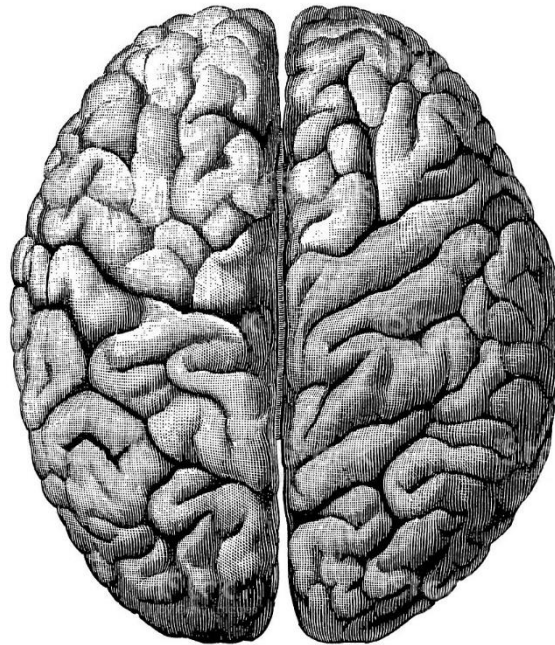


Polysomnography-based Sleep Regularity Assessment of a Single Healthy Individual



Emma Peters

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Donders Institute for Brain, Cognition and Behaviour, Sleep and Memory Lab

Supervisor: Martin Dresler

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Abstract

The adverse effects of poor sleep quality have been in the spotlight for decades. Day to day sleep regularity plays a significant role in sleep quality and has been highlighted as a novel risk factor for health implications such cardiovascular disease, obesity, insulin resistance, type 2 diabetes and breast cancer. In spite of this, sleep quality research often focuses on sleep duration and timing. The lack of research can be partly explained by the challenges accurate sleep regularity investigation poses. Sleep regularity has been assessed previously with the use of actigraphy. In this study, longitudinal polysomnography data was used, enabling a deep level of sleep regularity investigation, including specific NREM sleep, REM sleep, slow wave sleep and light sleep regularity. With the regularity index and the use of easy-to-use sleep wearables mapping longitudinal sleep structure will be highly accurate, detailed and efficient, providing insight in not only factors like duration and timing but also regularity, which has been shown to play an important part in healthy sleep.

Introduction

Sleep Regularity

Sleep is vital in supporting almost all aspects of healthy functioning. Specifically, insufficient or disturbed sleep plays a significant role in the development of a broad spectrum of health implications. However, these implications are not only dependent on the duration and disturbance of sleep. Sleep composition also heavily relies on circadian rhythm and regularity. The human population has a substantial inter-individual variability in sleep and circadian timing, as well as the alignment of the two. Preferred sleep time among a population follows a near-Gaussian distribution and is based on differences in a persons' circadian clock (Roenneberg et al., 2007). Circadian rhythmicity is a universal phenomenon in all living organisms. This endogenous human circadian rhythm is generated by a central clock located in the hypothalamus that regulates the timing of many physiologic and behavioral cycles, including sleep-wake cycles (D.-J. Dijk & Czeisler, 1995). For these cycles, the circadian rhythms are 24-hour oscillations in alertness and sleep propensity which is synchronized with the solar cycles. Therefore, light is the strongest synchronizing force for the circadian clock. However, other signals can also affect the rhythm, like social and physical activity and melatonin (Sletten, Vincenzi, Redman, Lockley, & Rajaratnam, 2010) Sleep regularity variability is not only visible in populations. Lately, intra-individual variation in sleep has been proposed to be even larger. Individuals who frequently change their sleep timing may experience circadian misalignment. As we live in a society where sleep timing no longer relies on light and melatonin alone, our daily schedules now largely influence the way we sleep. Intra-individual variability in circadian alignment and sleep may arise from differences in sleep timing on work days vs. free days, that is also known as 'social jetlag' (Murray et al., 2019). This occurs when an individual sleeps more on free days compared to work days in an attempt to catch up to the lost sleep during the work week. This irregularity in sleep is shown to be as damaging to sleep quality as the duration is (Gooley, 2016). As mentioned before, circadian misalignment might occur when sleep regularity is frequently disrupted. This disruption could result in adverse sleep outcomes (Farhud & Aryan, 2018; Zhu & Zee, 2012). Sleep regularity has been shown to have associations with important domains of healthy functioning. There is growing evidence suggesting associations between irregular sleep/wake patterns and several health implications such cardiovascular disease, obesity, insulin

resistance, type 2 diabetes and breast cancer (Barbadoro et al., 2013; Pan, Schernhammer, Sun, & Hu, 2011; Schernhammer et al., 2001; Vetter et al., 2016). Another study found that regular sleepers have better mood and psychomotor performance (Taub, 1978) and experience less sleepiness throughout the day (Manber, Bootzin, Acebo, & Carskadon, 1996). In general, sleep regularity has been often investigated using measures such as total sleep time, midpoint of sleep, sleep onset, or morning awakening time, all targeting one single nighttime sleep episode (Manber et al., 1996; Medeiros, Mendes, Lima, & Araujo, 2001). However, this poses problems for individuals who do not have regular nighttime sleep episodes. May it be because they have polyphasic sleep, shift work and therefore irregular sleep schedules or any other reason that prevents individuals from having a single nighttime sleep episode. This metric does not quantify rapid sleep pattern changes from day to day, but quantifies overall variability of a specific time point averaged across multiple days.

