SLEEP-WAKE
Research in the Netherlands

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28

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PREFACE

Sleep is red hot. We are flooded on a daily basis with reports in the media on the benefits of sleep and the disadvantages of poor sleep. Fundamental mechanisms of sleep and wake are being discovered and the basis and consequences of disordered sleep are under constant investigation. Our knowledge on the molecular, cellular, physiological, psychological and social aspects of sleep, wake and their disturbances are growing. This year saw the Nobel Prize being awarded to three scientists that made breakthroughs in our understanding of the sleep-wake rhythm and the biological clock. These are truly exciting times for being a sleep researcher and a sleep clinician.

The NSWO has set itself the goal of being the organisation that fosters research and communicates the findings of national and international projects to the media and the public. Together with our sister organisation, the Dutch Sleep Medicine Organisation (SVNL), we hope to inform sleep doctors about relevant insights and possible new therapeutic avenues.

With the rapidly changing field of sleep-wake research, the NSWO is evolving and will focus more strongly than before on research and science. I had the honour of following up Hans Hamburger as president of the organisation on March 24th of this year, at the annual meeting in Kempenhaeghe. We have since engaged the board and the committees in a lively discussion about our aims, goals and wishes and the means to reach them. We have installed a Young Scientist committee, that will add fire to our organisation, we have revisited our mission statement and we are restructuring the website, to be the main portal for anyone with questions about sleep and wake. Together with the publisher, we are currently planning to update and translate the successful handbook on Sleep and Sleep Disorders (ACCO publishers) in English. As every year since its inception in 2008, we have participated in the ISMC course, a yearly event to prepare the participants for the European Somnologist Exam of the European Sleep Research Society (ESRS). This year the course took place in Blankenberge, Belgium and next year it will feature in St-Michielsgestel, The Netherlands. Many more inspiring ideas and events are underway, make sure to keep updated!

A high point this year promises to be the national Sleep Congress, which we organise together with the SVNL in Ermelo for the second year running in its current two-day format, on the 30th of November and 1st of December 2017. The 2016 congress was an enormous success and on the wings of that event we have put together an equally exciting and diverse program that will cater to fundamental and applied scientists and clinicians alike. The congress will from now on be a bi-annual event, to alternate with the ESRS.

We look forward to an inspiring meeting and to novel insights in the years to come!

Ysbrand van der Werf

EDITORIAL NOTE

The Scientific Committee is very pleased to present to you the 28th edition of the annual proceeding of the NSWO. As previously, it represents the publications in the many fields of sleep related research, in the form of abstracts. It is promising to see so many publications, be it papers or posters, have originated from our little country. You will find more than 50 presented in the annual proceedings, but the editor is sure there are several other publications which are not represented here.

In addition to the many abstracts, we're proud to present 6 mini-papers, peer reviewed for this edition. As is often the case, smaller studies, student projects or just results that are not enough for full journal papers are not published. The scientific committee is happy that such findings can find their place in the annual proceedings, as even the smallest steps can eventually lead to a Nobel Prize.

This year we exchange the book presentation with an opinion piece. Roy Raymann reflects on the development of sleep measurements, especially by trackers. This can have an impact on how we approach sleep and health both and Raymann furthermore contemplates on what this means for us as researchers, in academia and industry both, as well as the layman using it.

And, not to forget, this year we're favored with two scientific meetings in which the NSWO has an organizing role; the Kempenhaeghe symposium, and SLAAP 2017. Overall, the positive reactions from Kempenhaeghe shows that it is still a robust symposium in the sleep field. We hope it will still stand strong alongside its popular new companion, SLAAP 2017. This year's program promises for an exciting and diverse two days' event. And, working in the industry myself, I'm happy to see that there is also an industrial session this year. It's crucial for the industry and research, as well as the clinic, to have a close connection with each other, especially in a topic as complex as sleep.

This yearbook is the result of the joined efforts of the scientific committee. The editor is grateful to Johan, Peter, Cathalijn, Marijke and Annemarie for their contributions in the editorial process and for their reviews. Of course, the editor would like to express her gratitude to all contributors for providing the content!

Els Møst
Editor

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Opionions

THE DIFFERENT WORLDS OF SLEEP: A CONSUMER TECHNOLOGY PERSPECTIVE

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THE START OF A JOURNEY

The fascinating world of the science of sleep opened to me almost 20 years ago. I had a great mentor, explored a lot of different topics (ranging from hard core circadian work to executing the ultimate applied *"Great Sleep Experiment"* in kids at NEMO, attended meetings and tried to absorb as much as possible. The first steps included a training in Polysomnography at the Holland Sleep School in The Hague. Being more a physiologist than a psychologist by training, I was kind of shocked by the way sleep was interpreted. Multiple physiological signals were collected and then evaluated by visual inspection of the signal in 30 seconds chunks. At that time, I expected that this way of classification of sleep would become outdated pretty soon, and an objective, machine-algorithm-based, more continuous way of sleep analyses would be introduced and well accepted in the very near future. Yes, I just started in sleep, I was naive, I could not have been more wrong. It is now 2017, and 30 sec epoch sleep staging still rules our world.

A NEW ERA

But something has changed. Sleep measurement is no longer the exclusive domain of sleep clinicians and scientists. With the introduction of the Fitbit Tracker in 2008, the first large scale consumer sleep tracker was introduced, opening up new possibilities. It was sold for $99,- in the USA and it was a fitness and sleep tracker. Since that introduction, it has been a wild-west of sleep tracking devices, ranging from apps on mobile devices, head bands, wrist worn trackers, in-bed sensors to nightstand monitors. And since the introduction of these trackers, the validity of these measurements has been questioned, by the consumer, by the media, and by the researchers. And although both PSG and Actigraphy are considered the preferred validated measures for sleep in research, the consumer sleep monitors entered the research community and were (and still are) frequently used in studies as the single standard of sleep measurement. One of the main reasons why these trackers have become popular tools of researchers is the fact that they are relatively inexpensive to include in a study as compared to a truly validated measure and most likely give more accurate (objective) information as compared to self-reported sleep data.

TRENDS IN SLEEP TRACKING

Since the introduction of the first wrist-worn sleep tracker, a few trends can be observed. In the early days, most trackers were wrist worn, and sold as fitness trackers. The sleep feature in these fitness trackers was just an extra. The accelerometer was the signal used to quantify sleep and high-level sleep data, like sleep duration, was presented to the user. A fast follower were the Sleep tracker Apps, that used the accelerometer in the smartphone to quantify sleep. The apps used the motion of the mattress to infer sleep versus wake. Over time, some of these apps and wearables, claimed to be able to infer sleep stages (not only sleep versus wake) from the motion data. De Zambotti and co-workers tested one of these devices against PSG and

kindly concluded that the device showed good agreement in measures of total sleep time and wake after sleep onset, leaving a solid conclusion on the sleep staging using accelerometry only in the open.[1]
The next generation of wearables focused on including extra physiological signals to infer sleep from. PhotoPlethysmoGraphy (PPG) measurement on the wrist to collect heart-rate information was introduced, and found its way into the sleep classification algorithms. PPG uses light to illuminate the skin on the wrist and measures the change in light absorption related to the pulse. A validation of a particular algorithm recently has been published in a leading journal in the field, reporting a kappa index of 0.42 and accuracy of 59.3% for a 4 stage sleep classifier.[2]

For a lot of people sleep is related to comfort. And a shortcoming of the design of a lot of wearables, is the fact that they are actually not very comfortable to wear, especially at night, in the bed. Another downside of a wearable, especially the ones that include the more advanced PPG measurement, is the fact that it needs to be charged more often, given the relative high power consumption of the PPG sensor. Both of these shortcomings are dealt with when using in-bed sensor techniques. The less advanced in-bed sleep monitors are using accelerometers only, and the more advanced ones include BallistoCardioGraphy (BCG) as an extra measure to infer sleep from. The (piezo or loadcell film) sensor on top or below the mattress detects the movement of the body on a very granular level, and as such can infer cardio-respiratory signals for the micro movement. Validation of this technology for sleep staging is at this moment limited. As an example, Migliorini and colleagues published a paper on automatic sleep staging using a BCG signal and concluded, based on a kappa index of 0.51 and an overall agreement of 79%, that their algorithm provided a good sleep evaluation.[3]

The in-bed sensor might not be the preferred way of sleep tracking for those people that do not like the fact that the sensor in the bed is connected to the power outlet. The third category of sleep trackers can be regarded as truly non-contact sleep monitors. These trackers are using Radar and more recently also Wifi signal to measure the gross and micro motion of the body and infer cardio-respiratory signals for the micro movement. The wifi technology in is still under development, but the Radar technology has been validated more widely. O'Hare and co-workers tested the sleep versus wake agreement with both actigraphy and PSG and reported a reasonable agreement in TST, with a tendency to overestimate sleep and underestimate WASO.[4]

Although the list of new sensor technologies for sleep is overwhelming, solid validation of the devices in different populations is currently lacking. Next to that, the life cycle of consumer goods can be fast, whereas the study cycles in research can be slow, and as a consequence data on accuracy and sensitivity of a particular sensor might become available at a time the sleep tracker is no longer available and replaced by a newer version. What is needed is a solid collaboration between the consumer sleeptech industry and the sleep research community, to optimize the consumer trackers and to build a common protocol to validate these trackers, most likely before or at the time they come to market. A step in the right direction is the announcement of the Consumer Technology Association (CTA) and the National Sleep Foundation (NSF) in the fall of 2017 to come up with a standard for measuring sleep cycles with wearables and other applications (CTA/NSF-2052.2).

SLEEP HEALTH

Related to the rise of the consumer sleep trackers is the emergence of the field of Sleep Health, next to Sleep Medicine, Chronobiology, Sleep Pharmacology and Basic Sleep research. It has become more apparent to the sleep scientist that most of our knowledge on the day-to-day (or better night-to-night) non-disordered sleep is derived from relatively small studies, measuring sleep in a controlled setting, in a particular population, or is measured in large groups using a self-report measurement of sleep quality. And although the evidence from epidemiologic studies that disturbed sleep is related to increased (chronic) disease risk, studies with truly objective data are limited. Next to that, the question has been raised if the results of controlled sleep studies are representing normal sleep in the general population in their own bedroom. Ohayon and co-workers published a great meta-analysis on sleep in 2004, which presented normative sleep values across the life-span.[5] This study has been really helpful to put the results of other controlled sleep studies into perspective, but it might not reflect the sleep as slept in your own bedroom.

Using the data of validated consumer sleep trackers, together with the vital signs they also collect every single night, month after month, might open up a whole new field of sleep research, gaining new insights on health and sleep, based on big data.

FUTURE

It seems that the boom in wearables for sleep is over, and the bang in no-touch sleep monitoring is going on right now. Some great consumer sleep technologies, like BASIS and ZEO are no longer available, showing it might be hard to be profitable in the sleep tracker business. However, sleep is no longer the exclusive domain of small start-ups or companies with their roots in sleep. Recent acquisitions (successful or not) and patent applications show that the big tech companies have serious interest in sleep (and health in general).

Merging knowledge of sleep, behavior, sensing, engineering and big data seems the logical next step. That requires opening up the way of thinking of all parties involved. Sleep researcher need to be open to look beyond R&K, engineers need to live with the fact that not all relevant sleep parameters can be accurately specified upfront, and sensor people need to accept that the best sensor might not be acceptable to a user. If we succeed to collaborate, we will pave the way to sleep science 2.0.

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Research papers

CORTISOL: A STRESS HORMONE AND A WAKE HORMONE

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Cortisol is a truly pleiotropic steroid hormone. It is probably best known for its role in stress physiology. Many call cortisol *the* stress hormone. This notion may require a revisit as will be discussed. During stress responses a cortisol surge is normally preceded by an adrenalin response. In fact, adrenalin, released immediately, in seconds following perception of a stressor, is the true stress hormone. It frees glucose (energy) rapidly from glycogen stores to prepare the organism for fight or flight. Cortisol comes in next and also frees energy (glucose, fatty acids) to allow the organism to adapt to stressful conditions and initiate recovery from disturbances.

In sleep-wake physiology cortisol is often referred to as the wake hormone. Proceeding from the notion that cortisol redistributes energy in the organism to cope with novel stress conditions or with recurring conditions of altered energy needs, for instance the activities of the day to come, requires a re-appreciation of cortisol. Cortisol is not merely a stress hormone, it is first of all an 'energy expenditure hormone' in 'normal' life and an adaptation hormone following stressful events.

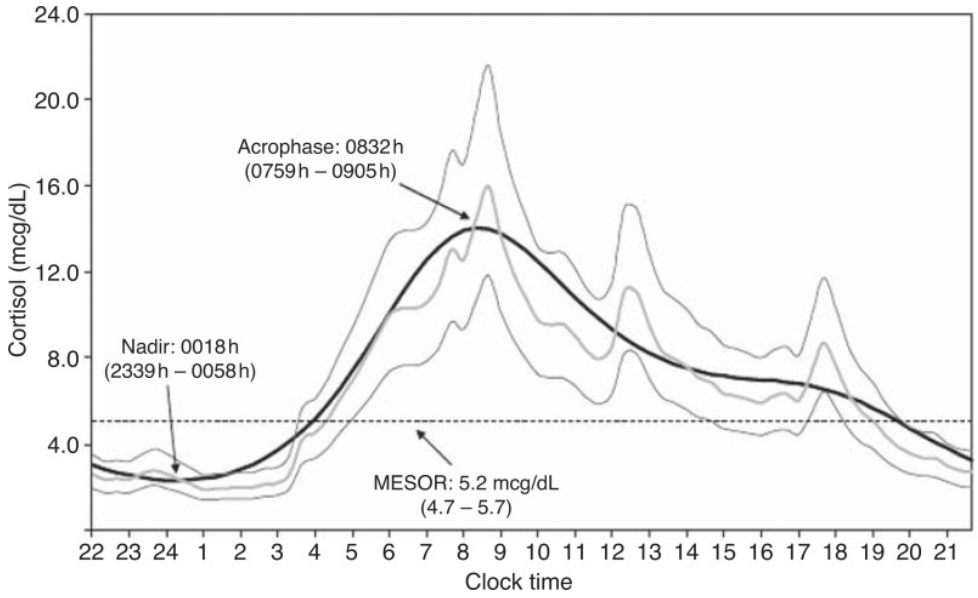

Figure 1. Circadian rhythm of plasma cortisol in humans. Peak cortisol levels (acrophase) are reached around 08:30; the trough (nadir) in cortisol levels is around midnight. Smaller cortisol peaks at 12.30 and 18:00 represent meal-induced cortisol secretions (after: Chan and Debono, 2010).

In healthy humans, plasma cortisol levels exhibit a circadian profile, in accordance with varying production and secretion to cover needs. The maximum in plasma cortisol levels 30 to 45 minutes after waking is called the 'cortisol awakening response' (CAR). Following this maximum, cortisol levels decline throughout the day with lowest levels during the late afternoon and early night (the circadian trough). Feeding events during the day (peaks around 12.30 and 18.00 hrs in Figure 1) coincide with milder peaks in plasma cortisol, again to handle and redistribute energy taken in. Over the night cortisol secretion will again abruptly rise, reaching the maximum just after waking (Figure 1). This rise which occurs normally during sleep seems specifically linked to the awakening event. The CAR is assumed to supply energy to prepare the body for the coming day, both for physical and mental activities, not in the least for vigilance and alertness, conditions and behaviors with key survival value.

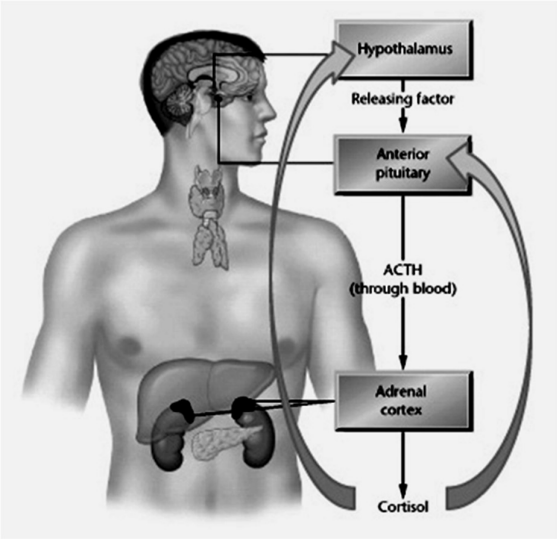

Figure 2. The hypothalamus-pituitary-adrenal cortex (HPA) axis, the endocrine cascade controlling cortisol levels in the blood. Note the negative feedback loops of cortisol on hypothalamus and pituitary gland. Cortisol also feeds back on the adrenal cortex (not shown) (after: Kalat, 2004).

In stress physiology cortisol is generally referred to as *the* stress hormone. In a situation interpreted as stressful, the hypothalamus-pituitary-adrenal (HPA) axis is activated. Hypothalamic neurons on which stress-information is conveyed, enhance release of corticotrophin releasing factor (CRF), which stimulates secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH travels to the adrenals to trigger secretion of the glucocorticoid cortisol from the zona fasciculata of the adrenal cortex (Figure 2). In parallel, but preceding in time, neural pathways induce release of fast acting catecholamines (adrenaline and noradrenaline) from the adrenal medulla (not shown). These two hormones prepare the body to cope with the demands of stress, they make up the fast adrenergic fight-or-flight stress response and the slower cortisol-mediated redistribution of energy to adapt to the stressful condition and energy requirements of adaptation to novel conditions evoked by the stressor. The availability of energy for brain and body mediated by cortisol allows for an optimal adaptation to the stressful situation. Thus, cortisol is not a genuine stress hormone, nor it is a wake hormone, but rather an 'adaptation hormone'. Both during stress and under

basal non-stressful conditions, cortisol supports brain and body with access to energy needs, fitting to the circumstances.

The notion put forward above that cortisol is in fact an adaptation hormone (and adrenalin *the* stress hormone) requires a rethinking on its role in normal conditions, in stress, and in sleep-wake physiology. In normal non-stressful conditions, it appears that behavioral performance seems best when cortisol levels are moderate, *i.e.* in the normal, basal range (0-20 ng/ml plasma) and the same seems true for cognitive processing and the influence of cortisol thereupon. It is well known that under stress behavioral performances, including cognitive performances, are impeded. In particular, chronic stress leading to elevated basal levels of cortisol, correlates with poor learning. Also other vital domains of bodily physiology including growth, reproduction and immune competence, become compromised under chronic stress. Yet, the association between circulating levels of cortisol and its effects on general performance and cognition is far from straightforward. The relationship(s) between cortisol and human functioning are difficult to unravel; experiments addressing this relation suffer too often from many confounders and are complicated by technical, individual, psychological and socioeconomic factors. However, a main line in the overwhelming literature on this topic is that hypercortisolemia is more associated with adverse effects and is a risk factor in proper cognitive performance.

Already in 1908 psychologists Yerkes and Dodson described the inverted-U shaped relationship between arousal and performance. When the level of vigilance heightens, performance improves, but further arousal (due to increasing stress levels), may lead to impaired cognitive efficiency. Indeed, moderate levels of cortisol seem to have positive effects on memory consolidation, too high cortisol levels may have detrimental effects on memory formation (Lupien et al., 2007; Roozendaal, 2002). Indeed, such differential concentration dependent effects of cortisol on memory and learning agree with the above described adaptive role of cortisol in normal physiology. But how to explain such differential actions? Is this just a matter of concentration of the hormone? It appears that we get a far better view on cortisol actions if we consider its targets: the mineralocorticoid and glucocorticoid receptors, members of the nuclear receptor superfamily.

Cortisol receptors are expressed in essentially every cell of the body, albeit in different concentrations and ratios. The receptors for cortisol are ligand-dependent transcription factors, which, upon binding cortisol in the cytosol and associating with a variety other proteins, migrate to the nucleus and lead to transactivation or transrepression of genes carrying specific steroid responsive elements. In addition, association of the steroid-receptor complex with other transcription factors may occur, expanding its actions in regulatory pathways beyond the cortisol pathway proper. Further, the presence of a large cohort of receptor isoforms with specific expressions, different gene regulatory actions and varied functional profiles deepens our insight and views on the potentials of cortisol in (cell) physiology tremendously.

Cortisol binds to two receptor subtypes: the mineralocorticoid (type I; MR) receptor and the glucocorticoid (type II; GR) receptor (Reul and De Kloet, 1985). As indicated above, GR subtypes following alternative splicing of the receptor gene and alternative translation initiation mechanisms expand the receptor landscape significantly; post-translational

modifications of receptor isoforms add further to this, which helps to understand the great diversity of glucocorticoid responses (Oakley and Cidlowski, 2013).

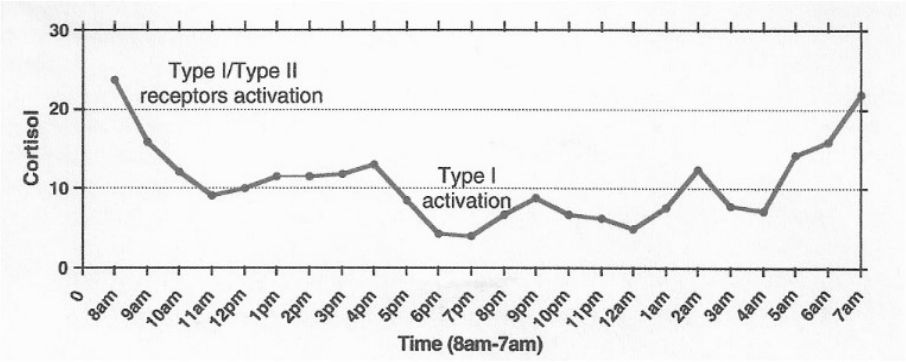

Figure 3. At the time of the peak in the circadian cortisol rhythm, there is activation of both type I and type II glucocorticoid receptors, while at the time of the cortisol trough in evening and early night there is mainly activation of the high affinity type I glucocorticoid receptors (after: Lupien et al. 2007).

When considering just the MR and GR class of receptors, there is a main intrinsic difference between these: MRs (type I) bind cortisol with a high affinity, roughly 5 to 10 times higher than the affinity for cortisol of GRs (type II). If we address the distribution of cortisol receptors in the brain, another important difference shows up, *viz.* the location in the brain. There is a high abundance of MRs in the hippocampus and limbic structures, while GRs are also present in these structures and are, additionally, prominent in frontal cortical areas. The difference in affinity of the two receptor classes results in major differences in the occupation of the receptors under different conditions and over time of day. Reul and de Kloet (1985) reason that during the circadian nadir (the trough in evening and early night) cortisol occupies more than 90% of the high affinity type I receptors and only 10% of the low affinity type II receptors. During the high cortisol level in the acrophase and during stress, the high affinity type I receptors become saturated and there is occupation of approximately 70% of the low affinity type II receptors (schematized in Figure 3). The presence of two receptor classes for cortisol with defined anatomical and differential expression profiles may explain some poorly understood stress phenomena and the various actions of the steroid in growth, reproduction and immunity. Regarding general and cognitive performance, de Kloet et al. (1999) formulated the type I/type II glucocorticoid hypothesis to explain the link between cortisolemia and memory performance (Figure 4). When type I cortisol receptors are completely saturated and there is only partial occupancy of type II receptors, maximum performance of memory is observed. On the other hand, when both type I and type II receptors are equally occupied, i.e. in stress conditions or at peaks in the diurnal rhythm, memory function may become impaired.

