPERFORMS POST-PROCESSING EEG/FMRI CORRECTIONS – A VALIDATION OF REAL-TIME SIMULTANEOUS EEG/FMRI CORRECTION METHOD

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Simultaneous EEG-fMRI combines two powerful neuroimaging techniques, but the EEG signal suffers from severe artifacts in the MRI environment that are difficult to remove. These are the MR scanning artifact and the blood-pulsation artifact--strategies to remove them are a topic of ongoing research. Additionally large, unsystematic artifacts are produced across the full frequency spectrum by the magnet's helium pump (and ventilator) systems which are notoriously hard to remove. As a consequence, experimenters routinely deactivate the helium pump during simultaneous EEG-fMRI acquisitions which potentially risks damaging the MRI system and necessitates more frequent and expensive helium refills. We present a novel correction method addressing both helium pump and ballisto-cardiac (BCG) artifacts, consisting of carbon-wire loops (CWL) as additional sensors to accurately track unpredictable artifacts related to subtle movements in the scanner, and an EEGLAB plugin to perform artifact correction. We compare signal-to-noise metrics of EEG data, corrected with CWL and three conventional correction methods, for helium pump off and on measurements. Because the CWL setup records signals in real-time, it fits requirements of applications where immediate correction is necessary, such as neuro-feedback applications or stimulation time-locked to specific sleep oscillations. The comparison metrics in this paper relate to: (1) the EEG signal itself, (2) the "eyes open vs. eyes closed" effect, and (3) an assessment of how the artifact correction impacts the ability to perform meaningful correlations between EEG alpha power and the BOLD signal. Results show that the CWL correction corrects for He pump artifact and also produces EEG data more comparable to EEG obtained outside the magnet than conventional post-processing methods.

*Neuroimage*. 2016 Jan 15;125:880-94. doi: 10.1016/j.neuroimage.2015.10.064. Epub 2015 Oct 24.



**SLEEP-WAKE**  
**Research in The Netherlands**

**Volume 27, 2016**

**Book Presentations**

## SLAPERS

Bart Heynen  
Freelance photographer

Summary and preface: Johan Verbraecken, Multidisciplinary Sleep Disorders Centre,  
Antwerp University Hospital, University of Antwerp (B)

Photographer Bart Heynen caught 25 interesting Flemings and Dutch in their sleep with a camera construction above their bed. Prof Johan Verbraecken was one of them and wrote the preface of this beautiful photo book. It is a unique photo book with intimate portraits of people as you never normally see them. For the pictures, the intervention of the photographer was limited to a minimum. No single picture was put in scene and the portrayed did not get any instruction. Among the portrayed are well known Flemings and Dutch, like Evi Hanssen, Kristien Hemmerechts, Nina Weijers, Elodie Ouédraogo, Paul Scheffer, Line Pillet, Kurt Van Eeghem, Lefto, Roos Van Acker, Rob Heyvaert, Sirin Zahed, Roderik Six, Felix van Groeninge, Jamal Ouariachi, Roger De Vlamincq, Gilles De Schryver, Bredan Corbey, Els Dottermans, Charlotte de Witte, Yannick Dangre, and Ilvy Njiokiktjien.

Slapers was published with hard cover in October 2015 and counts 144 pages.



**Figure 1.** Cover of the book “Slapers” (left side). The lens was chosen as a function of the height of the ceiling. The camera was mounted close to the flash (right side).

*Slapers, Bart Heynen, Luster (Antwerp) and ISBN 9789460581564.*

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*Bart Heynen is also grateful to all sleepers for their unqualified support in his project. They had guts to show them and to give oneself away in a manner which contradicts against the tradition for centuries to be portrayed in a flattering way.*

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**Volume 27, 2016**

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