NREM and REM

EEG PROPERTIES

Not only a binary distinction between wakefulness and sleep, but also specific sleep states might be assessed for regularity. Sleep is made up of two states: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. NREM sleep can be subdivided into three gradual sleep depth levels: stage N1, (transition between wake and sleep), stage 2 (light sleep) and finally stage 3 (deep, slow-wave sleep (SWS)). Throughout the different phases of NREM, two distinct kinds of EEG activity are seen. During the lighter stages and towards REM sleep, so called sleep spindles are present. These are short bursts of oscillations (12-14Hz). During deep sleep, or SWS (stage 3), we see large amounts of delta waves (0-4Hz) and large muscle activity is seen on the EMG. Following NREM sleep, theta waves become more abundant as REM sleep starts to kick in. EEG amplitude decreased as the frequency is increased. Muscle activity diminishes to almost nothing, thanks to the inhibitory activity of the brainstem (Clément, Sapin, Bérod, Fort, & Luppi, 2011). Finally during REM, muscle paralysis is present, except for eye movements. These are the signature rapid eye movements present during REM. REM is virtually always followed by wakefulness. While the two are easily distinguishable in an EEG signal, the differences in functionality are still largely debated (Krueger, Frank, Wisor, & Roy, 2016). With mapping out the function of specific sleep stages any correlates with sleep stage regularity might be identified.

MEMORY

The amount of REM sleep decreases throughout a person's life. This suggests REM sleep facilitates some kind of brain development. Sensorimotor development might be regulated by REM sleep as well, with muscle twitches during muscle atonia. During muscle atonia, there's no muscle activity elsewhere so the nervous system can monitor thoroughly the origins of these REM twitches (Peever & Fuller, 2017). A big part of childhood and adolescence is learning through memory formation and memory consolidation. REM sleep has been often shown to facilitate formation and consolidation of memories (Peever & Fuller, 2017). Inhibiting GABA theta activity driving neurons during REM causes failure in memory consolidation (Boyce, Glasgow, Williams, & Adamantidis, 2016), while outside of REM it doesn't. Although theta activity has been repeatedly shown to affect memory and learning, how and why theta activity does it remains unclear. Another role REM sleep is suggested to play in learning and memory facilitation is the regulation of neuronal synapse by pruning and maintaining new synapses (Li, Ma, Yang, & Gan, 2017). All of the REM functions either restore some kind of deficit incurred during wakefulness or prepare for wakefulness (Brooks & Peever, 2016). The amount of REM increases toward the end of a sleep period and REM sleep is almost always followed by wakefulness (Benington & Heller, 1994). NREM has been shown to also play a significant role in memory (Diekelmann & Born, 2010). It aids in consolidation by changing the main dependency locus of the structure from the hippocampus to

the neocortex and reactivation of specific hippocampal areas during learning and during subsequent SWS (Huber, Ghilardi, Massimini, & Tononi, 2004). NREM plays a major role in memory, even though some current hypotheses propose different mechanisms. Not only deep NREM sleep (SWS) seems essential for healthy memory, light NREM sleep (N1 and N2, LS) also adds to the mix. While SWS is suggested to aid in global reorganization of memory traces throughout the cortex, LS may help consolidate in a smaller scale, within brain areas (Genzel, Kroes, Dresler, & Battaglia, 2014).

HOUSEKEEPING

NREM sleep is mainly involved with different housekeeping processes like homeostatic synaptic plasticity (Chauvette, Seigneur, & Timofeev, 2012). An increase in slow wave activity (SWA) follows a period of wakefulness during which a learning process took place that increased the activity of certain involved synapses. This results in a subsequent downgrade of synapses orchestrated by SWA (Kennedy, Van Essen, & Christen, 2016). The downgrading of synapses is a way of saving energy during NREM sleep and enables the body to refuel energy consumed during the day. Not only by synaptic rescaling, but also by re-uptaking adenosine-triphosphate (ATP) does SWS save energy. In a study on rats, ketamine induced delta waves correlated with increase in energy (Dworak, Kim, McCarley, & Basheer, 2011). SWS plays a crucial role in hormone release and regulation. It has been linked to the modulation of growth hormone and prolactin (Sassin et al., 1969; Spiegel et al., 1995), and is correlated with an increase in parasympathetic activity (Stein & Pu, 2012). The immune system has a close bond to sleep, with SWS specifically creating an environment that supports an adaptive immune response (Lange, Dimitrov, & Born, 2010). Finally, SWS has a restorative role by aiding in the clearance of metabolites (Zhdanova, Wang, Leclair, & Danilova, 2001).