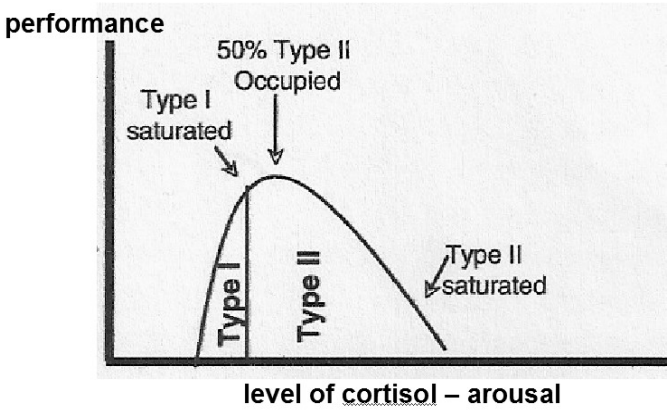

Figure 4. The hypothetical association between the arousal level expressed by the amount of circulating cortisol and behavioral performance, as indicated by the 'Yerkes-Dodson law of arousal'. The hypothetical occupancy of the glucocorticoid receptors as given by de Kloet et al. (1999) and Lupien et al. (2007) is indicated. When type I receptors are saturated there is a maximum of performance, but when type II receptors become occupied performance becomes impaired (modified after: Lupien et al., 2017).

An inverted U-shaped relationship between arousal and performance as originally described by Yerkes and Dodson (Yerkes and Dodson, 1908) might be explained in the same way as the relation between hypercortisolemia and cognitive performance: when type I receptors are occupied this gives rise to enhancement of behavioral performance, but when both type I and type II receptors are activated the performance becomes affected. Thus the inverted U-shaped function between circulating levels of glucocorticoids and cognitive and behavioral performance can be explained through differential activities of the cortisol receptor classes, which differ greatly in terms of brain localization and in their affinity for cortisol. Whether the balance in receptor occupation between the two classes plays a role in the negative effects, or simply the occupancy of the type II receptors with their prominence in cortical areas, is a matter of future research.

What about the role of cortisol in aspects of sleep-wake physiology related to cognitive performance? Interestingly, predominant MR activation is known to enhance declarative memory consolidation via sleep-dependent reactivation of hippocampal memories (in which cortisol-controlled synaptic plasticity plays a key role). However, this positive 'high affinity' (MR) effect is counteracted by 'low affinity' GR activation at high cortisol levels and this may explain mnemonic impairment in stress-induced pathologies (Groch et al., 2013). Evidence is accruing that acute and chronic stress (in particular the stress-induced release of glucocorticoids), induces changes in glutamate neurotransmission in prefrontal cortex and hippocampus, and influence cognitive processing. Dysfunction of glutamatergic neurotransmission is indeed more and more considered pivotal in stress-related neuropsychiatric disorders (Popoli et al., 2011). Sleep is important for memory consolidation. King and colleagues (King et al., 2017) address in a seminal review the multifaceted nature of sleep-related motor memory consolidation. Intriguingly, motor learning does not take place during the actual task but also between training sessions including periods of sleep. Sleep may increase performance of motor tasks in subsequent retests, an effect specific to the sleep towards the end of the sleep cycle (Plihal and Born, 1997), when receptor occupancies will change. Cortisol profiles show diurnal rhythms, which warrants further appreciation of the

pivotal role of this hormone in sleep-wake physiology and in behavioural performance. Cortisol is a truly pleiotropic hormone, not just a stress hormone but an adaptation hormone both during wake and during sleep.

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WIDESPREAD WHITE MATTER CONNECTIVITY ABNORMALITIES IN NARCOLEPSY TYPE 1 PATIENTS: A DIFFUSION TENSOR IMAGING STUDY

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INTRODUCTION

Narcolepsy type 1 is a severely disabling neurological condition, characterised by excessive daytime sleepiness, attention deficits, sleep paralysis, hypnagogic hallucinations and cataplexy. Even though patients show a selective loss of hypothalamic hypocretin-producing neurons, the exact pathophysiology remains to be discovered. In an average brain, roughly 50,000-80,000 hypocretin-producing neurons are exclusively localised within the lateral and posterior hypothalamus and their axonal projections mainly target the forebrain, amygdala, hippocampus, brainstem and retina and moreover diffusely disperse over the cortex.[1] Therefore, hypocretin affects various neural networks; its properties comprise maintaining sleep-wake state stability, energy homeostasis, reward system regulation and cognitive and mood control. Given the variety in narcolepsy-related complaints in combination with the specific lack of this neurotransmitter, the question arises to what extent white brain matter integrity and connectivity is being affected in these patients.

Diffusion tensor imaging (DTI) is an advanced MRI technique enabling in-vivo modelling of microstructural white matter morphology by means of water diffusivity variations in different tissue types. Water molecules can practically move freely – isotropically – in cerebrospinal fluid (CSF), compared to diffusivity properties being gradually more prominent along axon orientation when tissue density increases (anisotropy). Four diffusion tensor imaging (DTI) studies have previously been conducted.[2-5] Findings are inconsistent, but taken together, abnormalities were found in the hypothalamus–thalamus–orbitofrontal pathway and the brainstem as parts of the reticular activating system (RAS), as well as in the reward and limbic system and the corticospinal tract.

For this study, a multimodal methodology combining tract-based spatial statistics (TBSS), quantitative analyses and tractography was adopted. Where TBSS identifies whole brain microstructural white matter differences within regions with limited anatomical variation, the ROI-based analyses also assess average microstructural white matter integrity in predefined regions with anatomical variability and hypothalamus-seeded tractography specifically assesses the hypothalamic connectivity throughout the brain. The aim of this study was to identify the extent of microstructural white matter integrity disruptions as a possible backbone of narcolepsy type 1 patients' complaints.

METHODS

Twelve drug-naïve narcolepsy type 1 patients and 11 one-on-one age- and sex-matched healthy controls were included in this study. Subjects had to be 18-65 years old and be right-

handed. Narcolepsy type 1 patients were diagnosed according to the 3rd edition of the International Classification of Sleep Disorders (ICSD-3, 2014).[6]

MRI acquisition & pre-processing

A high-field 3T Philips Achieva MRI scanner (Best, the Netherlands) was used to obtain T1-weighted images and single-shot, gradient-echo, echo-planar imaging (EPI) sequences for DTI acquisition. DTI was performed twice with 46 diffusion-weighted b1000 scans and one unweighted b0 image, each.

Freesurfer's MRI analysis software package (v5.3.0 Developmental) was used for automatic whole brain (sub-) cortical and brainstem segmentation of the T1 scans[7] and the hypothalamus was manually segmented in both hemispheres using the anatomical criteria by Nieuwenhuys et al.[8]. DTI scans were processed with FMRIB Software Library's (FSL, v5.0) topup and eddy tools.[9,10] Subsequently, all T1-derived segmentations were linearly registered to the corresponding b0 images to precisely identify the predefined regions of interest (ROIs) for quantitative and tractography analyses. Incompletely imaged ROIs due to incorrect field-of-view alignment, were excluded.

Outcome measures consisted of fractional anisotropy (FA) and mean, axial and radial diffusivity (MD, AD and RD). FA reflects how directionally constrained the diffusion of water is along axons. While higher FA values might indicate more coherent, intact axons and/or higher myelination, lower FA may imply loss of white matter integrity and/or injury. Man diffusivity (MD) is composed by the mean diffusion in all three directions as a quantitative measure of alterations in the extracellular volume, while more distinguishing AD and RD measurements capture the most prominent eigenvalue, parallel to axon orientation and the mean of the remaining perpendicular two eigenvalues, respectively.

TBSS

In FSL's TBSS processing stream[11], the DTI scans were averaged and projected onto an alignment-invariant skeleton image controlling for interindividual anatomical variability and thresholded at a >0.2 FA level. All FA, MD, AD and RD maps were subsequently projected onto the skeleton, smoothed (5 mm) and fed into permutation-based voxelwise cross-subject statistics with 10,000 permutations and threshold-free cluster enhancement to identify between group differences. Additionally, excessive daytime sleepiness duration since diagnosis was incorporated as a covariate of interest in a separate analysis. All analyses were corrected for within group age and sex variability.

Quantitative analyses

Pre-processed DTI images by FSL and the T1-derived ROIs served as input for the volume-based pipeline of ExploreDTI's MATLAB-based MR diffusion toolbox.[12] Outcome measures (FA and MD) were generated by masking the corresponding maps with the ROIs in DTI subject space and they were hereafter used for statistical analyses.

Tractography

Deterministic tractography was performed using ExploreDTI's three-dimensional automated atlas-based tractography pipeline with a 0.2 FA threshold.[12] Tracts had to be within 10-500mm length and only the segment between the ROIs were extracted to guarantee intersubject tract correspondence.

Analyses focussed on fibres passing through the hypothalamus on its own, and in connection with the thalamus and amygdala in the corresponding hemisphere, or the midbrain or pons. Tracts were excluded if crossing the midsagittal plane and no tractography analyses were performed in connection to the other ROIs, as these tracts were not found for every subject. Tract bundle volume and mean FA and MD results served as input for statistical analyses.

Statistical analyses
P<0.05 was considered to be statistically significant and the quantitative and tractography analyses were Bonferroni corrected per outcome measure. All unprocessed scans, segmentations and registrations were blindly reviewed and corrected if needed by one reviewer.

RESULTS

Age-and-sex-matched patients and controls were included in an 8:4 and a 7:4 male-to-female ratio with an average age of 33.25 ± 10.50 and 31.82 ± 13.39 years, respectively. Compared to controls, narcoleptics had significantly higher mean (SD) ESS scores [10.08 (3.00) vs 2.64 (1.96), $p < 0.001$].

TBSS
Whole brain microstructural white matter differences were observed in NT1 patients in comparison to healthy sleepers by means of overall significantly lower FA and higher RD (Figure 1), including white matter regions in the ventral diencephalon (i.e. hypothalamus), thalamus, midbrain, pons, (orbito)frontal, anterior cingulate, primary motor and somatosensory white matter, internal capsule and the corpus callosum. Notably, the cerebellum showed no significant differences between the groups. Additionally, no significantly higher FA, lower RD and any MD and AD differences and no significant relationship between time since EDS onset and white matter FA morphology were found.

Quantitative analyses
Statistically significant lower FA was seen in the ventral diencephalon [left: $F(1,21)=16,466$, $p<0.001$; right: $F(1,21)=6.219$, $p<0.05$] and primary motor cortex [left: $F(1,18)=4.626$, $p<0.05$; right: $F(1,16)=5.591$, $p<0.05$] bilaterally, left thalamus [$F(1,21)=5.44$, $p<0.05$] and the right primary somatosensory cortex [$F(1,16)=5.144$, $p<0.05$]. Patients showed to have higher MD in the left ventral diencephalon [$F(1,21)=4.556$, $p<0.05$] and lower MD in the pons [$F(1,15)=5.581$, $p<0.05$]. After Bonferroni correction for multiple comparisons only the FA decrease in the left ventral diencephalon maintained its significance ($p<0.0023$).

Tractography
Uncorrected statistically significant lower FA was found (Figure 2) in the white matter tracts connecting the left hypothalamus with the midbrain [$F(1,21)=9.287$, $p<0.01$] and the pons [$F(1,15)=14.615$, $p<0.01$]. Only the pons preserved its significance after Bonferroni correction for multiple comparisons ($p<0.005$). No statistically significant differences were seen in MD and tract volume.

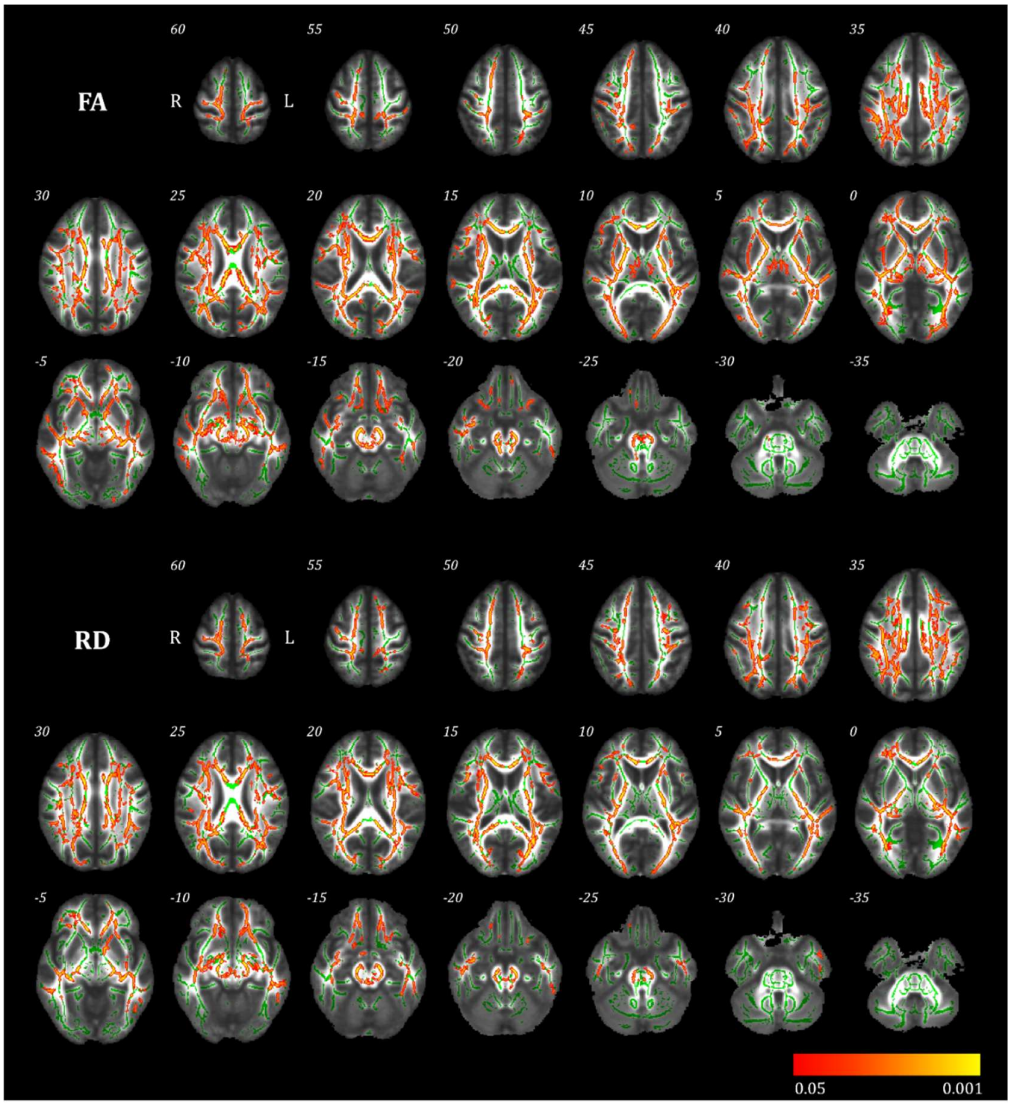

Figure 1. Axial slices displaying significantly lower FA and higher RD in narcolepsy patients compared to healthy controls. The average FA map forms the background with the skeleton image of all included voxels (green) and the significantly different voxels (red-yellow) on top. Significant results are 1mm inflated for visualisation purposes. The numbers represent the corresponding axial slice in MNI152 space. FA, fractional anisotropy; RD, radial diffusivity; R, right; L, left.

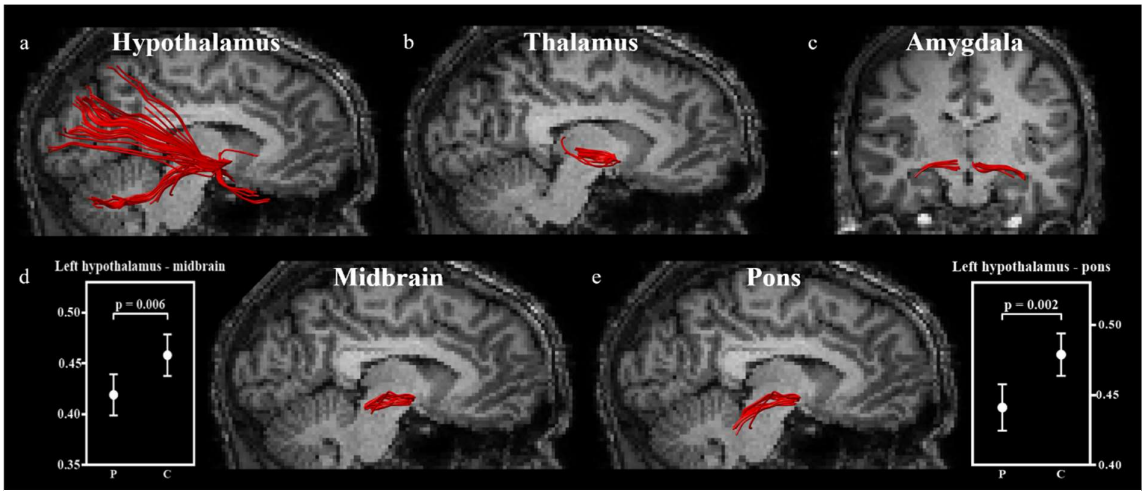

Figure 2. Connectivity of the hypothalamus of 1 subject. In "a" the overall connectivity of the hypothalamus by itself can be seen and "b-e" represent components of "a" connecting the hypothalamus with the mentioned ROIs. Significantly different FA values were plotted as mean with the corresponding 95% confidence interval. P, patients; C, control subjects.

DISCUSSION

The study showed whole brain lower FA and higher RD – excluding the cerebellum – in narcolepsy type 1 patients within functional networks such as the RAS, corticospinal tract, limbic and reward system. Moreover, mean lower FA was found in the left ventral diencephalon and in patients' tracts connecting the left hypothalamus with the pons. The ventral diencephalon comprises different motor nuclei, connecting fibre bundles and sleep-wake regulating areas such as the hypothalamus.

Our findings are generally in line with the previously performed TBSS study by Park et al. where widespread significantly lower FA and indifferent MD were found in narcolepsy patients (n = 22) compared with controls (n = 26). Significant areas included the left thalamus, bilateral anterior cingulate, frontal lobe, internal capsule and corpus callosum.[2] However, other DTI studies found conflicting results with alternating FA and MD de- and increases in a wide range of RAS, corticospinal tract and reward and limbic system areas.[3-5] These inconsistencies are likely due to the inadequate use of methodologies in divergent patient populations in these studies (diagnostic criteria, medication use and disease severity). As a solution, the present study only included drug-naïve patients and age- and sex-matched controls and used standardised data acquisition and multimodal analyses methodologies.

In this study, a three-way analysis approach proved the presence of microstructural white matter abnormalities in narcolepsy type 1 patients. Given the conjunction of profound whole brain significantly lower FA and higher RD compared to healthy controls, this suggests that narcolepsy type 1 patients suffer from a combination of lower axon density, lower myelination and/or greater axon diameter.[13,14] In resemblance with the highly profound changes in the ventral diencephalon, this study proposes a heretofore underestimated relationship between hypocretin deficiency and microstructural white matter morphology in narcolepsy patients.

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INCREASING DISTAL SKIN TEMPERATURE TO OPTMIZE SLEEP IN ATHLETES

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INTRODUCTION

The recovery and performance benefits athletes may gain from adequate sleep are striking[1]. However, despite the potential benefits, athletes experience difficulties initiating and maintaining sleep, and have been shown to report mediocre subjective sleep quality[2,3].
One of the many mechanisms that regulates sleep and alert wakefulness is body temperature[4]. Around sleep onset, skin temperature increases, which causes vasodilatation and facilitates a drop in core body temperature. Previous work has indicated a functional link between mild skin warming and the initiation of sleep, showing that increasing the distal-proximal skin temperature gradient (DPG) before lights-off is the best physiological predictor of sleep onset under strictly controlled experimental conditions[4,5]. Based on this initial observation, various protocols to manipulate skin temperature have been tested. According to Raymann et al., the most effective method to increase DPG and accelerate the initiation of sleep, is to increase (distal) foot temperature by approximately 6°C during or prior to sleep onset[6].
The current study aimed to conduct a field test of Raymann et al.'s (5) method, and examined whether increasing DPG by means of distal skin warming before bedtime can accelerate sleep onset among a cohort of Dutch athletes. Secondary outcomes measures included wake after sleep onset, sleep efficiency and subjective markers of sleep quality and morning state. We hypothesized that increasing distal skin temperature (DST) will increase the distal to proximal skin temperature gradient (DPG) and facilitate sleep onset in athletes.

METHODS

Participants

Nineteen athletes (field hockey players), aged 17-32 years (M ± SD: 22.21 ± 3.8 yrs; 13 female), all without (severe) subjective sleep complaints (mean PSQI = 3.68 ± 1.7, cut-off > 5; mean HSDQ = 1.47 ± 0.3, cut-off > 2.02), participated after informed consent. Athletes were recruited from the first (female and male) team of a regional hockey club and competed in the second national division. They had four (female team) or three (male team) practice sessions a week, with an additional match on Sundays. Practice sessions were scheduled between 5.00 and 9.30 PM.

Procedure

The study followed a within-subject crossover design, and had a duration of two weeks. Within each week, athletes' sleep was monitored during two nights of habituation and three experimental-nights by means of actigraphy and a wireless one-channel EEG sensor. During

the experimental-nights, athletes were either instructed to wear heatable socks (intervention condition) or neutral socks (control condition) during 30 minutes prior to lights-off. The order of conditions was counterbalanced between subjects and weekdays were matched across conditions. To maintain similar circumstances between conditions, athletes were instructed to follow a sleep hygiene protocol. Protocol adherence was monitored daily, by means of the Sleep Hygiene Index[7].

Temperature manipulation and assessment

Skin Temperature. Distal skin temperature (DST) was manipulated by means of heatable socks (Hot Feet, Gizzys), which contained a grain filling that could be heated using a microwave (2.30 min, 900 W). Temperature was measured using iButton Temperature Loggers (type: DS1922L #F50) [5], with 3-minutes intervals and a resolution of .0625ºC. In order to measure DST, two iButtons were taped onto each foot between the first and second webspace. Proximal skin temperature (PST) was measured by an iButton taped 2 cm below the right clavicle and on the abdomen (2cm above the navel). Ambient temperature (AT) was assessed by means of an iButton that was placed on the nightstand next to the bed. Athletes were instructed to attach the iButtons 60 minutes before lights-off (T1), hence 30 minutes before wearing the socks. Multiple measurements obtained from the same body-position (e.g. DST vs. PST) were averaged. Distal to proximal skin temperature gradient (DPG) was calculated using the following formula: DPG = DST – PST. For statistical analysis, values for DST, PST, DPG and AT were determined at three different time points: T1 (35 minutes before lights-off), T2 (5 minutes before lights-off) and T3 (sleep onset) and averaged across the three days within each condition.

Sleep Estimates. Sleep data were collected by means of an actigraph (Actiwatch 2, Philips Respironics, Murrysville, USA) and a wireless one-channel EEG-sensor (Zeo Inc., Newton, USA). The actigraph was attached to the wrist of the non-dominant hand one hour before lights-off. Motion and photophic light was sampled at 32Hz, averaged and stored in 60 second bins. Since actigraphy-based SOL is prone to errors, we also employed the ZEO-sleep manager, a wireless system validated for measuring sleep in healthy adults[8]. It has an overall agreement with PSG of 93.6%[8]. Athletes were instructed to attach the headband shortly before lights-off. Sleep onset was operationalized as the first of three consecutive epochs of “light sleep” (comparable to S1/S2 or N1/N2). For both measurement devices, variables of interest were sleep onset latency (SOL; min.), wake after sleep onset (WASO; min.) and sleep efficiency (SE; %). Subjective sleep quality was evaluated following lights-on, using a one-item question (scores: 1-10, with 10 indicating high sleep quality), the Groningen Sleep Quality Scale (GSQS)[9], the Global Vigor and Affect Scale (GVA)[10], the Karolinska Sleepiness Scale (KSS)[11], and an additional item on feeling of fitness (scale 1-10). Scores were analyzed as described in the respective validation papers and averaged within each condition. Comfort of the heatable socks was assessed by a single-item question, with scores ranging between 1 to 7, with 7 indicating the highest possible comfort.

Statistical analysis

Habituation nights were omitted from the analysis. Actigraphy and EEG-based SOL and WASO followed a non-normal distribution and were lg10-transformed. Protocol adherence (sleep hygiene) was tested using a paired t-test, temperature (DST, PST, DPG and AT) was tested

using 2x3 (condition x time) repeated measure ANCOVA's, and sleep estimates were tested using one-way (condition) repeated measure ANCOVA's. All ANCOVA's included group (female team vs. male team) as a covariate and significance was set at $\alpha = .05$.

RESULTS AND DISCUSSION

Analyses for protocol adherence (sleep hygiene) and ambient temperature (AT) indicated no significant differences between conditions (all p's > .19), indicating that the intervention and control condition were performed under similar circumstances. Athletes rated the heatable socks as fairly comfortable with an average score of 5 ± 1.7 (7-point scale).

As depicted in Figure 1, the heatable socks effectively increased DST by approximately 5°C from T1 to T2. PST showed no significant differences across conditions (Table 1). Consequently, DPG was significantly larger in the intervention condition compared to the control condition. Table 1 displays the means, standard deviations and results of the 2x3 repeated measures ANCOVA's.

Due to loss of data (e.g., equipment malfunctioning, not wearing or losing the ZEO-headband) the analyses of sleep estimates was based on 14 and 9 participants for the Actigraphy and ZEO-based measurements, respectively (see Table 2). Sleep onset latencies appeared to be slightly shorter in the intervention condition, but and despite the effective increase in DST and DPG, effects did not reach statistical significance (see Table 2). In addition, wake after sleep onset, sleep efficiency and the self-report estimates of sleep quality and morning state (i.e., sleep quality, GSQS, global vigor & affect, KSS) were not significantly different between conditions (all p's > .493; Table 2).

In the current study, wearing heatable socks during the last 30 minutes before bedtime, effectively increased DPG but was ineffective in significantly accelerating sleep onset (cf., [4,6]). Mean values for SOL, however, were in the expected direction. Given that the current study was conducted in a field setting, uncontrolled factors such as circadian and homeostatic components, stress, and other environmental (wake-promoting) circumstances, may have masked a potential effect of increased DPG on SOL. In addition, low power of the current study (especially in relation to our assessment of sleep onset) might have prevented finding statistically significant effects.

CONCLUSION

To conclude, the current study indicates that in a field setting, mild skin warming by means of wearing heatable socks close before bedtime, does not significantly accelerate sleep onset. Because positive effects of skin warming on sleep onset may naturally be expected to be small[5], especially in a healthy athletes, a critical field test involving a larger sample size and more sensitive measurement devices is warranted.

Table 1. Mean distal skin temperatures (DST), proximal skin temperatures (PST) and distal to proximal skin temperature gradient (DPG) at T1, T2 and T3.

	Intervention						Control						Results of Statistical Analysis				
	T1		T2		T3		T1		T2		T3						
ºC	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*Effect*	*Df2*	*F*	*p*	η^2_p
DST	30.42	1.76	35.50	1.35	34.63	0.77	31.21	1.59	31.76	1.93	32.98	1.93	Condition	16	5.60	.031	.256
													Time	32	20.81	.001	.565
													C x T[a]	32	6.84	.003	.299
PST	33.74	0.87	34.31	0.60	34.93	0.62	33.59	0.86	34.00	0.88	34.78	0.62	Condition	16	0.07	.796	.004
													Time	32	5.79	.007	.266
													C x T	32	0.09	.914	.006
DPG	-3.24	1.84	1.33	1.18	-0.31	0.83	-2.38	1.81	-2.17	1.92	-1.81	2.15	Condition	14	4.97	.043	.262
													Time	28	13.44	.001	.490
													C x T[b]	28	6.74	.004	.325

Note. T1 = 35 min before lights-off, T2 = 5min before lights-off, T3 = sleep onset. [a] Paired-sample t-tests on the interaction-effect revealed that DST_{int}: T1<T2>T3 at p <.001, while the increase in DST_{cont} was only significant for T2<T3 (p < .001). DST_{int}> DST_{cont}, at T2 (p < .001), and T3 (p < .004), but not at T1 (p = .130). [b] Paired-sample t-test on the interaction-effect revealed that DPG_{int}: T1<T2>T3 at p < .001, while there were no significant differences between T1, T2 and T3 for DPG_{cont} (all p > .075). DPG_{int}> DPG_{cont}, at T2 and T3 (p < .006). At T1DPG_{int}> DPG_{cont}, at p = .048.

Figure 1. Average DST and PST for the intervention (int) and control condition (cont) from 60 minutes before sleep onset (0) until 90 minutes thereafter. The manikin on the right displays the iButton-placement.

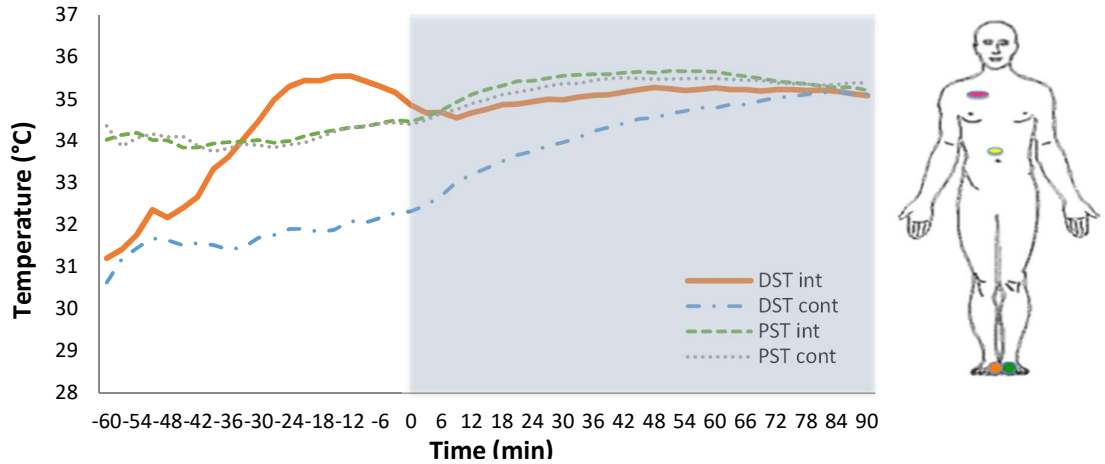

Table 2. Descriptive statistics and ANCOVA's results of all sleep measures of interest.

	Intervention		Control		Results of Statistical Analysis			
	M	*SD*	*M*	*SD*	*Df2*	*F*	*p*	η^2_p
Objective Estimates								
SOL_{ACT} (min)	9.56	6.99	11.10	7.97	12	1.42	.256	.106
SOL_{ZEO} (min)	11.46	3.81	14.69	3.32	7	1.07	.794	.010
$WASO_{ACT}$ (min)	50.36	19.04	49.89	18.29	12	2.02	.181	.144
$WASO_{ZEO}$ (min)	4.22	3.47	2.74	2.31	7	0.02	.900	.002
SE_{ACT} (%)	85.23	5.24	84.75	5.21	12	0.29	.599	.034
SE_{ZEO} (%)	94.79	0.72	95.03	0.60	7	0.10	.760	.008
Subjective Estimates								
Sleep Quality (1-10)	7.15	.90	7.00	1.02	16	0.18	.580	.011
GSQS (0-14)	1.84	2.07	2.33	2.51	17	0.26	.614	.015
Global Vigor (0-100)	74.57	1.57	74.73	1.84	17	0.03	.859	.002
Global Affect (0-100)	52.77	1.51	52.84	1.37	17	0.05	.821	.003
Fitness (1-10)	6.46	1.73	6.74	1.90	17	0.49	.493	.028
KSS (1-9)	3.74	1.30	3.77	1.33	17	0.10	.755	.006

Note. SOL = sleep onset latency, WASO = wake after sleep onset, SE = sleep efficiency. ACT = Actigraphy-based. ZEO = ZEO-based. GSQS = Groningen Sleep Quality Scale, KSS = Karolinska Sleepiness Scale; a higher score indicates higher sleepiness.

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SLEEP DURATION, AGE AND CHRONOTYPE IN SHIFTWORKERS

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INTRODUCTION

Shift work has become a signature feature of our contemporary 24-hour society. Approximately 17% of the working population in the Netherlands work in alternating shifts to sustain around-the-clock operations[1].
Rotating shift work leads to a mismatch between external zeitgebers, the timing of circadian rhythms and work/sleep schedule timing and gives rise to negative health consequences. Frequently shifting the periods of sleep and wakefulness poses a serious threat to the shift worker's physical, mental and psychosocial health[2].
Sleep/wake disturbances are the most prominent and challenging problems for shift workers[3]. Specifically, sleep length related to night shift and morning shift is shortened and associated with increased sleepiness[4].
Next to the impact of shift types on sleep, there is sustained inter-individual variability in sleep of shift workers[5]. Saksvik and colleagues[6] identified age and chronotype (morningness-eveningness) as potential factors to be associated with these individual differences in this so called shift work tolerance. The aim of this explorative study is to investigate sleep duration for each shift type with age and chronotype in a sample of shift workers who work a continuous fast forward rotating 5-shift schedule.

METHODS

Design: A cross-sectional survey was conducted as part of the 'Managing a shift work lifestyle' training program implementation (Circadian.com) at four industrial companies in the chemical sector located in the Netherlands. A total of 251 men (19-62 years old, mean age 42 years) completed the questionnaire. All participants worked a continuous fast forward rotating 5-shift schedule, of which one shift cycle was composed of two morning shifts 07:00-15:00 (M), two evening shifts 15:00-23:00 (E), two night shifts 23:00-07:00 (N) and four days off (O); MM-EE-NN-OOOO, MM-EE-NN, etcetera. Participation to the survey was anonymously and voluntary.
Measurements: Subjective sleep duration was measured by the amount of hours the participant slept associated to each shift type, that is night time sleep before morning shifts; night time sleep after evening shift; day time sleep after night shift and night time sleep during days off. Within each shift type, total sleep time was averaged over the two consecutive shifts (or the four days off), including naps during each period. Age was divided into three categories; younger than 35 years, 35-49 years; 50 years and older. Chronotype was measured with a 5-questions adjusted version of the morningness-eveningness questionnaire[7]. Based on the total score, participants could be categorized into four chronotypes; extreme morning types, moderate morning types, moderate evening types and extreme morning types. For the

purpose of this explorative study, we dichotomized chronotype into either morning types (morning larks) or evening types (night owls).

Statistical Analysis: The dependent variable sleep duration was analyzed with factorial Multivariate Analysis of Variance (MANOVA), with age and chronotype as independent fixed factors, followed by post-hoc Bonferroni-adjusted comparisons if a statistically significant main effect was present. All analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

RESULTS AND DISCUSSION

Descriptive outcomes of average sleep duration associated to each shift type (M-E-N-O) are presented in Table 1. Overall, shift workers reported 7 to 8 hours sleep on days off and after evening shifts, whereas sleep duration was approximately 6 hours for day time sleep after night shifts and night time sleep before morning shifts.

Table 1. Mean sleep duration in hours (hr:min and (standard deviation)) for each type of shift; before morning shift, after evening shift, after night shift and on days off.

	Morning shift	*Evening shift*	*Night shift*	*Days off*	*N*
Age					
< 35 years [a,]	5:52 (1:12)	8:06 (1:12)	6:41 (1:18)	8:12 (1:00)	81
35-49 years [b]	6:18 (1:00)	7:13 (1:00)	6:05 (1:24)	7:52 (0:54)	74
50 > years [c]	6:02 (1:12)	7:05 (1:18)	5:21 (1:18)	7:40 (1:12)	96
Chronotype					
Morning types [d]	6:32 (1:12)	7:14 (1:12)	5:41 (1:18)	7:49 (1:00)	82
Evening types [e]	5:50 (1:06)	7:31 (1:18)	6:09 (1:30)	7:56 (1:06)	169
Total group	6:04 (1:12)	7:25 (1:12)	6:00 (1:30)	7:54 (1.06)	251
Post hoc tests	*d>e*†	*a>b, c*††	*a>b, c*‡† *b>c*†	*a>c*†	

[a-e] subcategorizations of the independent variables Age and Chronotype in groups (see N).
†significant at $p < 0.01$, ‡ significant at $p < 0.05$.

Factorial MANOVA, using Pillai's Trace showed significant effects of Age, V (8,486)= 4.35, $p < 0.01$ and Chronotype, V(4,242)= 6.56, $p < 0.01$ on sleep duration. More specific, the separate univariate ANOVA's revealed significant Age effects on sleep duration after evening shift, (F (2,245)= , $p < 0.01$; on sleep duration after night shift, F(2,245)= 13,9, $p < 0.01$; and on sleep duration on days off, F (2,245)= 3.50, $p = 0.03$. Whereas Chronotype proved to be a significant factor for sleep duration before the morning shift. (F(1, 245)= 23.10 , $p < 0.01$.

Table 1 also shows the average scores of sleep duration subcategorized by age and chronotype and results of the post hoc tests. We found that sleep length of young shift workers under age 35 was longer than for both older age groups (35-49 years, 50 and older), both *p's* < 0.01. For day time sleep duration after night shifts, all three age groups differed significant from each other, showing a decline in sleep duration with increased age (*p's* < 0.05). For night time sleep during days off, there was only a significant difference between the youngest age group (< 35 years) and the oldest group (> 50 years), where the younger shift workers reported longer sleep duration**.**

Regarding Chronotype, it is demonstrated that evening types, compared to morning types, showed a shorter duration of sleep before the morning shift. This result is consistent with a recent study where late chronotype workers reported shorter sleep duration and more disturbed sleep during morning shift periods compared to early chronotype workers[8].
The observations of the age effect specific for evening shift, night shift and days off for is also consistent with earlier studies, where older workers have more sleep disturbances during night shifts[9,10]. Yet, a recent study found no associations between age and shift specific sleep duration, disturbed sleep and awakening complaints[8]. This explorative study found no interaction effects between age and chronotype for sleep duration among different types of shift. The overall finding that sleep duration was decreased by 1.5 to 2 hours after night shifts and morning shifts compared to days off is in line with previous research[4,6].

CONCLUSIONS

To conclude, our findings are consistent with previous studies, showing that sleep duration after night shifts and before morning shifts is mostly affected, i.e. shortened by shift work. Further, age as well as chronotype are important factors related to sleep duration, yet their impact across different types of shift vary. Sleep duration after evening shifts, night shifts and during days off are associated with age, whereas sleep duration before morning shifts is associated with chronotype. More specific, the evening types (night owls) seem to struggle mostly with early morning shifts, resulting in decreased sleep duration. As for age, older shift workers showed shortened sleep duration mostly after night shifts, after evening shifts and on days off. Therefore, for future sleep research in shift workers it is important to distinguish between different types of shift.

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THE EFFECTS OF A SPLIT-SLEEP SCHEDULE ON SLEEP AND VIGILANCE IN NURSES WORKING NIGHT SHIFTS

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INTRODUCTION

Due to the global 24h economy more and more people are working in shifts. The term shift work means that people have a work schedule outside the standard daytime 9AM to 5PM. In practice this means that a shift worker can work on mornings, evenings, nights, weekdays and weekend days, mostly in a roster schedule that is flexible implemented and has no clear sequence. In Europe 20% of the working population is involved in some kind of shift work[1]. According to Centraal Bureau voor de Statistiek (CBS) only 15% of the working population worked entirely during daytime on weekdays in 2014 in the Netherlands[2]. Especially in health care roster shift work is predominantly used.
During a period of night shifts, shift workers sleep during the day and need to be awake and alert during the night, which is in contradiction with their circadian rhythm. This internal biological clock promotes wakefulness during the biological day and reinforces sleep during the biological night[3]. As a result, shift workers often report shorter and disturbed sleep. It has been shown that sleep during daytime is about 1-4 hours shorter than sleep during nighttime and of less quality (i.e. interrupted sleep). Tepas et al[4] showed in a laboratory setting, that participants had a reduced reaction time and less mental functioning during night shifts. These findings are confirmed in several field studies in which higher accidents are errors are reported either during the night shifts or while driving home[5,6]. Moreover, already shown in 1977 by Harris[7], that single vehicle accidents have, by far, the greatest probability of occurring at night (early morning).
A possible solution that might counteract sleep deprivation and its associated impaired performance in shift workers is to implement a split-sleep schedule. By definition a split-sleep schedule means having 2 or more sleep bouts in 24h. In this study half of the participants were advised to sleep in 2 bouts after their night shifts, 5-6 hours after a shift and 2-3 hours before the next shift. The outcome measures were compared to the control group that was advised to sleep 8 hours in 1 bout after their night shift.

METHODS

Participants. In this preliminary analysis, 22 subjects participated, of which 2 males and 20 females. All were non-smoking, on average 25.1±2.4 years old, with a BMI of 21.9±2.9 kg/m^2 on average and had 3.2±2.4 years of experience with working night shifts (Table 1). Nurses that were included in the study worked 2 times at least 3 nightshifts in a row within 4-6 weeks, had less than 10 years' experience with working night shifts and did not use sleep medication.

Table 1. Subject characteristics.

Variable	*Overall (n=22)*	*Control (n=11)*	*Intervention (n=11)*
Age (years)	25.1 ± 2.4	24.7 ± 2.3	25.5 ± 2.5
BMI (kg/m^2)	21.9 ± 2.9	22.3 ± 3.5	21.4 ± 2.3
Experience with night shift (years)	3.2 ± 2.4	3.4 ± 2.4	2.9 ± 2.5
Nights worked during participation (#)	8.1 ± 1.7	8.4 ± 1.7	7.7 ± 1.7
PSQI	3.6 ± 1.3	3.6 ± 1.4	3.5 ± 1.1
MCTQ	1.6 ± 0.7	1.8 ± 0.8	1.3 ± 0.6

Data is expressed as means with standard deviation (SD) and range. No significant differences were found in subject characteristics between both groups.

Study design. In this field study, participants were instructed before study start on the measurements that were executed independently (i.e. without presence of researcher). During each night shift a 10-minute psychomotor vigilance test (PVT) was executed 3 times[8], at the beginning, in the middle and at the end of each night shift. Data of the PVT is expressed in reaction time (ms) and lapses (reaction times greater than 500 ms). Subsequently the Karolinska Sleepiness Scale (KSS) was completed to assess subjective sleepiness/alertness. Both the KSS and PVT were completed on an iPad. After waking up a sleep wake diary was completed and sleep was objectively measured with an ActiWatch Spectrum Pro (Philips Respironics, Murrysville, USA). Participants were randomly assigned to the control group or intervention group. In the control group participants were advised to sleep in 1 bout after their night shift, whereas participants in the intervention group were advised to sleep in 2 bouts; i.e. 5-6 hours after the night shift, and 2-3 hours before the next night shift. In both groups 8 hours of sleep was advised. In the exit interview questions about study participation, sleep in general and during the nights, health and the benefits and disadvantages of working night shifts were asked.

Data analysis. For this mini-paper data of the PVT and KSS were averaged for the first and second night shift of both series. Since the data were not normally distributed a Mann-Whitney U test was applied to study the differences between the control and the intervention group.

RESULTS AND DISCUSSION

Total sleep time (TST). TST was measured both objectively and subjectively. In both groups participants slept less than the recommended 8 hours per night during the night shift period. No differences were found between the groups on TST measured objectively. However, participants in the intervention group indicated that they slept significantly more during the night shift period via the sleep wake diary (Figure 1A). By splitting their sleep in 2 bouts outside their working hours the intervention group exceeded the minimum of seven hours of sleep per night, which is recommended by the National Sleep Foundation[9]. However, this was only on reported (subjectively measured) sleep. Sleeping 7-9 hours per day has a positive effect on health and well-being and it leads to noticeable improvements in daytime alertness, reaction time, and mood, as shown by the results from the PVT in the current study.

Reaction time. A significant Group*Time interaction was found in both reaction time and number of lapses (Figure 1B and 1C). At the start of the night shift both groups showed comparable lapses and reaction time, but in the control group both parameters deteriorate

significantly over time, while they remain stable throughout the night in the intervention group. Thus sleeping in 2 bouts, with the last episode just before the night shift, resulted in a diminished reduction in reaction time compared to sleeping in 1 bout relatively longer before the night shift. Van Dongen et al[8] showed that sleep-deprived subjects were largely unaware of their increasing cognitive deficits, which may explain why the impact of chronic sleep restriction on waking cognitive functions is often assumed to be benign.

Sleepiness/Alertness. Figure 1D shows the subjective sleepiness/alertness during the night shifts at the beginning, the middle and at the end of the night shift. Sleepiness was significantly higher at the end of the night shift compared to the start of the shift. No significant differences were found between the control and intervention group on all time points. This indicates that both groups experience the same sleepiness/alertness overnight.