SLEEP HOMEOSTASIS

Sleep is tightly regulated according to a two process model in which homeostatic and circadian processes regulate sleep duration and timing. The homeostasis process is regulated through a build-up of hypnogenic substances in the brain (Achermann, Borbély, Kryger, Roth, & Dement, 2017). The circadian rhythm as mentioned before, is managed by the internal clock located in the hypothalamus (D.-J. Dijk & Czeisler, 1995). SWS is special in that it does not seem to be regulated by the circadian rhythm but by time spent awake (D. Dijk, Brunner, & Borbély, 1990). SWA also seems to increase during deeper sleep and then decreases throughout the night (D.-J. Dijk, 2009; Sirota & Buzsáki, 2005). The homeostatic, negative feedback loop that NREM sleep seems to follow is evidently seen after long periods of wakefulness. They are followed by NREM sleep with higher SWA and shortening of sleep onset latency (Berger & Oswald, 1962), with an increase of NREM sleep propensity as a function of sleep debt (D. Dijk et al., 1990). The increase in SWA is seen mostly in the frontal areas suggesting that SWS responds to activation during wakefulness (D. Dijk et al., 1990). While total sleep debt of about 40 hours affects NREM sleep, it does not seem to affect the amount of REM sleep (Nakazawa, Kotorii, Ohshima, Kotorii, & Hasuzawa, 1978). Sleep extension, which is extra daytime sleep, reduces the amount of SWS in the following night, again showing the negative feedback loop. This loop does not seem to exist with REM sleep (Whitehead, Robinson, Wincor, & Rechtschaffen, 1969). In contrast to total deprivation, partial deprivation affects sleep in the opposite way. REM sleep is now reduced and NREM sleep stays unaffected (Dement & Greenberg, 1966). REM seems to be more resistant to changes in sleep time, however when affected, REM needs more time to return to steady state (Le Bon et al., 2001; Moses, Johnson, Naitoh, & Lubin, 1975). Sleep duration homeostasis seems to work differently for NREM and REM sleep with NREM being easily affected during total deprivation while REM sleep is affected during partial deprivation. The interaction between REM sleep and NREM sleep homeostasis has been investigated in rats. REM sleep deprivation typically impacts non-REM sleep and REM sleep timing is controlled by REM sleep propensity accumulated during NREM sleep (Benington & Heller,

1994). The role of NREM sleep in circadian sleep regulation is investigated using a sleep deprivation protocol. Throughout the experiment, sleep pressure builds up and follows 24-h rhythms with an alertness peak during the afternoon and a sleepiness peak during the night, which has been correlated with SWS (Carskadon & Dement, 1977; Fröberg, 1977).

STRESS AND MOOD

Emotion and sleep have an intertwined relationship. Particularly REM sleep and its role in emotion modulation, as well as the effect of emotion on sleep structure and quality have been shown (Vandekerckhove & Wang, 2017). Daytime emotional stress has a twofold effect on sleep by influencing sleep physiology as well as dream contents (R. D. Cartwright, Kravitz, Eastman, & Wood, 1991). This is also clear when looking at the many sleep related symptoms of most affective disorders (Shaver et al., 1997). REM sleep disturbances have been related to an individual's daytime affective state (Hauri & Hawkins, 1971), in particular awakening thresholds, dream recall, and REM duration, density, and latency (Perlis & Nielsen, 1993). Finally the amount of REM sleep arousals attenuating REM sleep continuity increase as a function of daytime stress (Halász, Terzano, Parrino, & Bódizs, 2004). REM sleep alterations seem to be more prevalent than NREM sleep as a consequence of acute stress exposure in healthy individuals (Germain, Buysse, Ombao, Kupfer, & Hall, 2003). However, other studies have shown inconsistent results related to REM density and duration after acute stress exposure ((R. Cartwright, Luten, Young, Mercer, & Bears, 1998; Cui, Li, Suemaru, & Araki, 2008). Individuals with chronic stress or depression experience increases in REM density and duration and a decrease in latency are evident often in the first REM cycle (R. D. Cartwright et al., 1991; Germain, Buysse, & Nofzinger, 2008). These REM alterations can disrupt emotional and cognitive processing (Nofzinger et al., 1994). Overall there is more than enough evidence showing a tight bond between stress exposure and consequent REM sleep alterations.

As mentioned before, sleep and emotion have a delicate relationship in which the one affects the other and vice versa (Walker, 2009). Sleep quality as well as quantity both have their own way of influencing our well-being. As we know, sleep has a restorative function not only in relation to homeostatic functioning but also for emotion, stress and mood. Sleep deprivation makes us more sensitive to emotional stimuli and events, whereas a good night's sleep helps us tackle emotional challenges the next day (Bonnet & Arand, 2003). Increased irritability and complaints of emotional difficulties were reported after a sleep restriction paradigm (Dinges et al., 1997). Additionally, sleep restriction seemed to amplify negative experiences and blunt out positive ones (Zohar, Tzischinsky, Epstein, & Lavie, 2005). In an fMRI study using a sleep restriction paradigm, amygdala responsiveness and activity was increased for the sleep-deprivation group. Notably, a decrease in functional connectivity between the amygdala and the inhibitory and modulatory medial prefrontal cortex was found (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Sleep is proposed to play a facilitating role in processing and regulation of stress and negative affect (Vandekerckhove & Cluydts, 2010). As REM sleep is most affected by daytime stress, it is also the sleep stage that seems to modulate stress the most, particularly via long term memory (Wagner, Hallschmid, Rasch, & Born, 2006). In the memory section of the introduction, the role of REM sleep in memory formation and consolidation was discussed. Consequently, REM sleep plays a major role in the way we process, consolidate and deal with our emotional experiences. The role of sleep in emotion regulation has been mostly focused on REM sleep. Recently, Pace-Shott et al. reported a role for SWS as well. It seemed that SWS was associated with a greater habituation of emotional responses than REM sleep (Pace-Schott et al., 2013). Another study explored this role further (Hot et al., 2016). Using a paradigm of 4 groups watching a negative movie scene followed by a nap or a period of wakefulness combined with an emotional reappraisal strategy or not. Before and after the nap, emotional scales were computed using a questionnaire. The presence of SWS during the nap was monitored using

PSG. The nap and reappraisal combination group had the lowest negative emotion score afterwards. This results suggests that SWS allows an emotional regulation process when this process has been explicitly initiated before sleep. Even with relatively short period of SWS (20 min) has the potential to facilitate this process. Even though the evidence is scarce, it proposes that sleep-mediated emotion regulation may involve both REM and NREM sleep. The relationship between sleep and emotion can develop into a dysfunctional vicious cycle and can even become pathological. Even though there is plenty of behavioral evidence showing the importance of sleep quantity and quality for healthy emotional processing, the importance of sleep regularity in this role is more scarce.

In summary, it is important to understand that NREM with SWA and REM are both influenced by homeostasis, circadian and allostatic factors in their own way, suggesting different roles in healthy functioning (Le Bon, 2020). It would be interesting to investigate their regularity separately, keeping their differences in mind.

Mood and sleep regularity

As sleep is a key player in emotion regulation, it also a main modulator of mood. There have been numerous papers written showing the effects of poor sleep quality on mood. One study tracked college students on sleep quality and mood, (good: content, happy, peaceful or poor: stressed, anxious, frustrated or angry) and found that participants with overall good mood also had longer sleep duration (Moturu, Khayal, Aharony, Pan, & Pentland, 2011). Another tracked self-reported sleep quality and mood with regular sleepers and irregular sleepers using a questionnaire targeting daytime sleepiness, sleep length, fatigue, need of sleep and sleep index (reported sleep length related to requirements) together with questions targeting mood. Sleep length was unrelated to mood and fatigue issues. The need of sleep and sleep index did however result in a significant effect on mood and fatigue problems. This indicates that chronic sleep loss does affect mood and fatigue (Oginska & Pokorski, 2006). These papers already hint that not only quality, but also regularity seems to be key in feeling good (Sano et al., 2015). Sano et al. looked into this relationship specifically by tracking participants' sleep and Happy-Sad mood for approximately 30 days. Two wearables were used. First, on the one hand, a wearable wrist sensor (Q-sensor, Affectiva, USA) tracking movement and skin conductance to track exercise which has been shown to improve mood (Ströhle, 2009). On the other hand they wore an actigraphy monitor (activity-based monitoring) measuring activity and light exposure. Mood was surveyed using visual non-numeric scales (later scored as 0: Sad, 100: Happy) and several mood questionnaires. They aimed to see how accurately they could predict mood based on the previous five days of sleep parameters. The parameters included, among others, sleep duration and regularity. Sleep regularity and duration predicted mood with 65-80% accuracy. Overall, a regular sleep pattern and low variability seems to positively affect mood. Positive mood is linked to many health benefits (Fredrickson, 2000). Physiological and neuroendocrine effects of prolonged exposure to stress are known as allostatic load, which has been shown to affect sleep quality significantly (McEwen & Stellar, 1993). Chronic stress is associated with insomnia, sleep apnea and shorter sleep duration (Chen, Redline, Shields, Williams, & Williams, 2014). This again suggests that poor sleep quality and poor mood affect each other in an negative feedback loop. Mood might thus be used as an indicator for poor sleep quality and perhaps an irregular sleep pattern as well as the other way around.

Measuring Sleep Regularity

Sleep regularity can be assessed using different metrics. Fischer et al. discussed the different options in a paper including traditional metrics as well as metrics that were more recently developed (Fischer, Klerman, & Phillips, 2021). The traditional metrics included standard deviation (StDev), Interdaily Stability (IS), and Social Jet Lag (SJL) whereas the novel metrics included Composite Phase Deviation (CPD) and the Sleep Regularity Index (SRI). In the StDev, daily sleep features such as onset and offset, duration and midsleep can be investigated by comparing variables of a single night to the mean of all

nights. A lower value represents more regularity. IS compares the activity pattern of each day to the average across multiple days. It is calculated as the ratio of the variance within the same time interval each day and the overall variance. A higher value reflects more regularity in the activity patterns. SJL represents the mismatch in sleep timing between workdays and free days by looking at the midsleep. The midsleep on free days can be either earlier than on work days, which is reflected by a negative SJL value, or it can be later, reflected by a positive value.

The two more recent metrics are consecutive, which means that they incorporate the idea that regularity changes from day to day affect the circadian system and cause circadian misalignment due to phase resetting. Therefore the metrics look at consecutive time points, not averages across the entire study. CPD qualifies circadian disruption using a person's chronotype to estimate the optimal sleep timing. There are two components calculated in CPD. The mistiming component is calculated by comparing a person's chronotype to the midsleep timing on one day. The irregularity component is calculated by comparing a person's midsleep timing on one day to the timing on the previous day. These two components are used to calculate the CPD, which ultimately represent the distance between the two components plotted against each other and the origin. A lower value reflects more regular sleep. The origin represents perfectly regular sleep. CPD required one main sleep episode per day so it cannot account for naps and nocturnal awakenings.