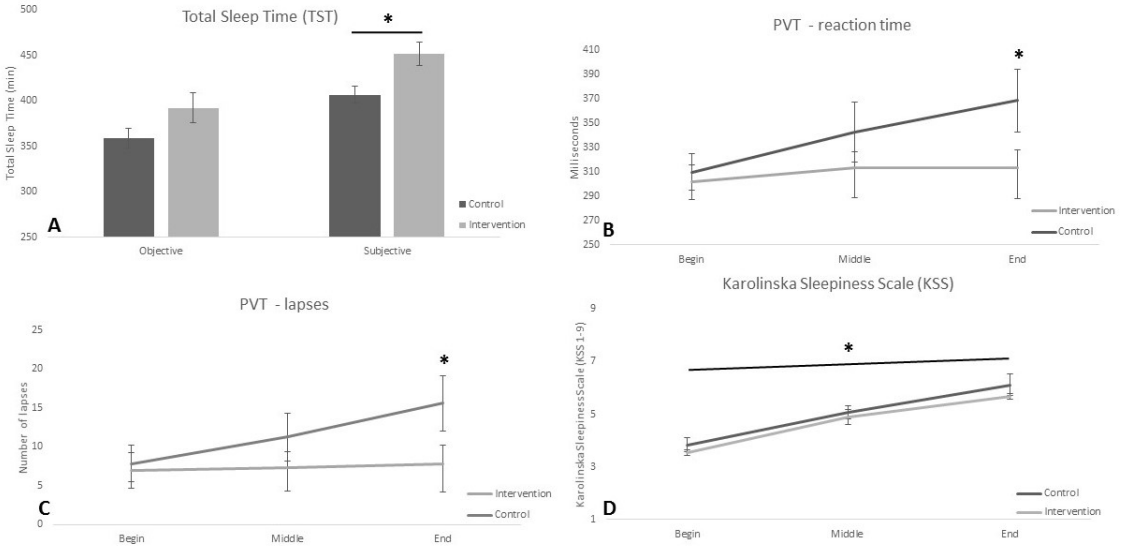

Figure 1. Results. **A**: Total sleep time (TST, in min) measured with ActiWatch Spectrum PRO (objective) and sleep wake diary (subjective). **B**: reaction time (in ms) during the night shifts measured with psychomotor vigilance test (PVT). **C**: lapses during the night shifts measured with PVT. **D**: Subjective sleepiness/alertness during the night shifts measured with the Karolinska Sleepiness Scale (KSS). During the night shifts PVT and KSS were completed at 3 time points (begin, middle and end). Data are expressed as means with SEM. Dark grey bars/lines represent values of the control group, light grey bars/lines represent values of the intervention group. * indicate significant ($p < 0.05$) differences between control and intervention group or significant difference between values at begin compared to end of night shifts.

Interviews. Most participants in the intervention group were positive and found it easy to follow the split-sleep schedule. They enjoyed more of the day, found it easier to plan meals and experienced positive effects during the night shifts. They felt more alert especially at the end of the night shift and had less difficulties in driving home in the early morning. The most often mentioned disadvantage of splitting their sleep was the negative influence on their social life. Other mentioned disadvantages are having to change their daily schedule and being preoccupied with sleep. Participants indicated that a personalized schedule based on their social agenda and sleep preference would make a split-sleep schedule easier to follow.

CONCLUSIONS

Sleeping according to a split-sleep schedule increased subjectively-measured total sleeping time and improved cognitive function during the night shifts in nurses. Sleeping in 2 bouts outside working hours might be a solution for the frequent reported sleep deprivation and reduced vigilance in shift workers. However, more research is necessary since this study only showed subjectively changed total sleeping time. Additionally, more research is needed to study if a split-sleep schedule could be beneficial for the health of shift workers on the longer term.

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RECURRENCE OF CIRCADIAN MELATONIN RHYTHM AFTER A MELATONIN HOLIDAY IN DAYTIME HEMODIALYSIS PATIENTS ON LONG TERM EXOGENOUS MELATONIN

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INTRODUCTION

Sleep problems are frequently seen in patients on hemodialysis. Melatonin plays an important role in the circadian sleep-wake rhythm of humans. The onset of the evening rise in endogenous melatonin is called the Dim Light Melatonin Onset (DLMO)[1]. The DLMO correlates with an increase in evening sleep propensity and onset of sleep [1]. A decrease in melatonin secretion in patients with renal impairment is often observed, associated with sleep onset difficulties. In hemodialysis patients the DLMO and melatonin peaks are completely absent[2]. After 6 weeks of exogenous melatonin in the evening in hemodialysis patients sleep onset latency, sleep efficiency, actual sleep time and sleep fragmentation showed a clinical improvement[3]. Unfortunately, long term effects of melatonin on sleep in hemodialysis patients were not confirmed. In the Melody study sleep parameters worsened after 6-12 months. They measured high melatonin levels in saliva samples of hemodialysis patients[4]. One hypothesis for a decrease in effect on sleep after 6 months is accumulation of melatonin, explaining the high melatonin levels during the day. These high melatonin concentrations prevent a sufficient rise in melatonin concentration to reach adequate DLMO[5]. Melatonin concentrations in saliva of 4 pg/ml or lower are proposed as adequate day time melatonin trough levels[5]. The aim of this study was to determine if melatonin accumulates after daily administration of dosages of 5 mg during a period of at least three months and to see if discontinuation improves the endogenous melatonin production and the circadian sleep-wake rhythm.

METHODS

Participants

All participants were stable daytime hemodialysis patients. They used melatonin 5 mg daily in the evening for a minimum period of 12 weeks. None of the participants had severe co-morbidities. The patients did not use excessive amounts of alcohol, drugs or other sleep medication. Hemodialysis efficiency is determined with eKt/V's (minimum of 1.2 per dialysis).

Melatonin rhythm

Melatonin was discontinued for 7 days (i.e. stop-week) starting on a hemodialysis day. On day 1, 3 and 7 after discontinuation 6 saliva samples were collected at 19:00, 21:00, 23:00, 01:00, 07:00, 15:00h. Sampling of melatonin using saliva was conducted as previously described using a validated method[4]. Melatonin concentrations were measured using commercially available RIA kit (Bühlmann Laboratories, Schönenuch, Switzerland)

The primary endpoint was recurrence of normal melatonin rhythm after discontinuation of melatonin in hemodialysis patients using 5 mg melatonin for at least 12 weeks.

Sleep measurements

Sleep parameters were monitored using model Actiwatch 2 (Philips Respironics®, Murrysville, USA) actiwatches validated for polysomnography in the hemodialysis population[6]. Actiwatch Activity & Sleep Analysis version 5.32 was used to score 1 minute epochs of actigraphic data as sleep or awake. Furthermore, participants completed two questionnaires at baseline, i.e. VOA and ESS. VOA (Vragenlijst Ochtend/Avond-typering) is a Dutch validated questionnaire to determine if participants are a morning or evening type[4]. The ESS (Epworth Sleepiness Scale) measures subjective day-time sleepiness and has been used in hemodialysis patients before[4].

Secondary endpoints regarding sleep parameters were sleep onset latency (SOL), which is the time period between 'lights off' and sleep onset, sleep efficiency (SE), a measure of sleep quality and actual sleep time (AST), defined as the total duration of recorded sleep periods were calculated according to standardized methods[4].

The medical ethical committee (MEC-U; Medical Research Ethics Committees United in the Netherlands) approved the protocol of the study (NL 43933.100.13) and informed consent was obtained from all participants.

RESULTS

General outcomes

All male participants used melatonin for a minimum period of 3 months and were on chronic hemodialysis. Two hemodialysis patients discontinued melatonin for 7 days and collected saliva samples. A third person used melatonin till day 6 (participant accidentally forgot to stop) and discontinued for one day. Relatively low eKt/V's were obtained at day 1. During the entire stop-week similar eKt/V's were seen.

Melatonin rhythm

Melatonin concentrations of case A showed accumulation of melatonin at day 1 and 3 (figure 1). Insufficient clearance of the exogenous melatonin and high day time levels were seen. Discontinuation of melatonin resulted after one day in recovery of melatonin rhythm However day time melatonin levels were still above 4 pg/ml on day 7 (1 day after discontinuation).

In case B melatonin rhythm was restored after discontinuation with day time melatonin levels of 4 pg/ml reached on day 3.

On day 3 and 7 of case C a melatonin rhythm was observed. Day time trough melatonin level of 4 pg/ml was reached on day 3.

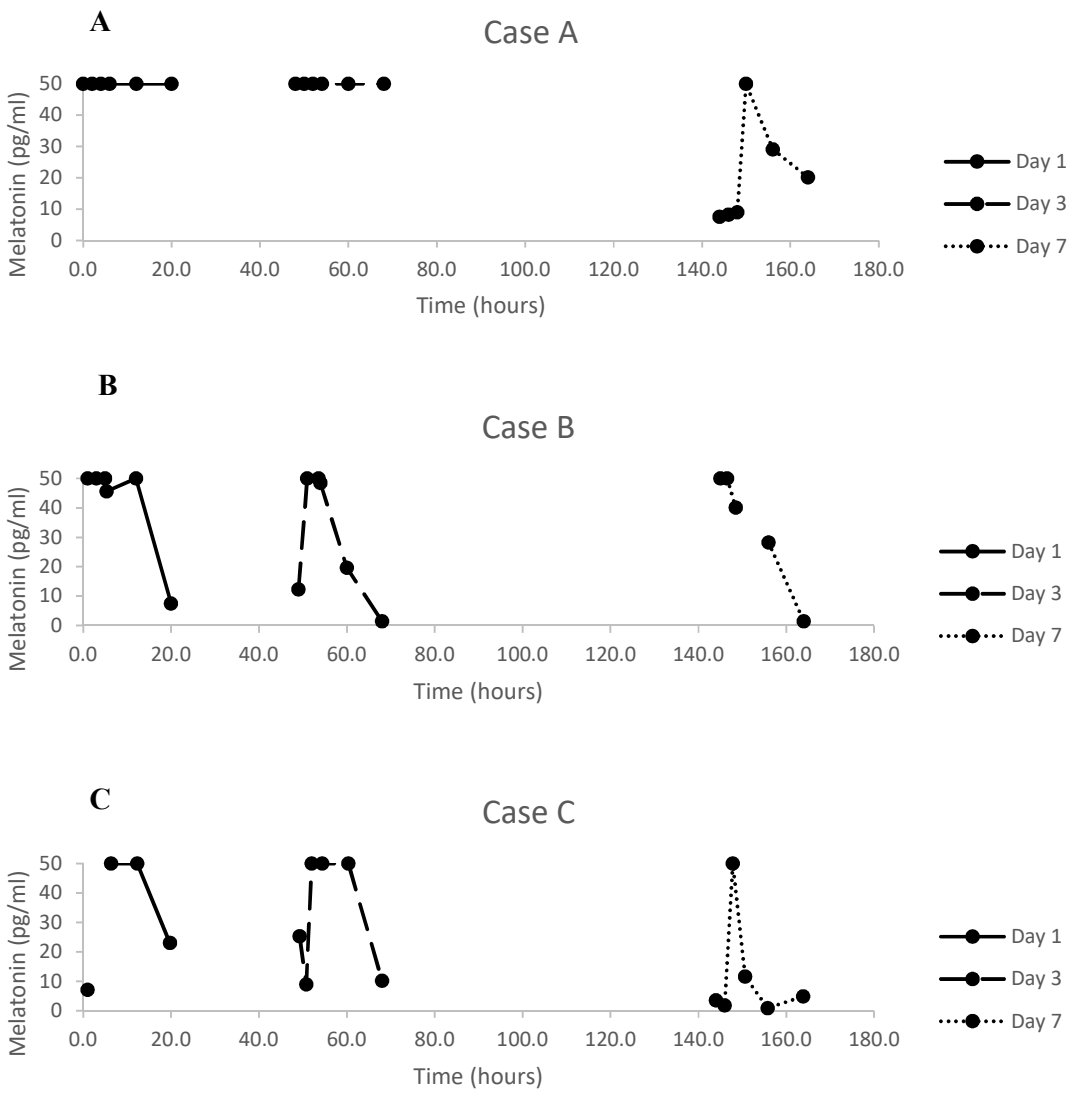

Figure 1. Melatonin concentrations after discontinuation at day 1, 3 and 7 for the three participants (panels A tot C). Case A used melatonin till day 6. The vertical axis reflects melatonin concentrations in saliva in pg/ml and the horizontal axis the time after discontinuation in hours calculated from day 1. The continuous line represents day1, the dashed line represents day 3 and the dotted line represents day 7.

Sleep parameters

The VOA questionnaire indicated that case A was a distinctly morning person (data not shown). The actigraphy showed high and erratic sleep onset latency in this participant compared to the other two. Actual sleep time decreased slightly during the week. Figure 2 shows the actual sleep time, sleep efficiency and sleep late onset. Day time sleepiness did not seem to differ between baseline, day 1 and 7.

Case B was also a distinctly morning person, although bed time was relatively late, i.e. between 23:30 and 01:00. Actual sleep time was stable during the week with a downward trend at the end. Sleep efficiency was the highest compared to the other participants and also stable during the week. An increase in sleep onset latency was observed indicating a delayed transition from full wakefulness to sleep.

At baseline the results of ESS showed mild sleepiness during the day, which changed in normal range during the week in case C. The participant was a distinctly morning person according to the VOA questionnaire. Sleep efficiency was very variable and actual sleep time increased slightly during the week. Furthermore, sleep onset latency seemed to increase at the end of the week after discontinuing for 7 days.

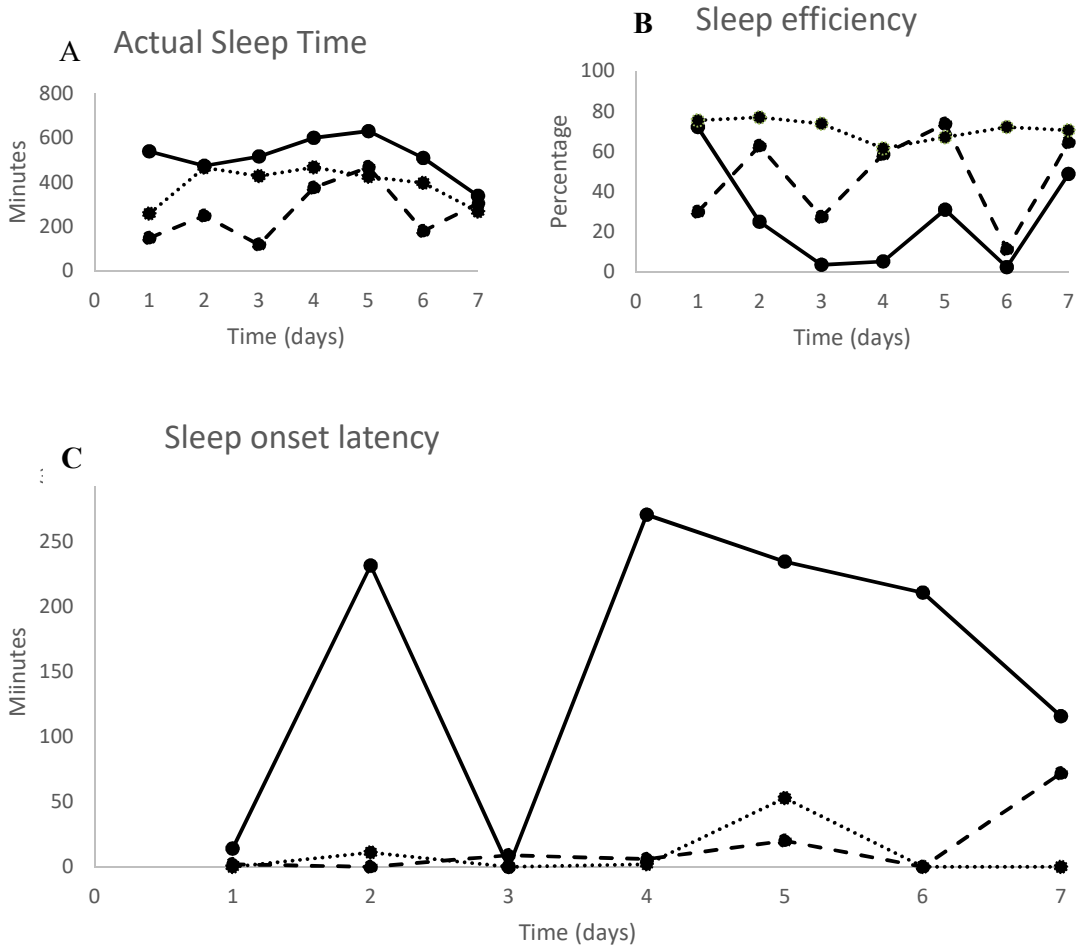

Figure 2. Sleep parameters of predicted values of actual sleep time in minutes (A), sleep efficiency in percentage (B) and sleep onset latency in minutes (C). The continuous line represents case A, the dotted line represents case B and the dashed line represents case C.

DISCUSSION

The main finding of our study is that the circadian rhythm of melatonin returns after discontinuing chronic intake of exogenous melatonin. After three days, daytime trough melatonin levels in saliva below 4 pg/ml were found in the two participants resulting in adequate DLMO. Sleep parameters

differed between the three participants. SOL seemed to increase during the week in all patients. A constant actual sleep time and irregular sleep efficiency were observed in the three participants.

To our knowledge this is the first case- study about accumulation of melatonin and its circadian rhythm caused by chronic use in hemodialysis patients and about the effects after discontinuation. An earlier study investigated the long term effect of exogenous melatonin in hemodialysis patients on sleep and found no beneficial effect after 6 months[4]. These findings could be due to the constant high melatonin concentrations during the day. Participant A showed no DLMO or adequate clearance of melatonin during the day when using 5 mg melatonin daily. Furthermore, adequate trough melatonin concentrations were found after discontinuation for 3 days in the other participants.

In patients with intellectual disabilities loss of effect of exogenous melatonin has been observed in time as well. Ineffectiveness after several weeks was found to be due to high (> 50 pg/ml) melatonin concentrations during the day. Accumulation of melatonin could be due to polymorphism of cytochrome P450 enzyme CYP1A2[7]in 4 of the 15 participants. However, the polymorphism was only based on melatonin concentrations. It was not confirmed with genetic research. Discontinuing and restarting with lower dosage resulted in improved sleep parameters[7]. Our results correspond with these findings in that we also found high day time melatonin concentrations with poor sleeping parameters.

The impaired renal function may contribute to the accumulation of melatonin. Melatonin is metabolized by CYP1A and CYP1A2 into inactive 6-sulfatoxymelatonin[7]. This metabolite and several other glucuronidated metabolites together with two percent unchanged melatonin are excreted by the kidneys. Fifty percent of endogenous melatonin is eliminated during three to four hours of hemodialysis [8]. Research has shown that after dialysis melatonin concentrations were still higher than in morning melatonin samples of participants with intact kidneys.

Decreasing exogenous melatonin dosage could also decrease the high day time melatonin trough levels. Further research is necessary to investigated if adequate DLMO will be reached in hemodialysis patients with lower melatonin dosage.

From these cases we hypothesize that a so called drug holiday, where melatonin is stopped during several days a month, could be a method to regain the effectiveness by prevention of accumulation. Drug holidays are used with positive results in children with Attention Deficit Hyperactivity Disorder[9]. In our population a drug holiday might be helpful when melatonin is no longer effective and sleep parameters decline. The ideal period is difficult to establish. At least adequate DLMO should be obtained. Therefore, day time trough saliva melatonin concentrations below 4 pg/ml are necessary[5]. In two participants the threshold was reached at day three after discontinuing. Furthermore, the results of the actigraphy show a downward trend in sleep parameters at the end of the week. In hemodialysis patients a drug holiday with a duration of 7 days would probably be the best time period to investigate first.

CONCLUSION

In conclusion we have demonstrated high melatonin concentrations during the day after chronic exogenous melatonin usage in hemodialysis patients. Discontinuing melatonin seems to result in recovery of the circadian rhythm of melatonin. Furthermore, adequate day time trough levels of melatonin during the day were not obtained on day 1 but on day 3.

Further research is necessary to confirm our results in a larger study and to investigate if sleep parameters improve after a drug holiday.

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SLEEP-WAKE

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Abstracts

DERIVATION AND MODELING OF TWO NEW FEATURES FOR THE CHARACTERIZATION OF RAPID AND SLOW EYE MOVEMENTS IN ELECTROOCULOGRAPHIC SLEEP RECORDINGS

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This work presents a method for the derivation of two new features characterizing the occurrence of both, saccadic and slow eye movements (SEM), in electrooculographic (EOG) sleep recordings. Analysis of EOG activity is of fundamental importance for the clinical interpretation of a subject's sleep pattern. The features here presented are derived from purely horizontal EOG recordings, and have been built to be patient-adaptive and relatively robust against a variety of artifacts. Using the two derived features, performance analysis of two derived Bayes classifiers (respectively for the automatic detection of saccades and of SEM) was validated. Experiments were carried out using a database of 21 whole-night recordings. Automatic and human detections were obtained on a 30-s time grid. Two clinical experts were used as the standard reference. Average kappa indexes were obtained to characterize the agreement between this reference and the automatic detector. Automatic-reference and human–human REM agreements were 0.80 and 0.87, respectively, for the detection of saccades. Corresponding SEM agreements were 0.59 and 0.64, respectively. Our results closely match the expected inter-rater agreement and therefore support the robustness of the method and the validity of the implemented features for the automatic analysis of sleep EOG recordings

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PLASTICITY IN THE PERIOD OF THE CIRCADIAN PACEMAKER INDUCED BY PHASE DISPERSION OF ITS CONSTITUENT CELLULAR CLOCKS

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The mammalian circadian pacemaker is commonly thought to be a rigid oscillator that generates output under a variety of circumstances that differ only in phase, period, and/or amplitude. Yet the pacemaker is composed of many cells that each can respond to varying circumstances in different ways. Computer simulations demonstrate that networks of such pacemaker cells behave differently under a light-dark cycle compared with constant darkness. The differences demonstrate that the circadian pacemaker is plastic: The pacemaker shapes its properties in response to the circumstances. A consequence is that properties of a pacemaker under a light-dark cycle cannot be derived from studies of the same system in constant darkness. In this paper we show that the dispersion of phase in a network of coupled oscillators can influence ensemble period: For the considered type of coupling, it is demonstrated that the more synchronous the cells are, the longer is the ensemble period. This is consistent with various data sets obtained in mammals, and even with a data set from fruit flies, in which circadian variation in behavior is regulated in a distinctly differently way from that in mammals. We conclude that environmental circumstances such as photoperiod and exposure to light pulses in otherwise darkness modify the phase distribution of the network and, thereby, the period of the ensemble. Our study supports the view that such properties as circadian period are not solely determined by clock genes but are also determined by the genes that regulate the communication in cellular networks.

Beersma DGM, Gargar KA, Daan S. Plasticity in the period of the circadian pacemaker induced by phase dispersion of its constituent cellular clocks. Journal of Biological Rhythms 32: 237-245, 2017.

SLEEP DISTURBANCES IN PHENYLKETONURIA: AN EXPLORATIVE STUDY IN MEN AND MICE

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Introduction: Sleep problems have not been directly reported in phenylketonuria (PKU). In PKU, the metabolic pathway of phenylalanine is disrupted, which, among others, causes deficits in the neurotransmitters and sleep modulators dopamine, norepinephrine, and serotonin. Understanding sleep problems in PKU patients may help explain the pathophysiology of brain dysfunction in PKU patients.