Finally, the SRI (Phillips et al., 2017). This metric compares sleep and wake states across adjacent 24-hour periods. It assesses the probability that an individual is in the same state (awake vs. asleep) at any two time points 24 hours apart, thus calculating the percentage probability of having the same state (sleep vs. wake) at any two time points (e.g. 30-s epochs) 24-h apart, averaged across the study. The SRI is scaled to range from 0 (random) to 100 (perfectly regular) and is calculated using the following equation:

$$(1) \text{ SRI} = -100 + \frac{200}{M(N-1)} \sum_{j=1}^M \sum_{i=1}^{N-1} \delta(S_{i,j}, S_{i+1,j})$$

With M being the number of daily epochs, N is the number of days, $S_{i,j} = 1$ for wake and $S_{i,j} = 0$ for sleep with i being the specific day and j being the specific epoch in question. $\delta(S_{i,j}, S_{i+1,j}) = 1$ if $S_{i,j}$ and $S_{i+1,j}$ match and 0 if there is no match. This metric is designed so that individuals with the same midsleep standard deviation but vastly different sleep durations have the same SRI score. The SRI ranges from 0 to 100, even though the full theoretical range would be -100 to 100. Any values under 0 would be theoretically possible but extremely unlikely in practice. It would describe a situation where a person would be asleep for 24 hours and awake throughout the following 24 hours. The SRI doesn't assume anything about the structure of the sleep, whether the sleep is a nap or a main sleep episode. Out of all sleep regularity metrics, the SRI showcases the least dependence on the duration of the study. All other metrics showed changes in values when increasing study length. Because of the large study length of this project and the day-to-day measurements, the SRI is a good metric to use. The SRI metric is often actigraphy-based, that is, using some kind of activity tracker, together with an additional sleep diary. Actigraphy has long been an essential tool in sleep research and medicine and has been used to document sleep-wake patterns. It has been shown to be effective in identifying certain sleep disorders and has been proven valuable in documenting the effects of different interventions on sleep-wake patterns. Actigraphy-based SRI metric have been used to investigate the health implications of intra-individual sleep variability. In a 2021 paper, actigraphy was used to investigate its relationship to depression, stating that variability in sleep parameters such as wake time, bed time, and total sleep time were correlated with mental health (Fang, Forger, Frank, Sen, & Goldstein, 2021). In another study intra-individual sleep regularity variability was studied using the SRI based on actigraphy. A higher SRI did not directly affect mood, however SRI mediated the effects of total sleep time, the misalignment of sleep and circadian rhythm that both affected daily functioning and mood (Murray et al., 2019). Finally, the validity of the SRI metric was assessed and correlated with a risk for cardiovascular disease (Lunsford-Avery, Engelhard, Navar, & Kollins, 2018). Despite the advantages of actigraphy, it also comes with its

pitfalls (Sadeh & Acebo, 2002). Its validity has not been established for all scoring algorithms or devices, or for all clinical groups. Additionally, actigraphy is insufficient for diagnosis of sleep disorders in individuals with motor disorders or high motility during sleep like sleep apnea. Finally, the use of computer scoring algorithms without controlling for potential artifacts, like movement, electrode or sweat artifacts, can lead to inaccurate and misleading results.

The Quantified Self project

Polysomnography (PSG) is electroencephalography (EEG) specifically for sleep and is combined with electrooculography (EOG), electromyography (EMG), and any other potential extra measures. It can also be a great tool for assessing sleep regularity. In many studies PSG would not be a suitable approach as this method has its own disadvantages. For proper assessment, in any case, PSG has to be applied for multiple nights. In most sleep studies, participants are often tested a couple of nights in a row, at most. With sleep regularity specifically, research is needed on a much larger time-scale. This has been lacking as it is extremely difficult to find healthy human volunteers that will participate throughout multiple months. Therefore, the participation of highly motivated human individuals is very valuable in such a demanding research field. In the Quantified Self Project (QSP), data has been collected from a single human individual at the Sleep and Memory lab in Nijmegen throughout approximately 18 months (Idesis, 2020). This invaluable longitudinal sleep data opens the door to many research possibilities, including the investigation of sleep regularity. This big data project provided the longitudinal daily PSG data required for this study. PSG data will provide a lot more detail about sleep regularity as compared to only discriminating between either awake or asleep. In the QSP, not only polysomnography data was recorded. Many other variables were included such as data on mood, which was assessed throughout the course of the study.

Polysomnography

With PSG, different sleep stages and cycles can be assessed for regularity. Oscillatory components of EEG are used to uncover sleep cycles and stages. Oscillations with certain frequency bands are seen in different sleep stages (Armitage, 1995). In this study, the AASM sleep stage classification will be used (Iber, 2007). During wakefulness, alpha waves are dominantly present (8-13Hz). Once we move into sleep stage N1, which is drowsy and light NREM sleep, we see a dominance of mixed frequency waves (4-7Hz). Following is N2, light NREM sleep, where a decrease in frequency is seen in addition to short (1-2 sec) spike clusters of 11-16 Hz oscillations called spindles. In addition to spindles, K-complexes are present. This corresponds to a delta wave with a larger positive spike. In NREM N3 sleep, slow delta waves are seen (0.5-2Hz). This stage is also known as slow wave sleep (SWS). Finally, during REM sleep, in addition to muscle atonia and rapid eye movements we move back to the desynchronized 'wake-like' alpha waves. This is why REM sleep is also known as paradoxical sleep. While consciousness of content is high in REM sleep during dreaming, as well as during wakefulness, the level of arousal is very different among the two, with muscle atonia during REM (La Berge, 1980; Mahowald & Schenck, 1992). As mentioned before, the regularity of specifically REM sleep and NREM sleep might be insightful for healthy functioning. This is another reason why PSG might be a great tool for investigating sleep regularity. With the arrival of easy-to-use yet accurate sleep wearables, longitudinal measurements require the same amount of effort as a simple activity tracker wrist band. A new application of the SRI is possible, using EEG measurements enabling more accurate data on sleep, including wakefulness, NREM sleep, and REM sleep, making the index more detailed and insightful.

Methods

Participant

The subject of this study is a 29 year old male located in Nijmegen, the Netherlands. The subject is right-handed and healthy, meaning that he does not have any neuropsychiatric disorders prior or during the study. Written informed consent was obtained before the experiment and the project was approved by the local ethics committee, commission for human research (CMO) region Arnhem-Nijmegen 2014/288, v.2. In the Quantified Self Project, a large data set has been collected that enables a very broad spectrum of new longitudinal studies (Idesis, 2020). The data set contains sleep data that will be used to develop a new SRI index, and thus investigate longitudinal sleep regularity in a single human.

Polysomnography

During the QSP, weekly polysomnography data has been collected using the Somnoscreen Plus (SOMNOMedics GmbH, Randersacker, Germany), a portable 15-electrode PSG device that includes electromyography (EMG), electrooculography (EOG) and electrocardiography (ECG). The electrodes are placed according to the 10-20 system for scalp electrode placement. Reference electrodes were placed on the mastoids. The midline prefrontal electrode was used as the ground electrode. In addition to this, daily ZMax recordings were done. The ZMax is a wearable sleep headband that enables participants to easily apply EEG themselves at home. In order to avoid bias, the subject did not have any insight into the data throughout the data collection period. To minimize the time-of-day effects known to affect neuroimaging studies, PSG recordings were performed the same time each week (Shannon et al., 2012). Sleep stage analysis on the Somnoscreen data was done using the SpiSOP toolbox manually following the AASM manual (Iber, 2007). Each night's scoring was verified by a colleague at the Sleep lab. An algorithm was developed to automatically score each ZMax night, based on the scorings of the Somnoscreen data. Because the SRI is a metric that incorporates day-to-day sleep variation, the Somnoscreen data was solely used to develop the ZMax autoscoring. The daily ZMax data was ultimately used for the assessment of sleep regularity. After autoscoring the ZMax nights, recordings were checked on quality. As the ZMax is comprised of two electrodes and a reference, both electrodes were checked for good data quality. If any data was lost on either electrode, a night was excluded.

SRI

In order to explore the combination of the ZMax data and regularity assessment, a binary distinction between wake and sleep was made, just like the original actigraphy-based SRI. The output of the ZMax score is a column of numbers resembling the different sleep stages. Different numbers represent different sleep stages; wake (0), light NREM sleep 1 (1), light NREM sleep 2 (2), deep NREM sleep (3) and finally REM sleep (4). This is different from the numbers representing the sleep stages according to Rechtschaffen and Kales, in which 4 represents sleep stage 4, SWS (Rechtschaffen & Kales, 1968). In the AASM manual, the number 4 is not used and REM sleep is assigned the number 5 (Iber, 2007). A timestamp indicating the starting time of the recording was used to match the separate recordings in time. It was assumed that before the starting time, the subject was awake, as well as after the recording. Because not every recording has the exact same length, zero-padding was used, filling in the 24 hours surrounding the recording, enabling day-to-day comparison. The question the SRI poses is: what is the chance that the state assigned to epoch x in night x is the same state of epoch x in night y ? As seen in (1), the original SRI equation is as follows:

$$(1) \text{ SRI} = -100 + \frac{200}{M(N-1)} \sum_{j=1}^M \sum_{i=1}^{N-1} \delta(S_i, j, S_{i+1}, j)$$

With M being the number of daily epochs, N is the number of days, $S_{i,j} = 1$ for wake and $S_{i,j} = 0$ for sleep with i being the specific day and j being the specific epoch in question. $\delta(S_{i,j}, S_{i+1,j}) = 1$ if $S_{i,j}$ and $S_{i+1,j}$ match and 0 if there is no match. Note that these are two binary distinctions. The first is the binary distinction between wake and sleep and the second is the distinction between match and no match. The original SRI is scaled so that the individual who experienced the same state (wake or sleep) at exactly the same times each day scores 100 for that state, whereas an individual who sleeps and wakes at random scores 0. The SRI was originally a single value that gives an estimation of how regular sleep is in general. Because we are looking at longitudinal data on sleep regularity, it is interesting to see whether regularity changes in correlation with other biological factors. That was why the use of a sliding window was incorporated as it might be very helpful to see gradual changes in regularity. Instead of using all the data at once, day-to-day variation was calculated for 14 successive days. The next regularity value was calculated by shifting the sliding window one day further. This process was repeated which constructed a timeline reflecting the sleep regularity variation throughout the entire study. In contrast to the original SRI, that distinguished only asleep vs. awake, information is now available that provides the possibility to include information on multiple specific sleep stages. It is thus possible to increase the detail of the index by distinguishing not only between wake and sleep, but additionally between wake, NREM and REM sleep and even SWS and LS. Using the SRI formula, the latter binary distinction was made in the same manner, telling us whether two successive nights' epochs match in stage. The former however, can be changed so it tells us whether an epoch is any stage X or not stage X . We want to compare $S_{i,j}$ and $S_{i+1,j}$ for general sleep, REM, NREM and SWS and LS. For instance, if assessing REM-sleep, we would calculate the SRI by filling in the equation. If $S_{i,j}$ is REM, $S_{i,j} = 1$. If $S_{i,j}$ is not REM, $S_{i,j} = 0$. Then, following the original equation, $\delta(S_{i,j}, S_{i+1,j}) = 1$ if $S_{i,j}$ and $S_{i+1,j}$ match (both REM or neither REM) and 0 if there is no match. This can be done with any of the scored sleep stages.