Methods: In this explorative study, we investigated possible sleep problems in adult treated PKU patients and untreated PKU mice. In the PKU patients, sleep characteristics were compared to healthy first degree relatives by assessment of sleep disturbances, sleep–wake patterns, and sleepiness with the help of four questionnaires: Holland sleep disorder questionnaire, Pittsburgh sleep quality index, Epworth sleepiness scale, and Munich Chronotype Questionnaire.

Results: The results obtained with the questionnaires show that PKU individuals suffer more from sleep disorders, a reduced sleep quality, and an increased latency to fall asleep and experience more sleepiness during the day. In the PKU mice, activity patterns were recorded with passive infrared recorders. PKU mice switched more often between active and non-active behavior and shifted a part of their resting behavior into the active period, confirming that sleep quality is affected as a consequence of PKU.

Conclusion: Together, these results give the first indication that sleep problems are present in PKU. More detailed future research will give a better understanding of these problems, which could ultimately result in the improvement of treatment strategies by including sleep quality as an additional treatment target.

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LONGITUDINAL ASSOCIATIONS OF SLEEP DURATION IN INFANCY AND EARLY CHILDHOOD WITH BODY COMPOSITION AND CARDIOMETABOLIC HEALTH AT THE AGE OF 6 YEARS: THE GENERATION R STUDY

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Background: A short sleep duration is associated with a higher obesity risk from middle childhood onward. However, whether sleep duration in early childhood is associated with body composition and cardiometabolic health remains unclear. This study aims to examine the prospective association of sleep duration in infancy and early childhood with body composition and cardiometabolic health at 6 years of age.
Methods: Data were available for 5161 children from a population-based cohort in the Netherlands. Sleep duration was assessed at ages 2, 6, 24, and 36 months by parental reports. When children were 6 years old, measures of body composition (iDXA), blood pressure, insulin, and lipid levels were collected. Longitudinal associations among sleep duration, body composition, and cardiometabolic health were studied with multivariable linear regression analyses. In addition, potential bidirectional associations between sleep duration and BMI were studied by using cross-lagged modeling.
Results: Shorter sleep duration at 2 months predicted higher BMI and fat mass in 6-year-old children, accounting for confounders and BMI at 2 months (e.g., for BMI, per hour sleep, B = -0.018, 95% CI = -0.026; -0.009). No temporal relationships among sleep duration at other ages, later body composition, and cardiometabolic outcomes were found. The cross-lagged model indicated a bidirectional association between sleep duration and BMI in early life (2 to 6 months of age).
Conclusions: Shorter sleep duration at 2 months, but not at later ages, predicted poorer body composition 6 years later. We found no clear evidence for an effect of sleep duration in early life on cardiometabolic health.

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the Erasmus University Rotterdam, School of Law and Faculty of Social Sciences, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond, Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives, and pharmacies in Rotterdam. This study was granted by the Dutch Diabetes Foundation (Grant number 2013.81.1664). Prof. H. Tiemeier was awarded with a Netherlands Organization for Scientific Research grant (NWO-VIDI 017.106.370). Prof. O.H. Franco works in ErasmusAGE, a center for aging research across the life course funded by Nestle Nutrition (Nestec Ltd.), Metagenics, Inc. and AXA. Prof. V.W.V. Jaddoe received a grant from the Netherlands Organization for Health Research and Development (VIDI 016.136.361) and a Consolidator Grant from the European Research Council (ERC-2014-CoG-64916) and funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 633595 (Dynahealth). Prof. M. Wake was supported by the Australian National Health & Medical Research Council (Senior Research Fellowship 1046518) and Cure Kids New Zealand. Research at the Murdoch Children's Research Institute is supported by the Victorian Government's Operational Infrastructure Support Program. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article.

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GUIDED WEB-BASED INTERVENTION FOR INSOMNIA TARGETING BREAST CANCER PATIENTS: FEASIBILITY AND EFFECT.

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Background: Insomnia is highly prevalent in breast cancer (BRC) patients, but non-pharmacological treatment is not widely available. The aim of this preliminary study was to investigate whether guided cognitive behavioral therapy via the Internet (I-CBT) is a feasible and effective solution for this undertreated condition in BRC patients, and to investigate who benefits most.

Methods: An existing evidence based I-CBT sleep intervention (I-Sleep) was adapted for BRC patients. An open mixed methods design was used including qualitative interviews and pre- and post-test questionnaires measuring sleep, fatigue, daily functioning, and psychological distress.

Results: 100 of the 171 participants (59%) completed the intervention fully and participants highly valued the intervention (7.5 out of 10). Large to small pre-post effect sizes were found on insomnia severity (d = 1.33) fatigue (d = 0.24), and daytime functioning (d = 0.30). Younger patients and patients with more severe insomnia at baseline benefited most from the intervention.

Conclusion: The I-CBT intervention I-Sleep is feasible, well-accepted, and effective for BRC patients who suffer from insomnia, especially for younger patients and those with more severe insomnia.

Dozeman, E., Verdonck-de Leeuw, I. M., Savard, J., & van Straten, A. (2017). Guided web-based intervention for insomnia targeting breast cancer patients: Feasibility and effect. Internet Interventions, 9, 1-6.

A SIMPLE AND ROBUST METHOD FOR THE AUTOMATIC SCORING OF EEG AROUSALS IN POLYSOMNOGRAPHIC RECORDINGS

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Introduction: Clinical diagnosis of sleep disorders relies on the polysomnographic test to examine the neurophysiological markers of the sleep process. In this test, the recording of the electroencephalographic activity and the submental electromyogram is the source of the analysis for the detection of electroencephalographic arousals. The identification of these events is important for the evaluation of the sleep continuity because they cause the fragmentation of the normal sleep process. This work proposes a new technique for the automatic detection of arousals in polysomnographic recordings, presenting a non-computationally complex method with the idea of providing an easy integration with other algorithms.
Methods: The proposed algorithm combines different well-known signal analysis solutions to identify relevant arousal patterns with special emphasis on robustness and artifacts tolerance. It is a multistage method that after obtaining an initial set of events, improves the detection finding common EEG arousal patterns. Finally, false positives are discarded after examining each candidate within the context of clinical definitions.
Results: Tweenty-two polysomnographic recordings from real patients were used to validate the method. The results obtained were encouraging, achieving a precision value of 0.86 and a F1 score value of 0.79. When compared with the gold standard, the method achieves a substantial agreement (Kappa coefficient of 0.78), with an almost perfect agreement with ten recordings.
Conclusions: The algorithm designed achieved encouraging results and shows robust behavior in presence of signal artifacts. Its low-coupled design allows its implementation on different development platforms, and an easy combination with other methods

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SLEEP DEPRIVATION HAS LONG TERM EFFECTS ON NEURONAL ACTIVITY IN 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 in unknown. By combining EEG recordings with electrical activity in several hypothalamic nuclei in the rat, we found that cortical SWA does not reflect the changes in electrophysiological activity in these brain structures after sleep deprivation (SD). Following a 6h SD, while cortical SWA recovered to baseline 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. In contrast, the Paraventricular nucleus (n=7) showed a sustained increase following SD which lasted 42h. These results show that SD has long term effects on neuronal activity in hypothalamic structures that regulate several important physiological and behavioural functions (i.e. food intake, sleep, cognitive function and fear). The duration of these effects extends beyond the after-effects of SD observed in the EEG SWA, which is the common marker to define the duration of recovery from SD. Our data provide a possible neuronal mechanisms of the many adverse effects on health associated with SD.

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CIRCADIAN AND SLEEP HOMEOSTATIC MODULATION OF NEURONAL ACTIVITY IN DOPAMINERGIC AND STRIATAL STRUCTURES

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Several neurological disorders associated with Basal Ganglia dysfunctioning, like Parkinson's and Huntington's disease, 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) with electrical multi-unit activity (MUA) recordings 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 12h:12h light/dark (LD) and constant dark (DD) conditions. In addition, we investigated the effects of a 6h sleep deprivation (SD) on MUA in these areas. Both under LD and DD conditions, the MUA 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 responded differently to SD. 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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SHORT BLUE LIGHT PULSES (30 MIN) IN THE MORNING SUPPORT A SLEEP-ADVANCING PROTOCOL IN A HOME SETTING

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Introduction: Many people in our modern civilized society sleep later on free days compared to work days. This discrepancy in sleep timing will lead to so-called 'social jetlag' on work days with negative consequences for performance and health. Light therapy in the morning is often proposed as the most effective method to advance the circadian rhythm and sleep phase. However, most studies focus on direct effects on the circadian system and not on posttreatment effects on sleep phase and sleep integrity. In this placebo-controlled home study we investigated if blue light, rather than amber light therapy, can phase shift the sleep phase along with the circadian rhythm with preservation of sleep integrity and performance.

Methods: We selected 42 participants who suffered from 'social jetlag' on workdays. Participants were randomly assigned to either high-intensity blue light exposure or amber light exposure (placebo) with similar photopic illuminance. The protocol consisted of 14 baseline days without sleep restrictions, 9 treatment days with either 30-min blue light pulses or 30-min amber light pulses in the morning along with a sleep advancing scheme and 7 posttreatment days without sleep restrictions. Melatonin samples were taken at days 1, 7, 14 (baseline), day 23 (effect treatment), and day 30 (posttreatment). Light exposure was recorded continuously. Sleep was monitored through actigraphy. Performance was measured with a reaction time task.

Results: As expected, the phase advance of the melatonin rhythm from day 14 to day 23 was significantly larger in the blue light exposure group, compared to the amber light group (84 min ± 51 (SD) and 48 min ± 47 (SD) respectively; $t36= 2.23$, $p < 0.05$). Wake-up time during the posttreatment days was slightly earlier compared to baseline in the blue light group compared to slightly later in the amber light group (–21 min ± 33 (SD) and +12 min ± 33 (SD) respectively; $F1,35= 9.20$, $p < 0.01$). The number of sleep bouts was significantly higher in the amber light group compared to the blue light group during sleep in the treatment period ($F1,32= 4.40$, $p < 0.05$). Performance was significantly worse compared to baseline at all times during ($F1,13= 10.1$, $p < 0.01$) and after amber light treatment ($F1,13= 17.1$, $p < 0.01$), while only in the morning during posttreatment in the blue light condition ($F1,10= 9.8$, $p < 0.05$).

Conclusions: The data support the conclusion that blue light was able to compensate for the sleep integrity reduction and to a large extent for the performance decrement that was observed in the amber light condition, both probably as a consequence of the advancing sleep schedule. This study shows that blue light therapy in the morning, applied in a home setting, supports a sleep advancing protocol by phase advancing the circadian rhythm as well as sleep timing.

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MELATONIN AND SLEEP-WAKE RHYTHMS BEFORE AND AFTER OCULAR LENS REPLACEMENT IN ELDERLY HUMANS

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Introduction: Light of short wavelengths has been shown to play a key role in non-image forming responses. Due to aging, the ocular lens becomes more yellow reducing the transmission of short wavelengths in the elderly.

Methods: In the present study, we make use of cataract surgery to investigate the effects of a relative increase of short wavelength transmission on melatonin- and sleep-wake rhythms (N = 14).

Results: We observed, on average, a delay of the sleep-wake and the nocturnal melatonin rhythms after cataract surgery.

Conclusion: This delay is tentatively attributed to a relatively large increase of light transmittance in the evening hours more than an increase of the already relatively high light intensities found in the daytime. The later phase that we observed after cataract surgery (clear lens) as compared to the earlier phase observed before cataract (yellowish lens) is in agreement with the general later phase reported in the young (clear lens) population.

Table: Sleep timing outcomes obtained by means of a combination of sleep diaries and actiwatch data after subtracting seasonal-confounding effects. Data are shown as average ˇ SD. N = 14.

	Before Surgery	*After Surgery*	*F*	*p*	*Difference*
Sleep Onset (CET)	23:12 ± 1:06	23:28 ± 1:13	5.8	< 0.05	16 ± 25 min
Midsleep (CET)	03:10 ± 0:51	03:28 ± 0:59	10.3	< 0.01	17 ± 19 min
Sleep Offset (CET)	07:08 ± 0:49	07:25 ± 0:50	10.7	<0.01	17 ± 10 min
Sleep Duration (CET)	07:56 ± 0:38	07:56 ± 0:40	0.006	0.94	0.5 ± 24 min
Sleep Onset Latency (min)	10.5 ± 6	13.0 ± 9.8	2.26	0.16	2.5 ± 6 min

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A RODENT MODEL OF NIGHT-SHIFT WORK INDUCES SHORT-TERM AND ENDURING SLEEP AND ELECTROENCEPHALOGRAPHIC DISTURBANCES

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Millions of people worldwide are working at times that overlap with the normal time for sleep. Sleep problems related to the work schedule may mediate the well-established relationship between shift work and increased risk for disease, occupational errors and accidents. Yet, our understanding of causality and the underlying mechanisms that explain this relationship is limited. We aimed to assess the consequences of night-shift work for sleep and to examine whether night-shift work-induced sleep disturbances may yield electrophysiological markers of impaired maintenance of the waking brain state. An experimental model developed in rats simulated a 4-day protocol of night-work in humans. Two groups of rats underwent 8-h sessions of enforced ambulation, either at the circadian time when the animal was physiologically primed for wakefulness (active-workers, mimicking day-shift) or for sleep (rest-workers, mimicking night-shift). The 4-day rest-work schedule induced a pronounced redistribution of sleep to the endogenous active phase. Rest-work also led to higher electroencephalogram (EEG) slow-wave (1-4 Hz) energy in quiet wakefulness during work-sessions, suggesting a degraded waking state. After the daily work-sessions, being in their endogenous active phase, rest-workers slept less and had higher gamma (80-90 Hz) activity during wake than active-workers. Finally, rest-work induced an enduring shift in the main sleep period and attenuated the accumulation of slow-wave energy during NREM sleep. A comparison of recovery data from 12:12 LD and constant dark conditions suggests that reduced time in NREM sleep throughout the recorded 7-day recovery phase induced by rest-work may be modulated by circadian factors. Our data in rats show that enforced night-work-like activity during the normal resting phase has pronounced acute and persistent effects on sleep and waking behavior. The study also underscores the potential importance of animal models for future studies on the health consequences of night-shift work and the mechanisms underlying increased risk for diseases.

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SLEEP SPINDLE DYNAMICS SUGGEST OVER-CONSOLIDATION IN POST-TRAUMATIC STRESS DISORDER

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Introduction
Devastating trauma memories are a central symptom of PTSD. Sleep problems, which occur in around 70% of patients, are thought to play an important role in the etiology of the disorder, but the underlying mechanism is unclear. Interestingly, sleep hosts important memory consolidation processes, in association to intermittent 11-16 Hz events so-called sleep spindles. Here we assess the hypothesis that disturbed excessive memory consolidation in PTSD is reflected in exaggerated spindling.

Methods
Spatial characteristics of sigma power (11-16 Hz) were compared between PTSD patients (n=13) and trauma controls (n=14) to determine the best location for further spindle analysis. Next, a detailed analysis of individual spindle events was performed. To obtain an unbiased representation of spindle activity, a new detection method was used, which entails minimal assumptions about spindle "anatomy".

Results
Spindle activity was significantly increased in PTSD, apparent in: increased NREM frontal sigma power, increased spindle peak amplitude and a shift towards larger spindle amplitudes in an amplitude density distribution. No differences between groups were found in waxing and waning speed.

Conclusion
Our findings show increased spindle activity in PTSD, suggesting exaggerated memory consolidation. This provides a mechanism through which the profound sleep disturbance in PTSD contributes to emotional memory problems. Our analyses suggest that the increased spindle activity in PTSD is mainly due to an increased density of spindle events, rather than alterations in the physiology of individual spindles.

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PREVALENCE OF POSITIONAL OBSTRUCTIVE SLEEP APNEA IN A DUTCH SLEEP CENTER POPULATION

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Introduction: The prevalence of positional obstructive sleep apnea syndrome (pOSAS) depends on the definition of pOSAS. Cartwright defines pOSAS as Apnea Hypopnea Index (AHI)supine ≥ 2*AHInonsupine (Sleep 1984; 7:110-114). Mador uses the same criterium with the addition of AHInonsupine<5 (Chest 2005; 128(4):2130-2137). The Dutch criteria are equal to the Mador criteria with the addition of timesupine -between 10% and 90% of total sleep time (e.g. J Clin Sleep Med 2015; 11(2):139-47). The aim of this study was to retrospectively assess the prevalence of pOSAS in a Dutch sleep center population using the Cartwright, Mador and Dutch criteria.

Methods: Data of 2312 successive type III portable monitoring (PM) recordings (mean age 55.5±12.8 years, mean BMI 30.6±5.7 kg/m2, 73.5% males) with AHI ≥ 5 were screened for the presence of pOSAS using the Cartwright, Mador and Dutch pOSAS criteria.

Results: The prevalence of pOSAS using the Cartwright, Mador and Dutch criteria, subdivided by OSAS severity, is shown in table 1.

Conclusion: The prevalence of pOSAS in our Dutch population is low compared with earlier reported values and highly depends on the used definition of pOSAS.

Table 1: Prevalence of pOSAS using the Cartwright, Mador and Dutch pOSAS criteria subdivided by OSAS severity. Data are presented as number of subjects meeting the criteria (%).

	Cartwright	*Mador*	*Dutch*
AHI ≥ 5 (N=2312)	1404 (60.7%)	623 (26.9%)	542 (23.4%)
AHI 5-15 (N=1128)	800 (70.9%)	499 (44.2%)	461 (40.9%)
AHI 15-30 (N=660)	413 (62.6%)	86 (13.0%)	69 (10.5%)
AHI ≥ 30 (N=524)	191 (36.5%)	38 (7.3%)	12 (2.3%)

Reference: European Respiratory Journal 2016 48: PA2327; DOI: 10.1183/13993003.congress-2016.PA2327. Presented at the European Respiratory Society Congress 2016 in London, United Kingdom.

SMARTPHONE-DELIVERED COGNITIVE BEHAVIOURAL TREATMENT FOR INSOMNIA: A RANDOMISED WAITING-LIST CONTROLLED TRIAL

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Background: This study is one of the first randomized controlled trials investigating cognitive behavioral therapy for insomnia (CBT-I) delivered by a fully automated mobile phone app. Such an app can potentially increase the accessibility of insomnia treatment for the 10% of people who have insomnia.
Objective: The objective of our study was to investigate the efficacy of CBT-I delivered via the Sleepcare mobile phone app, compared with a waitlist control group, in a randomized controlled trial.
Methods: We recruited participants in the Netherlands with relatively mild insomnia disorder. After answering an online pretest questionnaire, they were randomly assigned to the app (n=74) or the waitlist condition (n=77). The app packaged a sleep diary, a relaxation exercise, sleep restriction exercise, and sleep hygiene and education. The app was fully automated and adjusted itself to a participant's progress. Program duration was 6 to 7 weeks, after which participants received posttest measurements and a 3-month follow-up. The participants in the waitlist condition received the app after they completed the posttest questionnaire. The measurements consisted of questionnaires and 7-day online diaries. The questionnaires measured insomnia severity, dysfunctional beliefs about sleep, and anxiety and depression symptoms. The diary measured sleep variables such as sleep efficiency. We performed multilevel analyses to study the interaction effects between time and condition.
Results: The results showed significant interaction effects (P<.01) favoring the app condition on the primary outcome measures of insomnia severity (d=–0.66) and sleep efficiency (d=0.71). Overall, these improvements were also retained in a 3-month follow-up.
Conclusions: This study demonstrated the efficacy of a fully automated mobile phone app in the treatment of relatively mild insomnia. The effects were in the range of what is found for Web-based treatment in general. This supports the applicability of such technical tools in the treatment of insomnia. Future work should examine the generalizability to a more diverse population. Furthermore, the separate components of such an app should be investigated. It remains to be seen how this app can best be integrated into the current health regimens.

Horsch, C., Lancee, J., Griffioen-Both, F., Spruit, S., Fitrianie, S., Neerincx, M.A., Beun, R.J., Brinkman, W.P. (2017). Smartphone-delivered cognitive behavioural treatment for insomnia: A randomised waiting-list controlled trial. Journal of Medical Internet Research, 19(4), e70. Doi: 10.2196/jmir.6524

VALIDATION OF THE DUTCH STOPBANG SCREENING QUESTIONNAIRE FOR OSAS IN HEALTHY WORKERS

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Introduction*:* OSAS is a serious health problem and is often underdiagnosed. The STOPBANG questionnaire has shown to be a useful screening tool for OSAS, especially in the preoperative setting. In developing a two-step screening tool for OSAS in Dutch healthy workers population (Eijsvogel et al. J Clin Sleep Med. 2015) we aimed to validate the Dutch translation and assess the diagnostic properties of the STOP-Bang Questionnaire

Methods*:* 240 employees were included. They completed the Dutch version of the STOPBANG questionnaire and performed a home polysomnography. The questionnaire was translated into Dutch with forward and backward translation and compared with factor analysis to the English version. A score of ≥2 on the STOP questionnaire and ≥3 on the STOPBANG questionnaire indicated a high risk for OSAS.

Results*:* 186 respondents underwent home polysomnography; 37.1% were diagnosed with OSAS (AHI ≥5 with symptoms). Significant differences between risk groups were found for AHI and all STOPBANG related characteristics. Factor analysis revealed that the Dutch version of the STOPBANG questionnaire was valid and resulted in a one-factor model. Sensitivity of the STOP questionnaire was 65.2% and of the STOPBANG 79.7%, while specificity was 66.7% and 56.4% respectively. A female-specific cut-off point of the neck circumference of 32.5cm (instead of 40 cm) improved the sensitivity for women from 54.6% to 81.8%.

Conclusions*:* The Dutch version of the STOPBANG questionnaire is a valid tool for screening for OSAS in a healthy workers population. With a female-specific cut-off point of the neck circumference, a substantial increase in sensitivity can be accomplished in women.

Reference: European Respiratory Journal 2016 48: OA4791; DOI: 10.1183/13993003.congress-2016.OA4791. Presented at the European Respiratory Society Congress 2016 in London, United Kingdom.

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 26: 5-13 , 2017.

THE IMPACT OF SLEEP ON COGNITIVE AND SPORT-SPECIFIC PERFORMANCE IN ELITE ATHLETES

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Introduction: Performance capacity in elite athletes strongly depends on the ability to recover from past exercise. While there is evidence to suggest that athletic performance decreases following (partial) sleep deprivation and may increase following sleep extension, it is unclear to which extent natural (day-to-day) variation in sleep impacts cognitive and sport-specific performance.

Methods: To investigate this, objective measures of sleep quantity and sleep stage distributions were assessed among 98 (youth) elite athletes on three non-consecutive nights, and paired with outcomes on performance tests that were taken on standardized times each following morning. Performance tests included a 10-minute psychomotor vigilance task (cognitive performance) and sports-specific tests of fine motor performance (e.g., accuracy) and gross motor performance (e.g., endurance, maximum power). Mixed-effects models were used to assess the effect of sleep quantity (total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency) and sleep stage distributions (REM, light, deep) on performance.

Results: Regarding sleep quantity, longer total sleep times were associated with better cognitive performance (i.e., faster reaction times; $p = .04$) and shorter sleep onset latencies with better gross motor performance ($p = .03$). Sleep quantity was not associated with fine motor performance. Regarding sleep stage distributions, no significant associations with performance were observed.