The Script

An empty matrix was first created that had the size of 2880 epochs and X nights corresponding to 2880 30 second epochs that made up a full 24 hours. The nights were imported as the corresponding start times were read. The start times of the recordings were converted to epoch numbers starting from 12 pm and the corresponding recordings were inserted in the matrix at the right place. Because a night starts in one day and crosses over in the next, this matrix started at 12 pm and ended at 11:59 am so that the sleep recordings generally fell nicely in the middle of the 24 hour column. In some cases, the participant slept after noon. This part was then cut off and added to the next column. Now the nights were perfectly aligned in time. Missing nights were imputed with the most frequent measure across the entire dataset. Any missing start times were filled in by the median of all start times. During summer holiday, the participant did not record for 22 nights. 21 nights will not be imputed as this will affect the SRI values too much. The remaining night will as this might preserve any potential weekly patterns. As wake was indicated by the number 0, any nonzero number was simply replaced by 1, indicating sleep in general. Next, binary distinctions were made indicating each specific sleep stage, creating different matrices for each sleep stage; general sleep, REM, NREM in general and specifically SWS and LS. Next, the SRI was calculated for each 14 day window and followed a one day sliding window mapping out the entire course of the study for each matrix. The Sleep Regularity Index was calculated as originally described by Phillips et al. with code provided by Lunsford-Avery et al. (Lunsford-Avery et al., 2018; Phillips et al., 2017).

Mood assessment

In order to demonstrate the application of the sleep stage specific sleep regularity, a behavioral parameter is needed. Mood was assessed throughout the entirety of the study using a questionnaire with a single scale producing values ranging from 0 (happy) to 100 (sad). General mood was then inverted to a scale of 0 (sad) to 100 (happy). The same scale was used to assess a subcategory of mood, that is, 'feeling

tired'. These two behavioral parameters will be used to demonstrate applications of a sleep stage specific regularity assessment.

Results:

The SRI scores for general sleep, e.g. a binary distinction between wake and sleep were plotted. To see how REM sleep regularity and NREM sleep regularity affect the general sleep regularity, the three parameters were visualized in Figure 1.