Conclusion: The current study is the first to combine objective information about day-to-day variation in elite athletes' sleep, with representative indicators of performance. Findings suggest that even minor changes in sleep quantity can significantly affect different aspects of performance (i.e., cognitive performance, gross motor performance), thereby highlighting the significance of a good night rest for elite athletes.

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TRAIN HARD, SLEEP WELL? PERCEIVED TRAINING LOAD, SLEEP QUANTITY AND SLEEP STAGE DISTRIBUTION IN ELITE LEVEL ATHLETES

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Objectives: Sleep is essential for recovery and performance in elite athletes. While it is generally assumedthat exercise benefits sleep, high training load may jeopardize sleep and hence limit adequate recovery. To examine this, the current study assessed objective sleep quantity and sleep stage distributions in eliteathletes and calculated their association with perceived training load.
Design: Mixed-methods.
Methods: Perceived training load, actigraphy and one-channel EEG recordings were collected among 98elite athletes during 7 consecutive days of regular training.
Results: Actigraphy revealed total sleep durations of 7:50 ± 1:08 h, sleep onset latencies of 13 ± 15 min, wake after sleep onset of 33 ± 17 min and sleep efficiencies of 88 ± 5%. Distribution of sleep stages indicated 51 ± 9% light sleep, 21 ± 8% deep sleep, and 27 ± 7% REM sleep. On average, perceived training load was 5.40 ± 2.50 (scale 1–10), showing large daily variability. Mixed-effects models revealed no alteration in sleep quantity or sleep stage distributions as a function of day-to-day variation in preceding training load (all p's > .05).
Conclusions: Results indicate healthy sleep durations, but elevated wake after sleep onset, suggesting a potential need for sleep optimization. Large proportions of deep sleep potentially reflect an elevated recovery need. With sleep quantity and sleep stage distributions remaining irresponsive to variations in perceived training load, it is questionable whether athletes' current sleep provides sufficient recovery after strenuous exercise.

Knufinke M, et al. Train hard, sleep well? Perceived training load, sleep quantity and sleep stage distribution in elite level athletes. J Sci Med Sport (2017), http://dx.doi.org/10.1016/j.jsams.2017.07.003

EARLY CHILDHOOD SLEEP PATTERNS AND COGNITIVE DEVELOPMENT AGE AGE 6 YEARS: THE GENERATION R STUDY

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Background: To explore the association of sleep duration and awakening frequency with cognitive outcomes in young children.
Methods: Mothers of 2,800 children from the Generation R cohort reported sleep duration and awakenings at children's age 24 months. At age 6 years, validated Dutch measures were used to assess children's nonverbal intelligence and language comprehension.
Results: We found a nonlinear association of total sleep time at 24 months with nonverbal intelligence (p=0.03) and language comprehension (p=0.04) at 6 years. Toddlers sleeping within the recommended 11–14 hr had more favorable cognitive development compared with both extremes. Frequent awakenings were negatively associated with nonverbal intelligence, but not with verbal comprehension.
Conclusion: Sleep duration in toddlerhood has an inverted-U-shaped relation with childhood cognitive measures. Frequent awakenings are associated with lower nonverbal intelligence. Given the marked decline in sleep duration and awakenings in toddlerhood, developmental changes of sleep patterns might be important for cognitive development.

Funding: The first phase of the Generation R Study was made possible by financial support from the Erasmus Medical Centre and The Netherlands Organization for Health Research and Development (Zon MW Geestkracht Program 10.000.1003 and VIDI Grant 017.106.370 to HT). ERAWEB scholarship grant financed by the European Commission was granted to D.K. (grant agreement 2013-2548/001-001-EMA-2). O.H.F. works in ErasmusAGE, a center for aging research funded by Nestle´ Nutrition (Nestec Ltd), Metagenics Inc, and AXA. Nestle´ Nutrition, Metagenics Inc, and AXA had no role in design and conduct of the study; collection, analysis, and interpretation of the data; and preparation, review, or approval of manuscript.

Early Childhood Sleep Patterns and Cognitive Development at Age 6 Years: The Generation R Study.
Kocevska D, Rijlaarsdam J, Ghassabian A, Jaddoe VW, Franco OH, Verhulst FC, Tiemeier H.
J Pediatr Psychol. 2017 Apr 1;42(3):260-268. doi: 10.1093/jpepsy/jsv168.

MACRONUTRIENT INTAKES IN INFANCY ARE ASSOCIATED WITH SLEEP DURATION IN TODDLERHOOD

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Background: Dietary composition has been associated with sleep indexes. However, most of the evidence is based on cross-sectional data, and studies in young children are lacking. The aim of this study was to explore the longitudinal associations of macronutrient composition of the diet with sleep duration and consolidation (number of awakenings) in infancy and early childhood.
Methods: The study was performed in 3465 children from the Generation R Study, a population-based cohort study in the Netherlands. Mothers reported their child's food intake at 13 mo of age by using a validated food-frequency questionnaire and their child's sleep patterns at 2 and 3 y of age. We used nutrient substitution models to assess the associations of relative macronutrient intakes with sleep indexes and adjusted the models for sociodemographic and lifestyle factors.
Results: Isocaloric substitution of fat intake by protein or carbohydrate in infancy was associated with longer total sleep duration at 2 but not 3 y of age. For each 5% increase in energy intake of either protein or carbohydrate at the expense of fat, sleep duration at 2 y of age was longer by 6 min (95% CI: 0.4, 12 min) and 4 min (95% CI: 2, 6 min), respectively. Further exploration of macronutrient subtypes indicated no consistent differences between saturated or unsaturated fat and that intake of plant compared with animal protein or Trp did not explain the association of higher total protein intake with longer sleep duration at 2 y of age. Replacing unsaturated with saturated fat was associated with 7 min (95% CI: -13, -1 min) shorter total sleep duration at 3 y of age. Macronutrient intakes were not associated with sleep consolidation.
Conclusions: Our results suggest that the macronutrient composition of the diet is associated with sleep duration in young children. Future research should further study the causality of this association and explore the underlying mechanisms.

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Macronutrient Intakes in Infancy Are Associated with Sleep Duration in Toddlerhood. Kocevska D, Voortman T, Dashti HS, van den Hooven EH, Ghassabian A, Rijlaarsdam J, Schneider N, Feskens EJ, Jaddoe VW, Tiemeier H, Franco OH. J Nutr. 2016 Jun;146(6):1250-6. doi: 10.3945/jn.115.225847. Epub 2016 May 4.

THE DEVELOPMENTAL COURSE OF SLEEP DISTURBANCES ACROSS CHILDHOOD RELATES TO BRAIN MORPHOLOGY AT AGE 7: THE GENERATION R STUDY

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Background: Little is known about the impact of sleep disturbances on the structural properties of the developing brain. This study explored associations between childhood sleep disturbances and brain morphology at 7 years.
Methods: Mothers from the Generation R cohort reported sleep disturbances in 720 children at ages 2 months, 1.5, 2, 3, and 6 years. T1-weighted Magnetic Resonance Imaging (MRI) images were used to assess brain structure at 7 years. Associations of sleep disturbances at each age and of sleep disturbance trajectories with brain volumes (total brain volume, cortical and subcortical grey matter, white matter) were tested with linear regressions. To assess regional differences, sleep disturbance trajectories were tested as determinants for cortical thickness in whole-brain analyses.
Results: Sleep disturbances followed a declining trend from toddlerhood onwards. Infant sleep was not associated with brain morphology at age 7. Per SD sleep disturbances (one frequent symptom or two less frequent symptoms) at 2 and 3 years of age, children had −6.3 (−11.7 to −0.8) cm3 and −6.4 (−11.7 to −1.7) cm3 smaller grey matter volumes, respectively. Sleep disturbances at age 6 years were associated with global brain morphology (grey matter: −7.3 (−12.1 to −2.6), p value = .01). Consistently, trajectory analyses showed that more adverse developmental course of childhood sleep disturbances are associated with smaller grey matter volumes and thinner dorsolateral prefrontal cortex.
Conclusion: Sleep disturbances from age 2 years onwards are associated with smaller grey matter volumes. Thinner prefrontal cortex in children with adverse sleep disturbance trajectories may reflect effects of sleep disturbances on brain maturation.

The general design of Generation R Study is financially supported from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, ZonMw, the Netherlands Organization for Scientific Research, and the Ministry of Health, Welfare and Sport, and is conducted by the Erasmus Medical Center in collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. The first phase of the Generation R Study was financially supported from the Erasmus Medical Centre and The Netherlands Organization for Health Research and Development (Zon MW Geestkracht Program 10.000.1003 and VIDI Grant 017.106.370 to HT). ERAWEB scholarship grant financed by the European Commission was granted to DK (grant agreement 2013–2548/001-001-EMA-2). The work of Tonya White (MRI component of the study) was supported by the Netherlands Organization for Health Research and Development (ZonMw) TOP project number 91211021. Furthermore, the study was financially supported from the European Union's Horizon 2020 research and innovation program (No.:633595, DynaHealth). Supercomputing resources were supported by the NOW Physical Sciences Division (Exacte Wetenschappen) and SURFsara (Lisa compute cluster www.surfsara.nl).

The Developmental Course of Sleep Disturbances Across Childhood Relates to Brain Morphology at Age 7: The Generation R Study. Kocevska D, Muetzel RL, Luik AI, Luijk MP, Jaddoe VW, Verhulst FC, White T, Tiemeier H. Sleep. 2017 Jan 1;40(1). doi: 10.1093/sleep/zsw022.

SEDENTARY TIME ASSESSED BY ACTIGRAPHY AND MORTALITY: THE ROTTERDAM STUDY

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Introduction: Research suggests that sedentary behavior is a risk factor for mortality. However, most studies rely on questionnaires, which are prone to reporting error. We examined the association between sedentary time assessed by actigraphy and mortality.
Methods: The study included 1839 participants, aged 45–98 years, from the prospective population-based Rotterdam Study, enrolled between 2004 and 2007. Participants wore an actigraph around the wrist for seven days. Sedentary time was evaluated continuously, per 1 h/day increase, and categorically in three groups (<8, 8–11, ≥11 h/day). The lowest category was used as reference. Mortality risks were examined using Cox proportional hazard models, adjusted for confounders and biological risk factors. We examined the association between sedentary behavior and mortality over and beyond other activity measures (including physical activity (PA) and activities of daily living (ADL)) in a final model.
Results: During 11 years of follow-up (median: 7.5 years, interquartile range: 6.6–8.3 years), 212 participants (11.5%) died. In the multivariable model, the hazard ratio (HR) and 95%confidence interval (95% CI) per 1 more hour/day sedentary time was 1.09 (1.00, 1.18). The HR (95% CI) after adjustment for PA and ADL was 1.04 (0.96, 1.13). Participants sedentary for ≥11 h/day had a higher mortality risk (HR: 1.80, 95% CI: 1.14, 2.84) than those sedentary b8 h/day, in the multivariable model. After adjusting for PA and ADL, this association was clearly attenuated (HR: 1.50, 95% CI: 0.93, 2.41).
Conclusion: Our study suggests that sedentary behavior is a risk factor for mortality. Further investigation is needed to examine whether this association is distinct from the effect of other measures of activity.

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Koolhaas CM, Dhana K, van Rooij FJ, et al. Sedentary time assessed by actigraphy and mortality: The Rotterdam Study. Prev Med. 2017;95:59-65.

CIRCULATION TIME IN OBSTRUCTIVE SLEEP APNEA.

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Introduction. Unlike in central sleep apnea it is not known if in obstructive sleep apnea patients without heart failure a prolonged circulation time might play a role.

Objectives. To measure the duration of circulation time in snorers and patients with obstructive sleep apnea and to explore if there is a correlation between circulation time and disease severity.

Methods. The circulation time was measured from the lung to the finger in 10 selected obstructive apneas per patient using data from polygraphic recordings. Four groups of patients similar for age and body mass index were selected. Eleven snorers with an apnea hypopnea index less than 5. The other groups(n=20) consisted of obstructive sleep apnea patients with mild, moderate and severe sleep apnea as defined by AASM criteria.

Results. In snorers the lung-to-finger circulation time was 19.5 ± 5.2 seconds, in the mild, moderate and severe obstructive sleep apnea patients 21.9 ± 5.0, 22.4 ± 4.4 and 25.1 ± 6.1 seconds respectively. A significant linear relation was found between the severity of obstructive sleep and the lung-to-finger circulation time ($p = 0.005$). The prevalence of a previous cardiac history was low and evenly distributed among the groups.

Conclusions. The lung-to-finger circulation time was significantly increased in obstructive sleep apnea patients as compared to snorers. This finding can be caused by latent cardiac dysfunction not revealed by history. Alternatively it can be hypothesized that otherwise healthy individuals with a prolonged circulation time are more prone to develop severe sleep apnea.

BODY TEMPERATURES, 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 rise in heat loss via 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 NREMS to REMS 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 (slow wave sleep). More reproducible systematic investigations, applying temperature levels within the thermo-neutral zone on different skin regions are needed to develop applicable thermal therapeutic strategies for sleep disturbances.

The pre-optic-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 physiological processes occur as during normal entrance into sleep, however this is observed in a more extreme way providing an excellent opportunity to investigate these processes in more detail.

In Kryger MH, Roth T, Dement WC (Eds.) Principles and Practice of Sleep Medicine 6th edition, Elsevier, Philadelphia, PA, pp 220-228, 2017.

EFFICACY OF IMAGERY RESCRIPTING AND IMAGINAL EXPOSURE FOR NIGHTMARES: A RANDOMIZED WAIT-LIST CONTROLLED TRIAL

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Introduction: Nightmares can be effectively treated with cognitive-behavioral therapies. Though it remains elusive which therapeutic elements are responsible for the beneficial effects on nightmare symptoms, imagery rescripting (IR) and imaginal exposure (IE) are commonly identified as active treatment components of nightmare therapies. With this randomized controlled trial, we compared IR and IE as individual treatments to a wait-list (WL) condition to determine whether these particular therapeutic elements ameliorate nightmare symptoms.
Methods: For this purpose, 104 patients with a primary DSM-5 diagnosis of nightmare disorder were randomly assigned to three weekly individual sessions of either IR or IE, or WL.
Results showed that compared to WL, both interventions effectively reduced nightmare frequency ($d_{IR\text{-}WL}$ = 0.74; $d_{IE\text{-}WL}$ = 0.70) and distress ($d_{IR\text{-}WL}$ = 0.98; $d_{IE\text{-}WL}$ = 1.35) in a sample that predominantly consisted of idiopathic nightmare sufferers. The effects of IR and IE were comparable to those observed for other psychological nightmare treatments. Initial effects at post-treatment were sustained at 3- and 6-months follow-up, indicating that IR and IE both seem to be efficacious treatment components of nightmare therapies.
Conclusions: Additional research is needed to directly compare IR and IE among both idiographic and posttraumatic nightmare sufferers with respect to treatment expectancy, acceptability, and effectiveness.

Kunze, A. E., Arntz, A., Morina, N., Kindt, M., & Lancee, J. (2017). Efficacy of imagery rescripting and imaginal exposure for nightmares: A randomized wait-list controlled trial. Behaviour Research and Therapy, 97, 14-25. Doi: 10.1016/j.brat.2017.06.005

ATTENTIONAL BIAS MODIFICATION TRAINING FOR INSOMNIA: A DOUBLE-BLIND PLACEBO CONTROLLED RANDOMIZED TRIAL

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Background. Attentional bias toward sleep-related information is believed to play a key role in insomnia. If attentional bias is indeed of importance, changing this bias should then in turn have effects on insomnia complaints. In this double-blind placebo controlled randomized trial we investigated the efficacy of attentional bias modification training in the treatment of insomnia.
Method. We administered baseline, post-test, and one-week follow-up measurements of insomnia severity, sleep-related worry, depression, and anxiety. Participants meeting DSM-5 criteria for insomnia were randomized into an attentional bias training group (n = 67) or a placebo training group (n = 70). Both groups received eight training sessions over the course of two weeks. All participants kept a sleep diary for four consecutive weeks (one week before until one week after the training sessions).
Results. There was no additional benefit for the attentional bias training over the placebo training on sleep-related indices/outcome measures.
Conclusions. The absence of the effect may be explained by the fact that there was neither attentional bias at baseline nor any reduction in the bias after the training. Either way, this study gives no support for attentional bias modification training as a stand-alone intervention for ameliorating insomnia complaints.

Lancee, J., Yasiney, S.L., Brendel, R.S., Boffo, M., Clarke, P., Salemink, E. (2017). Attentional bias modification training for insomnia: A double-blind placebo controlled randomized trial. PlosOne, 12(4),e0174531, doi: 10.1371/journal.pone.0174531

ADHERENCE TO CONTINUOUS POSITIVE AIRWAY PRESSURE IN ADULTS WITH AN INTELLECTUAL DISBILITY

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Introduction: This retrospective study evaluated the feasibility of continuous positive airway pressure (CPAP) therapy in adults with intellectual disabilities (ID).

Methods: CPAP therapy of 24 obstructive sleep apnea syndrome (OSA) patients with ID were compared to age- and sex-matched adults with normal cognitive functioning. All ID patients received an intensive in-hospital training protocol to stimulate adherence. Good adherence was defined as a use of >70% of the nights and > 4 h/night. Influencing factors were assessed.

Results: Baseline apnea-hypopnea index (AHI) was significantly higher in ID patients compared to controls (median 34 /h (range 6-101) versus 17/h (range 5-50), p=0.013). The required average duration of in-hospital training was 4 nights (range 1-8 days). At 6 weeks, 60% of the ID patients showed good adherence and 65% at 6 months, compared to 71% and 50% respectively in the control group. Mean CPAP use per night was equal in both groups both at 6 weeks (5h in both groups) and 6 months (ID 6:30h vs control 5h (p=0.18)). CPAP adherence correlated with baseline AHI in the control patients, but not in ID patients. There was no correlation between CPAP adherence and the level of ID or the degree of support at home.

Conclusions: Using an intensive training protocol it is very well feasible to apply CPAP therapy in OSA patients with any degree of ID. CPAP adherence in ID patients was comparable to the control patients in this study as well as to previously published adherence numbers.

Luijks KA, Vandenbussche NL, Pevernagie D, Overeem S, Pillen S. Adherence to continuous positive airway pressure in adults with an intellectual disability. Sleep Med. 2017 Jun;34:234-239.

DIET QUALITY AND EATING PATTERNS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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Introduction: Obstructive sleep apnea (OSA) is a disorder within the category of sleep disordered breathing. It is caused by an obstruction of the upper airways and characterised by repeated pauses in breathing during sleep. This results in a decrease in oxyhemoglobin saturation and fragmentation of sleep (Young et al, 1993). Because OSA is associated with metabolic dysfunctioning it is interesting to know more about eating patterns and diet quality of these patients. Until now, just a few studies have been conducted on the diet of patients with OSA.

Methods: This study was a cross-sectional study, that analyzed the eating patterns of 73 adults who had obstructive sleep apnea or were suspected to have this disorder. To analyze eating patterns, we investigated meal frequency, breakfast skipping, time of the latest food consumption of the day and the time window of food consumption during the day. Data from 73 participants were analyzed to compare eating patterns and diet quality between a No and Light OSA (AHI 0-15) and a Moderate and Severe OSA (AHI 15-30) group. To assess diet quality the adherence of patients to dietary guidelines intake of vegetables, fruit, fish, fibers, alcohol, saturated fat, trans-fat and salt was determined. In addition to these eight components, also the adherence to the physical activity guideline was scored. Data on both eating patterns and diet quality were collected from questionnaires that were distributed on paper or online. Data analysis was done in SPSS and at first independent sample T-tests, Mann-Whitney U tests, Chi-Squares were performed. From the p-values the ones that scored lower than 0.10 were taken into account in a binary logistic regression model.

Results: Our study suggests a lower total diet quality for people with moderate and severe OSA (OR=0.916, 95%CI=0.853-0.984) than for those with no or light OSA. Especially the fruit score (OR=0.797, 95%CI=0.650-0.977) and the sodium score (OR=0.764, 95%CI=0.610-0.956) were lower for people with moderate and severe OSA. Regarding to eating patterns, only dinner regularity was found to be significantly lower in males with moderate and severe OSA (OR=0.196, 95%CI=0.043-0.885) than with no or light OSA.

Table 1 diet quality aspect scores of participants that completed Eetscore questionnaire (mean ± standard deviation)

N=68	No and Light OSA (AHI 0-15) N=41	Moderate and Severe OSA (AHI>15) N=27	P-value*
Physical activity	4.9(3.6)	3.9(3.9)	0.317
Vegetables	5.5(2.8)	5.4(2.2)	0.885
Fruit	6.9(3.6)	5.4(3.6)	0.042
Fiber	7.5(2.3)	6.9(2.1)	0.227
Fish	4.9(3.0)	4.5(3.4)	0.529
Saturated fatty acids	6.3(4.1)	3.6(4.4)	0.017
Trans fatty acids	7.3(4.5)	7.0(4.7)	0.803
Sodium	6.1(4.0)	3.7(2.7)	0.018
Alcohol	8.7(3.1)	8.7(2.5)	0.478
Total diet quality	57.3(12.2)	48.9(10.2)	0.004†

*p-value derived from Mann-Whitney U test unless: †=independent-sample t-test

Conclusion: We conclude that diet quality in patients with moderate and severe OSA was lower than in patients with no and light OSA. This was shown by lower scores for adherence to the Dutch dietary guidelines for total diet quality, and especially for fruit and sodium intake. For eating patterns only an association for dinner regularity in men was found, and more research will be needed to confirm this association.

VERSTOORDE SLAAP ALS CAUSALE FACTOR BIJ HET ONTSTAAN VAN DEPRESSIE

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Slaapgebrek is een veel voorkomend probleem in onze moderne maatschappij. Een grote groep mensen krijgt regelmatig niet genoeg slaap vanwege bijvoorbeeld werkdruk, stress, of slaapstoornissen. Omdat slaap een belangrijke rol speelt bij herstel, onderhoud en plasticiteit van zenuwcellen kan onvoldoende slaap ernstige gevolgen hebben voor het functioneren van de hersenen en voor de gezondheid in zijn algemeenheid. Talloze studies hebben aangetoond dat slecht of weinig slapen geassocieerd is met een verhoogd risico op allerlei ziektes, met name ook psychiatrische aandoeningen. Vooral de associatie tussen verstoorde slaap en depressie is erg sterk. Alhoewel verstoorde slaap nog vaak gezien wordt als een symptoom en gevolg van depressie zijn er steeds meer aanwijzingen dat verstoorde slaap bij veel patiënten juist een causale factor zou kunnen zijn die bijdraagt aan het ontstaan en in stand houden van depressie en bovendien de efficiëntie van behandelingen verminderd. Ook laten gecontroleerde experimenten met proefdieren zien dat chronisch verstoorde slaap geleidelijk aan kan leiden tot veranderingen in het brein zoals die ook voorkomen bij depressieve patiënten. Dit artikel geeft een overzicht van verschillende studies aan mensen en proefdieren die suggereren dat verstoorde slaap kan bijdragen aan depressie en bespreekt mogelijke onderliggende neurobiologische mechanismes.

Meerlo P. Verstoorde slaap als causale factor bij het ontstaan van depressie. In: Lancel M, Koenraadt F, 't Lam K (eds.) Gestoorde slaap: een onschuldig probleem? Wolf Legal Publishers, Nijmegen, 2016.

COMPARING INTER BEAT AND INTER PULSE INTERVALS FROM ECG AND PPG SIGNALS DURING SLEEP

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Introduction: Heart rate (HR) monitoring is crucial in several clinical fields. The gold standard technique for measuring HR dynamics is ECG. However, photoplethysmography (PPG) is becoming a reliable alternative to ECG for long-term monitoring, because of its unobtrusiveness. Studies have shown that features calculated from beat-to-beat intervals (RR), such as HRV, can be accurately derived both from ECG and PPG measurements (Schäfer and Vagedes 2013; van Andel et al. 2015). However, the correspondence of RR and PPG pulse-to-pulse intervals (PP) is not widely explored especially in unsupervised low-noise conditions, such as sleep.

Methods: In this research, we investigate the match between RR and PP for three landmarks on the PPG waveform in ten overnight sleep recordings of healthy subjects. R-peaks and pulse-landmarks (foot (FL), peak (PL), maximum gradient of the rising slope (ML)) were detected using the algorithms developed by (Hamilton and Tompkins 1986) and (Papini et al. 2017). R-peaks and pulse-landmarks were considered matched when detected within a 125 ms window. The distributions of the RR-PP differences were compared.

Results and Conclusion: The distributions derived from ML and FL had a lower mean±std than the PL, -0.3±20 ms and -1.8±39 ms respectively. However, the ML distribution had the lowest median skewness (-0.014). This, along with the mean±std, shows a symmetrically centered around distribution 0.0 ms (Figure 1). While other studies disagree with our findings (Hemon and Phillips 2016; Kane et al. 2016), their results are based on short and supervised recordings, which minimize the physiological RR-PP variability. We conclude that the modulation of cardiovascular variation (e.g. arterial stiffness) influences more FL and PL than ML, therefore ML is more reliable for HRV calculation.

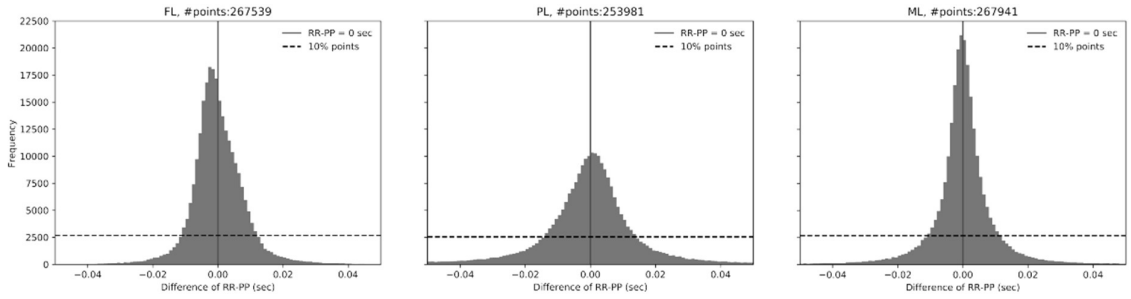

Figure 1. Distribution of RR-PP differences for the three different pulse landmarks.

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RESTLESS ROOSTS: LIGHT POLLUTION AFFECTS BEHAVIOR, SLEEP, AND PHYSIOLOGY IN A FREE-LIVING SONGBIRD

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The natural nighttime environment is increasingly polluted by artificial light. Several studies have linked artificial light at night to negative impacts on human health. In free-living animals, light pollution is associated with changes in circadian, reproductive, and social behavior, but whether these animals also suffer from physiologic costs remains unknown. To fill this gap, we made use of a unique network of field sites which are either completely unlit (control), or are artificially illuminated with white, green, or red light. We monitored nighttime activity of adult great tits, Parus major, and related this activity to within-individual changes in physiologic indices. Because altered nighttime activity as a result of light pollution may affect health and well-being, we measured oxalic acid concentrations as a biomarker for sleep restriction, acute phase protein concentrations and malaria infection as indices of immune function, and telomere lengths as an overall measure of metabolic costs. Compared to other treatments, individuals roosting in the white light were much more active at night. In these individuals, oxalic acid decreased over the course of the study. We also found that individuals roosting in the white light treatment had a higher probability of malaria infection. Our results indicate that white light at night increases nighttime activity levels and sleep debt and affects disease dynamics in a free-living songbird. Our study offers the first evidence of detrimental effects of light pollution on the health of free-ranging wild animals.

Ouyang JQ, De Jong M, Van Grunsven RHA, Matson KD, Haussmann MF, Meerlo P, Visser ME, Spoelstra K. Restless roosts: light pollution affects behavior, sleep and physiology in a free-living songbird. Global Change Biology, in press, 2017.

DIFFERENCES IN ELECTROENCEPHALOGRAPHIC NON-RAPID-EYE MOVEMENT SLEEP SLOW-WAVE CHARACTERISTICS BETWEEN YOUNG AND OLD MICE

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Changes in sleep pattern are typical for the normal aging process. However, aged mice show an increase in the amount of sleep, whereas humans show a decrease when aging. Mice are considered an important model in aging studies, and this divergence warrants further investigation. Recently, insights into the network dynamics of cortical activity during sleep were obtained by investigating characteristics of individual electroencephalogram (EEG) slow waves in young and elderly humans.

In this study, we investigated, for the first time, the parameters of EEG slow waves, including their incidence, amplitude, duration and slopes, in young (6 months) and older (18–24 months) C57BL/6J mice during undisturbed 24 h, and after a 6-h sleep deprivation (SD).

As expected, older mice slept more and, in contrast to humans, absolute NREM sleep EEG slow-wave activity (SWA, spectral power density between 0.5–4 Hz) was higher in the older mice, as compared to the young controls. Furthermore, slow waves in the older mice were characterized by increased amplitude, steeper slopes and fewer multipeak waves, indicating increased synchronization of cortical neurons in aging, opposite to what was found in humans. Our results suggest that older mice, in contrast to elderly humans, live under a high sleep pressure.

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THE EFFECT OF CHRONIC EXERCIZE ON SLEEP ARCHITECTURE AND THE ELECTROENCEPHALOGRAM IN YOUNG AND AGED MICE

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Physical activity is thought to be beneficial for health. Studies in young humans have shown that sleep quality can be improved with regular exercise, whereas the impact of exercise on sleep in elderly humans is still under investigation. We recently showed that aged mice have increased absolute slow-wave activity (SWA, electroencephalogram power density between 0.75-4.0 Hz) compared to young controls, suggesting changes in brain connectivity in the course of aging.

To investigate whether exercise can reduce this aging effect, mice were divided in three age groups and were either provided with a running wheel for 1-3 months (6 months old, n=9; 18 months old, n=9; 24 months old, n=8) or were used as controls (6 months old, n=11; 18 months old, n=8; 24 months old, n=6). One week before the sleep recordings, the wheel was removed. We recorded continuously the electroencephalogram (EEG) and electromyogram, without the running wheel, during undisturbed 24h baseline (BL) and conducted a sleep-deprivation during the first 6h of the second day.

Increased waking and decreased NREM sleep was found during the first 6-h of the BL dark period in young mice exposed to the running wheel compared to controls, whereas decreased REM sleep was found at the end of the BL dark in the 18 months old and at the beginning of the light period in the 24 months old, compared to their age-matched controls (t-tests, $p<0.05$ after significant ANOVAs). Notably, SWA was increased with aging and attenuated with exercise, exhibiting the lowest levels in the young mice exposed to the running wheel.

The data show a more moderate effect of exercise on sleep architecture in aged mice provided with a wheel. Nevertheless, SWA was markedly reduced when a wheel was available in aged mice, suggesting that exercise can alter brain connectivity towards a younger state.

Presented at the XV European Biological Rhythms Society Congress, Amsterdam, August 2017

A PATH TOWARDS BRAIN REJUVENATION: THE EFFECTS OF CHRONIC PHYSICAL ACTIVITY ON EEG SLOW-WAVE ACTIVITY IN MICE

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Physical activity is beneficial for health. It has been shown to improve brain functioning and cognition, reduce severity of mood disorders as well as promote healthy sleep and healthy aging. We recently found that aged mice have increased absolute electroencephalogram (EEG) slow-wave activity (SWA, EEG power density between 0.75-4.0 Hz) during non-rapid eye movement (NREM) sleep compared to young controls, suggesting changes in brain connectivity in the course of aging. To investigate whether exercise can counteract this aging effect, we provided mice of three different ages with running wheels for 1-3 months (6-months old, n=9; 18-months old, n=9; 24-months old, n=8) that were compared with control sedentary mice (n=11, n=8 and n=6, respectively). All animals with a wheel used the wheel daily. One week before the sleep recordings, the wheel was removed. We recorded the EEG and electromyogram during undisturbed 24-h baseline and during and after a 6-h sleep-deprivation. Increased waking and decreased NREM sleep was found in the first part of the BL dark period in young mice provided with a running wheel compared to controls, (t-tests, $p<0.05$ after significant ANOVAs) whereas no differences in the amount of NREM sleep were found in the aged groups. Interestingly, NREM sleep SWA showed a strong increase across age groups and a strong decrease with wheel availability within the age groups. The lowest SWA levels were observed in the young mice that had a wheel (126 $\mu V^2/Hz$) and the highest in the old mice without a wheel (227 $\mu V^2/Hz$, $p<0.0001$). Therefore, although we found only a modest effect on sleep architecture in aged mice provided with a wheel, SWA was markedly reduced when a wheel was used daily. The data suggest that moderate regular exercise in aging can alter cortical brain connectivity towards a younger state.

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DEEPER SLEEP DURING CHRONIC CAFFEINE CONSUMPTION IN MICE

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Caffeine is one of the world's most widely consumed psychostimulants. It impacts human sleep and circadian physiology, and the acute effect of caffeine has been studied extensively. In the current study, we investigated the chronic effect of caffeine consumption on sleep and the sleep electroencephalogram (EEG) in mice (C57BL/6J, n=7). We recorded the EEG and electromyogram (EMG) continuously for control 36-h and subsequent 36-h where mice had exclusively access to caffeinated drinking water (0.8g/L) (acute condition). The recordings were repeated after 14 days of caffeinated water consumption for baseline 24-h and during and after 6-h sleep deprivation (SD). An additional control group (n=11) with normal drinking water was recorded and sleep deprived. The total amount of waking, NREM and REM sleep over 24-h did not change in acute and chronic caffeine vs. control, however the amplitude of the light-dark vigilance state rhythm was increased (rANOVAs, $p<0.05$), with the highest amplitude in the chronic condition. Increased waking in the dark period was apparent in both the acute and chronic condition, however, chronic caffeine consumption resulted, additionally, in decreased waking in the light period. EEG slow-wave activity (0.75-4.0 Hz) during the light period was increased in the chronic condition compared to control. In the waking EEG, enhanced theta (7-9 Hz) and decreased slow-wave activity (0.5-5.0 Hz) were evident in the chronic condition, compared to control, denoting increased alertness. SD, by gentle handling, was remarkably difficult after chronic caffeine consumption and less successful than in the control group. Together with the baseline SWA results, our data suggest that the animals under chronic caffeine experience increased sleep pressure during the light period. Concluding, we show that chronic and acute caffeine consumption induce different effects on sleep architecture and the sleep EEG.

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CHRONIC HIGH-CALORIC DIET AND SLEEP IN YOUNG AND AGED MICE

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Obesity and sleep disturbances comprise major health problems which are likely interrelated. In this study, we investigated the effect of chronic (12 weeks) high-caloric diet (HCD, 45% fat) consumption on sleep and the sleep electroencephalogram (EEG) in three age groups (6-months old, n=9; 18-months old, n=8) and compared with age-matched controls that were fed on normal chow (n=11 and n=9, respectively). We recorded EEG and the electromyogram for continuous 48-h and performed a 6-h sleep deprivation at the beginning of the second day. Young HCD fed mice showed an altered sleep homeostasis pattern, characterized by increased likelihood of consecutive NREM-REM sleep cycles, increased REM sleep in the light period, and decreased baseline (BL) slow-wave activity levels (SWA, EEG power density between 0.5-4.0 Hz) in NREM sleep, compared to the young controls (t-tests, $p<0.05$; after significant ANOVAs). 18-months old HCD treated mice showed increased NREM sleep and decreased waking, compared to age-matched controls, denoting an enhanced aging phenotype. In aged HCD fed mice, compared to young HCD fed mice, an aging effect was still evident, characterized by decreased waking in the dark period, increased NREM sleep at the beginning and end of the light period and decreased REM sleep, as well as increased SWA. Our data suggest that the effect of aging is more pronounced compared to the effect of HCD. At young age HCD has a clear impact on sleep and the sleep EEG, but with increasing age, the influence of the diet on sleep architecture decreases.

Presented at the Worldsleep 2017 meeting, Prague, October 2017.

EFFECT OF CHRONIC DIM-LIGHT-AT-NIGHT EXPOSURE ON SLEEP EEG AND BEHAVIOR IN YOUNG AND AGED MICE

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Dim-Light-at-Night (DLAN) exposure is associated with health problems, such as metabolic disruptions, immunological modulations, oxidative stress, sleep problems, and altered circadian timing. Neurophysiological parameters, including sleep patterns, deteriorate in the course of aging in a similar way. In this study, we investigated the effect of chronic (3 months) DLAN (12L:12Dim, 50-100:5 lux) exposure on sleep and sleep electroencephalogram (EEG) as well as rest-activity behavior in young (6-month-old, n=7) and aged (18- n=8, 24-month-old, n=6) C57BL/6J mice and compared with age-matched controls (n=11, n=9 and n=8, respectively). We recorded the EEG and electromyogram continuously for 48-h and conducted a sleep-deprivation (SD) during the first 6-h of the second day. A general disturbance of the daily distribution of vigilance states was evident in the young mice in which the effect of chronic DLAN exposure was most pronounced. This was characterized by increased Waking and decreased NREM sleep during the light period and decreased Waking and increased NREM and REM sleep in the first part of the Dim period, compared to age-matched controls (t-tests, $p<0.05$ after significant ANOVAs). These patterns were very similar to those found in aged DLAN mice. Both aged DLAN groups showed a 2-h delayed response to the transition between Light and Dim periods. Additionally, a second free-running rhythm was noted in 4 young DLAN mice (44%), whereas for the old mice this was not the case. In contrast to young control, slow-wave-energy lost during SD was not totally recovered by mice exposed to chronic DLAN and aged control mice. Our data show a disruption of sleep patterns and a reduced response to SD under DLAN exposure. DLAN altered the sleep architecture in young mice, towards an aging phenotype, whereas it only mildly changed sleep in the older groups.

Presented at the Worldsleep 2017 meeting, Prague, October 2017.

PULSE-BY-PULSE PHOTOPLETHYSMOGRAPHY QUALITY INDEX FOR SIGNAL RELIABILITY ASSESSMENT BASED ON PULSE MORPHOLOGY

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Introduction: In the last decades, photoplethysmography (PPG) has been employed in a wide spectrum of applications, ranging from sleep trackers to polysomnographic equipment. The pulsatile PPG signal recorded contains valuable information on the cardio-vascular and -respiratory system. Several features can be derived from the PPG and these can be used to infer physiological states of the human system, for instance to estimate the sleep structure or the fitness level of a subject. As every sensing technology, the PPG can be corrupted by artifacts so it needs to be enhanced and, sometimes, parts of it have to be rejected. The rejection becomes fundamental especially when features are based on the shape of the signal. In literature, several methods are available to determine a quality index (QI) of parts of the PPG and use this QI as criterion for segment rejection. However, these methods exclude entire segments of the signal rather than single pulses, or they calculate a QI susceptible to the physiological PPG variation.
Methods: In this study, a new algorithm for single PPG pulse QI calculation is proposed. This QI ranges between 0 and 1 and it is assessed by comparing each pulse with a template. The template is derived from PPG by using dynamic time warping (DTW) barycenter averaging. Each pulse is warped, using DTW, to maximize the match with the template and the QI is calculated as a normalized root mean square error of the remaining mismatch. The QI is resilient to physiological pulse deformations, but still able to quantify the pulse morphology corruption and to recognize artifacts.
Results: The algorithm is validated on the Complex System Laboratory database, according to the ANSI/AAMI standards. For each pulse the beat location is calculated and it is rejected if QI is lower than 0.5. The positive predictive value and sensitivity (PPV, SEN) are calculated with respect to human beat annotations, with a true positive detection criterion of 30 ms distance from the annotated beat. The developed algorithm has a PPV of 99.43% and a SEN of 95.43% while the one in Aboy et al. 2005 has, respectively, 97.98% and 98.99%. The QI thresholding allows to obtain a significantly higher PPV, a consequence of an improved corrupted beat rejection, at the expense of a lower SEN.
Conclusion: The proposed algorithm provides a single pulse QI, resilient to physiological deformation, based on the morphology comparison with a data-derived template. The algorithm gives the possibility to choose the QI depending on the features that will be derived. For instance, in case of morphology related features, a high QI threshold can increase the likelihood that only uncorrupted beats are kept.

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

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Objectives: 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. We have now developed a new procedure for oscillatory phase targeting, in combination with high-density EEG recording, which 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 raw 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, and 3) the preferred phase is expected within 24-34 ms in the future. The method was validated for both 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 frequency rhythms. When a full sine wave of 360° is evaluated, the phase error is 5.71° ± 50.74° off target, with a total closed-loop speed of 24 ± 8.49 ms.
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 high-density recording, real-time analysis and stimulus presentation, is convenient and can be run on any EEG set-up. This can be of great importance in Targeted Memory Reactivation (TMR) studies during sleep, where stimuli needs to played in specific phases of the ongoing brain wave.

Table: Overview of currently available oscillatory phase targeting methods. Data represent mean ± SD.

	Cox et al. (2014)	*Santostasi et al. (2016)*	*van Poppel et al. offline performance*	*van Poppel et al. real-time performance*
Phase error	22.25° ± 70.70°	12.51° ± 28.85°	8.22° ± 28.50°	5.71° ± 50.74°
Possible target state	Up and down	Up	Up and down	Up and down
Cues in right state	?	79%	99%	81%
Total closed-loop delay	?	70 ± 5 ms	6.33 ± 2.54 ms	24 ± 8.49 ms
Amount cues / min	?	?	2.60	3.43 ± 1.16

As presented on the Sleep and cognition event, Amsterdam, May 2016 and the ESRS conference, Bologna, September 2016

FIRST DESCRIPTIVE STUDY ON CHRONO-NUTRITION IN DUTCH ADOLESCENTS WITH DELAYED SLEEP PHASE DISORDER

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Introduction: Delayed sleep phase disorder (DSPD) is characterized by a pattern of markedly late sleep onset and awakening times and is mostly prevalent in adolescents; it affects not only individual's sleep but also their daytime functioning and thus far treatment options are limited. Several studies have suggested chrono-nutrition could presents a possible modifiable risk factor for DSPD. Chrono-nutrition is the study of the impact of the timing of eating and includes three elements of time: irregularity, frequency and clock time of meal intakes. In this study, we aimed to describe for the first time the association between DPSD and chrono-nutrition in Dutch adolescents.

Methods: This observational study consisted of a sample of 30 adolescent patients with DPSD and 18 adolescent controls aged 14-22 years. Male and female patients were recruited from the Sleep Center of the Gelderse Vallei Hospital, Ede (ZGV-NL). The control group consisted of acquaintances of the researcher and of patients coming to ZGV, who were not diagnosed with DSPD. Actometer and melatonin saliva samples were used to measure patients sleep and DLMO values. Chrono-nutrition and dietary patterns were assessed by 2 questionnaires. Linear regression models were used to describe the association between DSPD and chrono-nutrition in adolescents with and without DSPD.

Results: DPSD patients consumed their last meal during the weekend at 22:09±0:48h whereas adolescents without DSPD consumed their last meal at 21:03±1:22h (Table). They also consumed their last meal on weekdays and first meal on weekend days.

Table main findings descriptive study of Dutch DPSD adolescents (n=30) compared to controls (n=18)

	DPSD patients(n=30)	**Controls (n=18)**	**P value**
First meal weekend days	09:47 ± 0:24	09:15 ± 0:42	0.002
Last meal weekdays	21:22 ± 1:07	20:23 ±1:19	0.009
Last meal weekend days	22:09 ± 0:48	21:03 ±1:22	0.001

Conclusion: We observed differences in chrono-nutrition between patients with and without DPSD pointing in the direction that their chrono-nutritional clock is also delayed. These findings warrant further investigation studying the possible effects of chrono-nutrition as possible treatment of DPSD.

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SLEEP RESEARCH GOES WILD: NEW METHODS AND APPROACHES TO INVESTIGATING THE EVOLUTION AND FUNCTIONS OF SLEEP

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Despite being a prominent aspect of animal life, sleep and its functions remain poorly understood. As with any biological process, the functions of sleep can only be fully understood when examined in the ecological context in which they evolved. Owing to technological constraints, until recently sleep has primarily been examined in the artificial laboratory environment. However, new tools are enabling researchers to study sleep behavior and neurophysiology in the wild. The initial studies to 'go wild' have revealed a wealth of inter-individual variation in sleep, and shown that sleep duration is not even fixed within an individual, but instead varies in response to an assortment of ecological demands. Determining the costs and benefits of this inter- and intra-individual variation in sleep may reveal clues to the functions of sleep. Perhaps the greatest surprise from these initial studies is that the reduction in neurobehavioral performance resulting from sleep loss demonstrated in the laboratory is not an obligatory outcome of reduced sleep in the wild. Here we summarize the various methods that have enabled sleep researchers to go wild, their strengths and weaknesses, and the discoveries resulting from these first steps outside the laboratory.

Rattenborg NC, de la Iglesia HO, Kempenaers B, Lesku JA, Meerlo P, Scriba MF. Sleep research goes wild: new methods and approaches to investigate the ecology, evolution and functions of sleep. Philosophical Transactions B, in press, 2017.

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

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

Raven F, Van der Zee EA, Meerlo P, Havekes R. The role of sleep in regulating structural plasticity and synaptic strength: implications for memory and cognitive function. Sleep Medicine Reviews, in press, 2017.

THE FLEXIBLE CLOCK: PREDICTIVE AND REACTIVE HOMEOSTASIS, ENERGY BALANCE AND THE CIRCADIAN REGULATION OF SLEEP–WAKE TIMING

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The Darwinian fitness of mammals living in a rhythmic environment depends on endogenous daily (circadian) rhythms in behavior and physiology. Here, we discuss the mechanisms underlying the circadian regulation of physiology and behavior in mammals. We also review recent efforts to understand circadian flexibility, such as how the phase of activity and rest is altered depending on the encountered environment. We explain why shifting activity to the day is an adaptive strategy to cope with energetic challenges and show how this can reduce thermoregulatory costs. A framework is provided to make predictions about the optimal timing of activity and rest of non-model species for a wide range of habitats. This Review illustrates how the timing of daily rhythms is reciprocally linked to energy homeostasis, and it highlights the importance of this link in understanding daily rhythms in physiology and behavior.

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THE PROSPECTIVE ASSOCIATION OF THE DIURNAL CORTISOL RHYTHM WITH SLEEP DURATION AND PERCEIVED SLEEPING PROBLEMS IN PRE-SCHOOLERS: THE GENERATION R STUDY

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Background: Cortisol, the end product of the hypothalamic-pituitary-adrenal axis, plays an important role in modulating sleep. Yet, studies investigating the association between diurnal cortisol rhythm and sleep patterns in young children are scarce. We tested the hypothesis that the diurnal cortisol rhythm is associated with shorter sleep duration and more sleep problems across early childhood.
Methods: This study was embedded in Generation R, a population-based cohort from fetal life onward. Parents collected saliva samples from their infant at five moments during day 1. In 322 infants aged 12 to 20 months, we determined the diurnal cortisol rhythm by calculating the area under the curve (AUC), the cortisol awakening response (CAR), and the diurnal slope. Sleep duration and sleep behavior were repeatedly assessed across ages of 14 months to 5 years. Generalized estimating equation models were used to assess related cortisol measures to sleep duration and sleep behavior.
Results: The diurnal cortisol slope and the CAR, but not the AUC, were associated with sleep duration across childhood. Children with flatter slopes and children with a more positive CAR were more likely to have shorter nighttime sleep duration (β per nmol/L/h slope = -0.12, 95% confidence interval = -0.19 to -0.05, p = .001; β per nmol/L CAR = -0.01, 95% confidence interval = -0.02 to 0.00, p = .04). Cortisol measures did not predict sleep problems.
Conclusions: The present study suggests that a flatter diurnal cortisol slope and a more marked morning rise, which can indicate stress (or hypothalamic-pituitary-adrenal dysregulation), have a long-term association with sleep regulation.

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Psychosom Med. 2017 Jun;79(5):557-564. doi: 10.1097/PSY.0000000000000440. The Prospective Association of the Diurnal Cortisol Rhythm With Sleep Duration and Perceived Sleeping Problems in Preschoolers: The Generation R Study. Saridjan NS1, Kocevska D, Luijk MPCM, Jaddoe VWV, Verhulst FC, Tiemeier H.

P-GLYCOPROTEIN FUNCTION IN THE RODENT BRAIN DISPLAYS A DAILY RHYTHM, A QUANTITATIVE IN VIVO PET STUDY

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The blood-brain barrier (BBB) contributes to brain homeostasis by protecting the brain from harmful compounds. P-glycoprotein (P-gp) is one of the major efflux transporters at the BBB. In the present study, we assessed whether (1) P-gp function in the brain is constant or fluctuates across the day and (2) if it is affected by sleep deprivation. Four groups of rats were PET scanned with a radiolabeled P-gp substrate [18F]MC225, each at a different moment of the 12-h light-dark cycle to study diurnal variations: early sleep phase (ZT3), late sleep phase (ZT9), early active phase (ZT15), and late active phase (ZT21). In two additional groups, controls were allowed to sleep normally while experimental animals were sleep-deprived for 10 h in a slowly rotating drum during the sleep phase. Kinetic modeling with a one-tissue compartment model fit resulted for all brain regions in 1.2–1.8-fold higher distribution volumes (VT) at ZT15 than at other time points. VT-values at ZT3, ZT9, and ZT21 were not significantly different from each other. Regional tracer distribution volumes in controls and sleep-deprived animals were also not significantly different. Our results indicate that P-gp function in rats displays a daily rhythm with reduced function at the beginning of the active phase. This rhythm is not dependent on sleep since acute sleep deprivation had no effect. Knowing the diurnal variation of P-gp function could be important for the design of PET studies and for choosing the correct administration time for P-gp dependent drugs.

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STROKE AND OTHER CARDIOVASCULAR EVENTS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME AND THE EFFECT OF CONTINUOUS POSITIVE AIRWAY PRESSURE

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Introduction. Obstructive sleep apnea (OSA) is a known-risk factor for cardiovascular diseases. There are indications that treatment with continuous positive airway pressure (CPAP) reduces the risk of new cardiovascular events. In this study, we analyzed the incidence of cardiovascular events in patients with OSA and compared for the impact of CPAP therapy.
Methods. All polysomnographies performed in 2009 and 2010 were selected with an AHI ≥5 and patients older than 18 years. These 1110 patients were approached with a questionnaire about cardiovascular events and CPAP treatment. Finally, 554 patients were included in analyses. CPAP treatment was based on compliance (level 1 treatment) and extended with residual respiratory events (level 2 treatment). OSA was set as AHI ≥5 and classified in mild (AHI 5-15), moderate (AHI 15-30) and severe (AHI ≥30) OSA.
Results. 50 cardiovascular events occurred in 44 patients during follow-up (mean follow-up time 5.9 years) in 554 patients. The events were significantly higher in patients with increasing classification of OSA-severity ($p = 0.016$). A first-ever cardiovascular event did not differ significantly between mild, moderate and severe OSA. Untreated CPAP patients had significantly more cardiovascular events as compared to treated patients with a hazard ratio of 2.66 partially adjusted for age, AHI and smoking. There was no significant contribution of other cardiovascular risk factors.
Conclusion. Patients with OSA with an indication for CPAP treatment have more cardiovascular events when untreated compared to treated patients. This indicates that treatment of OSA by CPAP can reduce the risk for cardiovascular events.

Schipper MH, Jellema K, Thomassen BJW, Alvarez-Estevez D, Verbraecken J, Rijsman RM. Stroke and other cardiovascular events in patients with obstructive sleep apnea and the effect of positive airway pressure. J Neurol. 2017;264:1247-1253.

LONG-TERM EFFECTS OF BENZODIAZEPINE USAGE ON ACTUAL DRIVING AND NEUROCOGNITIVE PERFORMANCE

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Introduction: The classification system of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) is used to assess fitness to drive when taking potentially impairing medicinal drugs. Driving is prohibited when a medicinal drug is classified as category III (i.e. do not drive). However, the ICADTS classification system is mainly based on research with healthy participants assessing the acute or subchronic effects of medicinal drugs. Information regarding the effects of long-term medicinal drug use on driving performance is, however, lacking.

Methods: A multicenter study in the Netherlands was conducted to examine the effect of long-term category III anxiolytic or hypnotic use on driving performance. Patients prescribed with medicinal drugs for at least 6 months were matched with healthy controls, based on age, gender, and driving experience. The hypnotics' user group consisted out of two subgroups based on duration of treatment, either between 6 months - 3 years, or, longer than 3 years. Measures included a neurocognitive test battery (e.g. attention, reaction speed, executive functioning) and a standardized on-the-road highway driving test. In total, 79 participants completed the study (Anxiolytics, N=12; Hypnotics, N=32; Healthy controls, N = 35). Analyses were two-folded. First, a between-group comparison (patient vs. control) was made to assess statistical significant differences. Second, non-inferiority analyses were used to evaluate the clinical relevance of group differences in relation to a non-inferiority limit obtained at a Blood Alcohol Concentration (BAC) of 0.5mg/mL, the legal limit for driving under the influence in the Netherlands.

Results: For the standardized on-the-road highway driving test, analysis showed significant performance impairment between patients treated with hypnotics and healthy controls. Non-significant differences were found for patients treated with anxiolytics. Non-inferiority analysis revealed that for anxiolytics and hypnotics, the upper limit of the 95% confidence interval (CI) of the mean difference exceeded the BAC 0.5mg/mL criteria, indicating clinically relevant impairment. Subsequent subgroup analysis for hypnotic users based on duration of treatment revealed that patients treated for a period shorter than 3 years showed statistical and clinically relevant impairment. These effects were absent in patients treated for >3 years. For the neurocognitive test battery, analysis showed a non-significant difference between patient groups and healthy controls on most performance measures. Due to large inter-individual differences, the 95% CI of the mean difference exceeded the BAC 0.5mg/mL criteria, thus indicating clinically relevant impairment.

Conclusion: Outcomes are used to develop and update regulatory policies with regard to long-term medicinal drug use in the Netherlands. Based on the obtained results, it is proposed to classify long-term (>3 years) use of hypnotics as category II (i.e. be careful).

This study was financially supported by the Dutch Ministry of Infrastructure and the Environment

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NOCTURNAL EXPOSURE TO WHITE LIGHT WITHOUT MELATONIN SUPPRESSION: USING SPECTRAL TUNING TO TURN LIGHT INTO BIOLOGICAL DARKNESS

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Introduction: In modern society, humans are commonly exposed to too much light in the evening and at night. This has been shown to have acute suppressive effects on melatonin levels in the human body, as well as phase-delaying effects on the circadian rhythms underlying sleep. Previous studies have shown that melatonin suppression by light exposure can be reduced by selectively filtering out the short wavelengths. However, these studies confounded the spectral manipulation with decreases in illumination level and/or correlated color temperature. Moreover, the light they used mostly had a very orange appearance and poor color rendering properties. Here, we show for the first time that even under typical indoor white light conditions melatonin suppression can be drastically reduced, or enhanced, by tuning the spectral composition of the light.

Methods: We created two white light spectra with the same illuminance at the eye (175 lx) and the same color temperature (2700 K), but with different power in the range 450-530 nm. In one spectrum, short wavelength power was boosted, predicting high melanopic stimulation. In the other, reduced power in the 450-530 nm range was combined with an extra peak around 420 nm, to maintain the same color temperature. Sixteen participants were exposed to the spectra during 3 h, on different evenings. Salivary melatonin measurements and alertness measurements (KSS, PVT) were compared to those from a dim (< 5 lx) light baseline evening.

Results: Strong melatonin suppression was observed for the spectrum with high power in 450-530 nm. At the same time, melatonin levels were not significantly different from the dim light baseline for the other spectrum, with low 450-530 nm power. No differences in alertness were found.

Conclusions: These results open up new opportunities for light at night or in the evening, allowing for good visual performance with minimal non-visual impact of light exposure, thereby reducing the potential negative health consequences associated with the use of conventional lighting.

JS, TB, LS and ML are employed by Philips Lighting. IG did her M.Sc. graduation project at Philips Lighting. BV was employed by Philips Research until February 28th, 2017.

SLTBR 2017 conference abstract

DIM LIGHT AT NIGHT DISTURBS THE DAILY SLEEP-WAKE CYCLE IN THE RAT

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Exposure to light at night (LAN) is associated with insomnia in humans. Light provides the main input to the master clock in the hypothalamic suprachiasmatic nucleus (SCN) that coordinates the sleep-wake cycle. We aimed to develop a rodent model for the effects of LAN on sleep.

Therefore, we exposed male Wistar rats to either a 12 h light (150–200lux):12 h dark (LD) schedule or a 12 h light (150–200 lux):12 h dim white light (5 lux) (LDim) schedule.

LDim acutely decreased the amplitude of daily rhythms of REM and NREM sleep, with a further decrease over the following days. LDim diminished the rhythms of 1) the circadian 16–19 Hz frequency domain within the NREM sleep EEG, and 2) SCN clock gene expression. LDim also induced internal desynchronization in locomotor activity by introducing a free running rhythm with a period of ~25 h next to the entrained 24 h rhythm. LDim did not affect body weight or glucose tolerance.

In conclusion, we introduce the first rodent model for disturbed circadian control of sleep due to LAN. We show that internal desynchronization is possible in a 24 h L:D cycle which suggests that a similar desynchronization may explain the association between LAN and human insomnia.

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COGNITIVE AND BEHAVIORAL THERAPIES IN THE TREATMENT OF INSOMNIA: A META-ANALYSIS

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Introduction: Insomnia is a major public health problem considering its high prevalence, impact on daily life, comorbidity with other disorders and societal costs. Cognitive behavioral treatment for insomnia (CBTI) is currently considered to be the preferred treatment. However, no meta-analysis exists of all studies using at least one component of CBTI for insomnia, which also uses modern techniques to pool data and to analyze subgroups of patients.
Methods: We included 87 randomized controlled trials, comparing 118 treatments (3724 patients) to non-treated controls (2579 patients).
Results: Overall, the interventions had significant effects on: insomnia severity index (g = 0.98), sleep efficiency (g = 0.71), Pittsburgh sleep quality index (g = 0.65), wake after sleep onset (g = 0.63) and sleep onset latency (SOL; g = 0.57), number of wakenings (g = 0.29) and sleep quality (g = 0.40). The smallest effect was on total sleep time (g = 0.16). Face-to-face treatments of at least four sessions seem to be more effective than self-help interventions or face-to-face interventions with fewer sessions. Otherwise the results seem to be quite robust (similar for patients with or without comorbid disease, younger or older patients, using or not using sleep medication).
Conclusions: We conclude that CBTI, either its components or the full package, is effective in the treatment of insomnia.

Van Straten, A., van der Zweerde, T., Kleiboer, A., Cuijpers, P., Morin, C.M., Lancee, J. (in press). Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Medicine Reviews.

MEMORY ENHANCEMENT OR DEPRESSION DURING SLEEP, USING PRECISE, BRAIN-WAVE GUIDED MEMORY REACTIVATION

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Objectives: An elegant way to manipulate the sleeping brain is through the alignment of stimuli with specific electrophysiological brain signals. We have previously developed the first closed-loop brain stimulation procedure based on signal modelling, which we used to demonstrate differential processing of real-world sounds targeted to slow oscillation (SO) up- and down-states (Cox et al., 2014, Plos One). We have now developed a new procedure for oscillatory phase targeting that is faster, more accurate and more convenient than any previously reported method. Using this procedure, we aimed to show that memory reactivation and consolidation are specifically linked to the SO up-state. Indeed, we hypothesised that the tight alignment of specific memory cues to SO up-states during sleep would enhance memory performance compared to SO down-state locked stimuli.

Methods: Participants were exposed to a vocabulary-learning task in the evening and tested for vocabulary acquisition. During ensuing sleep, memory reactivation was induced through subtle auditory presentation of foreign words. One group of participants received SO up-state targeted memory cues, a second groups received SO down-state locked cues. In each group only part of the pre-sleep learned items was cued, counterbalanced for pre-sleep acquisition (hit/miss). The next morning, vocabulary memory was tested again and expressed as a proportion of performance on the previous night.

Results: Using this procedure, we showed that the tight alignment of specific memory cues to SO up-states during sleep enhances performance on a pre-sleep presented vocabulary-learning task, compared to either no cueing or down-state cueing. Interestingly, down-state cueing suppresses memory performance with respect to no cueing. An analysis of sleep macrostructure, moreover, shows that up-state cueing significantly enhances stage four sleep.

Conclusions: These results provide strong evidence for the notion that sleep-related memory consolidation occurs during slow oscillation up-states. Moreover, they show that declarative memory can be either enhanced or suppressed during sleep, depending on the precise alignment of reactivating cues to specific neural activity patterns. Finally, we show for the first time that sleep, as whole, can be deepened using intermittent, up-state locked sound stimulation during NREM sleep.

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DIFFERENT EFFECTS OF SLEEP DEPRIVATION AND TORPOR ON EEG SLOW-WAVE CHARACTERISTICS IN DJUNGARIAN HAMSTERS

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It has been shown previously in Djungarian hamsters that the initial electroencephalography (EEG) slow-wave activity (power in the 0.5–4.0Hz band; SWA) in non-rapid eye movement (NREM) sleep following an episode of daily torpor 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 torpor and SD are similar. EEG slow waves recorded in the neocortex during sleep reflect synchronized transitions between periods of activity and silence among large neuronal populations.

We therefore set out to investigate characteristics of individual cortical EEG slow waves recorded during NREM sleep after 4 h SD and during sleep after emergence from an episode of daily torpor in adult male Djungarian hamsters.

We found that during the first hour after both SD and torpor, the SWA increase was associated with an increase in slow-wave incidence and amplitude. However, the slopes of single slow waves during NREM sleep were steeper in the first hour after SD but not after torpor, and, in contrast to sleep after SD, the magnitude of change in slopes after torpor was unrelated to the changes in SWA. Furthermore, slow-wave slopes decreased progressively within the first 2 h after SD, while a progressive increase in slow-wave slopes was apparent during the first 2 h after torpor.

The data suggest that prolonged waking and torpor have different effects on cortical network activity underlying slow-wave characteristics, while resulting in a similar homeostatic sleep response of SWA. We suggest that sleep plays an important role in network homeostasis after both waking and torpor, consistent with a recovery function for both states.

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DAILY LIGHT EXPOSURE PATTERNS REVEAL PHASE AND PERIOD OF THE HUMAN CIRCADIAN CLOCK

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Light is the most potent time cue that synchronizes (entrains) the circadian pacemaker to the 24-h solar cycle. This entrainment process is an interplay between an individual's daily light perception and intrinsic pacemaker period under free-running conditions. Establishing individual estimates of circadian phase and period can be time-consuming. We show that circadian phase can be accurately predicted (SD = 1.1 h for dim light melatonin onset, DLMO) using 9 days of ambulatory light and activity data as an input to Kronauer's limit-cycle model for the human circadian system. This approach also yields an estimated circadian period of 24.2 h (SD = 0.2 h), with longer periods resulting in later DLMOs. A larger amount of daylight exposure resulted in an earlier DLMO. Individuals with a long circadian period also showed shorter intervals between DLMO and sleep timing. When a field-based estimation of tau can be validated under laboratory studies in a wide variety of individuals, the proposed methods may prove to be essential tools for individualized chronotherapy and light treatment for shift work and jetlag applications. These methods may improve our understanding of fundamental properties of human circadian rhythms under daily living conditions.

Woelders T, Beersma DGM, Gordijn MCM, Hut RA, Wams EJ. Daily light exposure patterns reveal phase and period of the human circadian clock. Journal of Biological Rhythms 32: 274-286, 2017.

LOWER SCHOOL PERFORMANCE IN LATE CHRONOTYPES: UNDERLYING FACTORS AND MECHANISMS

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Introduction. Success at school determines future career opportunities. We described a time-of-day specific disparity in school performance between early and late chronotypes. Several studies showed that students with a late chronotype and short sleep duration obtain lower grades, suggesting that early school starting times handicap their performance. How chronotype, sleep duration, and time of day impact school performance is not clear.

Methods. At a Dutch high school, we collected 40,890 grades obtained in a variety of school subjects over an entire school year.

Results. We found that the strength of the effect of chronotype on grades was similar to that of absenteeism, and that late chronotypes were more often absent. The difference in grades between the earliest 20% and the latest 20% of chronotypes corresponds to a drop from the 55th to 43rdpercentile of grades. In academic subjects using mainly fluid cognition (scientific subjects), the correlation with grades and chronotype was significant while subjects relying on crystallized intelligence (humanistic/linguistic) showed no correlation with chronotype.

Conclusion. Based on these and previous results, we can expand our earlier findings concerning exam times: students with a late chronotype are at a disadvantage in exams on scientific subjects, and when they are examined early in the day.

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Zerbini G, van der Vinne V, Otto LKM, Kantermann T, Krijnen WP, Roenneberg T, and Merrow M. Lower school performance in late chronotypes: underlying factors and mechanisms. Scientific Reports, 7: 4385, 2017.

HUMAN AND RAT GUT MICROBIOME COMPOSITION IS MAINTAINED FOLLOWING SLEEP RESTRICTION

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Insufficient sleep increasingly characterizes modern society, contributing to a host of serious medical problems. Loss of sleep is associated with metabolic diseases such as obesity and diabetes, cardiovascular disorders, and neurological and cognitive impairments. Shifts in gut microbiome composition have also been associated with the same pathologies; therefore, we hypothesized that sleep restriction may perturb the gut microbiome to contribute to a disease state. In this study, we examined the fecal microbiome by using a cross-species approach in both rat and human studies of sleep restriction. We used DNA from hypervariable regions (V1-V2) of 16S bacteria rRNA to define operational taxonomic units (OTUs) of the microbiome. Although the OTU richness of the microbiome is decreased by sleep restriction in rats, major microbial populations are not altered. Only a single OTU, TM7-3a, was found to increase with sleep restriction of rats. In the human microbiome, we find no overt changes in the richness or composition induced by sleep restriction. Together, these results suggest that the microbiome is largely resistant to changes during sleep restriction.

Zhang SL, Bai L, Goel N, Bailey A, Jang CJ, Bushman FD, Meerlo P, Dinges DF, Sehgal A. Human and rat gut microbiome composition is maintained following sleep restriction. PNAS 114: E1564-E1571, 2017.

COST-EFFECTIVENESS OF I-SLEEP, A GUIDED ONLINE CBT INTERVENTION, FOR PATIENTS WITH INSOMNIA IN GENERAL PRACTICE: PROTOCOL OF A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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Background: Insomnia is a highly prevalent disorder causing clinically significant distress and impairment. Furthermore, insomnia is associated with high societal and individual costs. Although cognitive behavioural treatment for insomnia (CBT-I) is the preferred treatment, it is not used often. Offering CBT-I in an online format may increase access. Many studies have shown that online CBT for insomnia is effective. However, these studies have all been performed in general population samples recruited through media. This protocol article presents the design of a study aimed at establishing feasibility, effectiveness and cost-effectiveness of a guided online intervention (i-Sleep) for patients suffering from insomnia that seek help from their general practitioner as compared to care-as-usual.
Methods/design: In a pragmatic randomized controlled trial, adult patients with insomnia disorder recruited through general practices are randomized to a 5-session guided online treatment, which is called "i-Sleep", or to care-as-usual. Patients in the care-as-usual condition will be offered i-Sleep 6 months after inclusion. An ancillary clinician, known as the psychological well-being practitioner who works in the GP practice (PWP; in Dutch: POH-GGZ), will offer online support after every session. Our aim is to recruit one hundred and sixty patients. Questionnaires, a sleep diary and wrist actigraphy will be administered at baseline, post intervention (at 8 weeks), and at 6 months and 12 months follow-up. Effectiveness will be established using insomnia severity as the main outcome. Cost-effectiveness and cost-utility (using costs per quality adjusted life year (QALY) as outcome) will be conducted from a societal perspective. Secondary measures are: sleep diary, daytime consequences, fatigue, work and social adjustment, anxiety, alcohol use, depression and quality of life.
Discussion: The results of this trial will help establish whether online CBT-I is (cost-) effective and feasible in general practice as compared to care-as-usual. If it is, then quality of care might be increased because implementation of i-Sleep makes it easier to adhere to insomnia guidelines. Strengths and limitations are discussed.
Trial registration: Netherlands Trial register NTR 5202 (registered April 17st 2015).

van der Zweerde, T., Lancee, J., Slottje, P., Bosmans, J., Van Someren, E., Reynolds, C., Cuijpers, P & van Straten, A. (2016). Cost-effectiveness of i-Sleep, a guided online CBT intervention, for patients with insomnia in general practice: protocol of a pragmatic randomized controlled trial. BMC psychiatry, 16(1), 1.

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