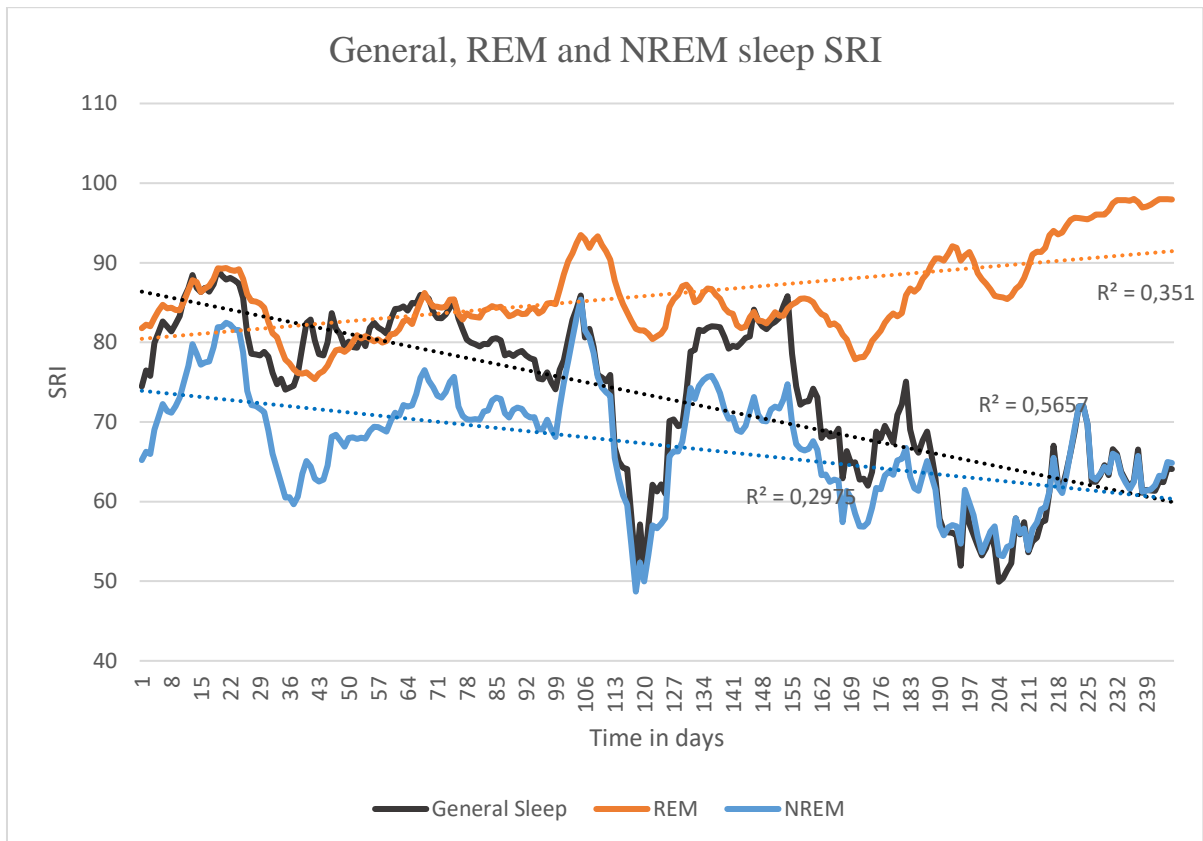


Figure 1: The SRI calculated per 14 day sliding window for general sleep, REM and NREM. As can be seen in figure 1, sleep regularity varies throughout the study with a large dip around day 118. General sleep regularity seems to follow a negative trajectory, which is reflected by NREM sleep as well. REM sleep seems to be largely stable throughout time. General sleep starts out as reflecting some kind of average but ends up following a very similar track to NREM sleep.

To further investigate NREM sleep regularity, a distinction was made between SWS and LS. As LS takes up most of NREM sleep, LS regularity should show a relatively similar trajectory as NREM sleep.

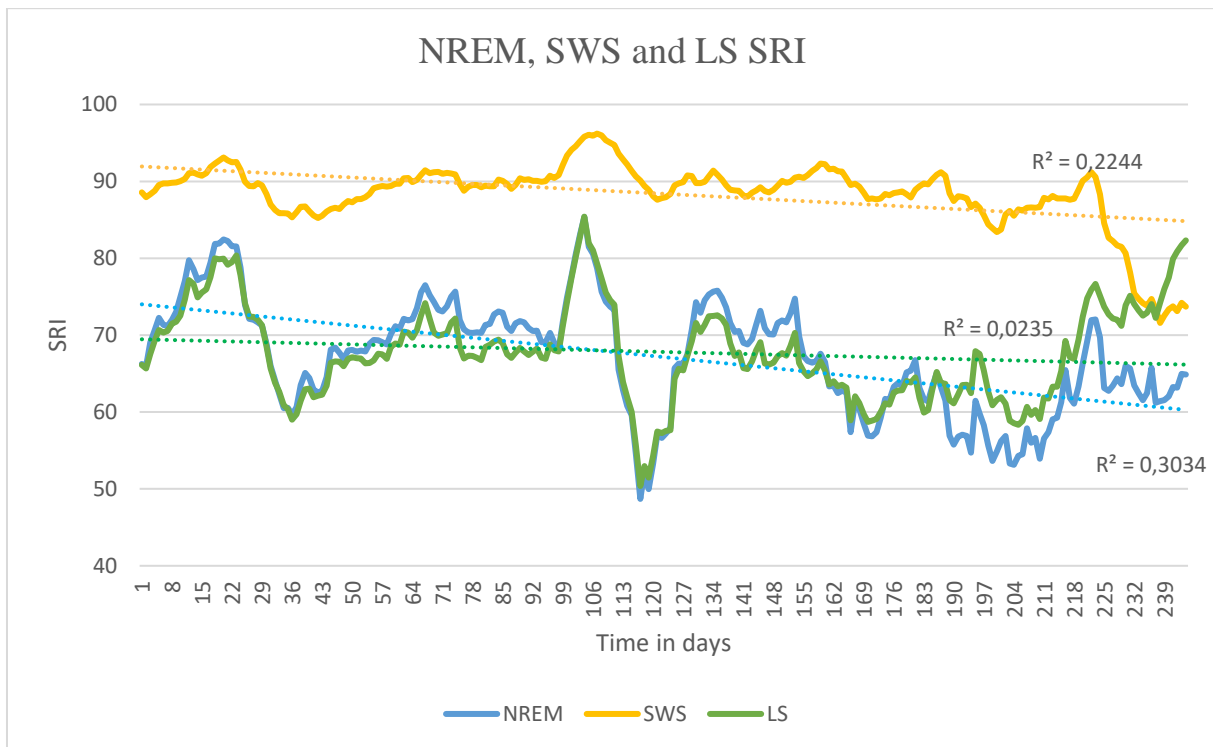


Figure 2: SWS, LS and NREM SRI. While NREM regularity in general seems to vary throughout time, SWS is very stable. Any variation in regularity could be accounted for by N1 and N2 sleep, as can be seen by the trajectory LS follows, which resembles NREM sleep regularity very closely. SWS shows a very high sleep regularity which, throughout the study, stays around 90 with a slight dip starting around day 221 that continues to the end.

The SRI can be used to assess different sides of human functioning. As discussed in the introduction, each sleep stage has its own function and poor sleep regularity has been associated with many health implications. This detailed sleep regularity index can thus be used to assess different aspects of healthy functioning related to a specific sleep stage. This dataset considers a healthy human being, there are thus no health implications to be assessed using this metric in combination with the available data. Mood however has been recorded throughout the study and can be used as an example parameter. In order to demonstrate the application of the detailed regularity assessment, REM sleep regularity and mood are investigated as REM sleep properties are closely related to mood and vice versa (Figure 3).

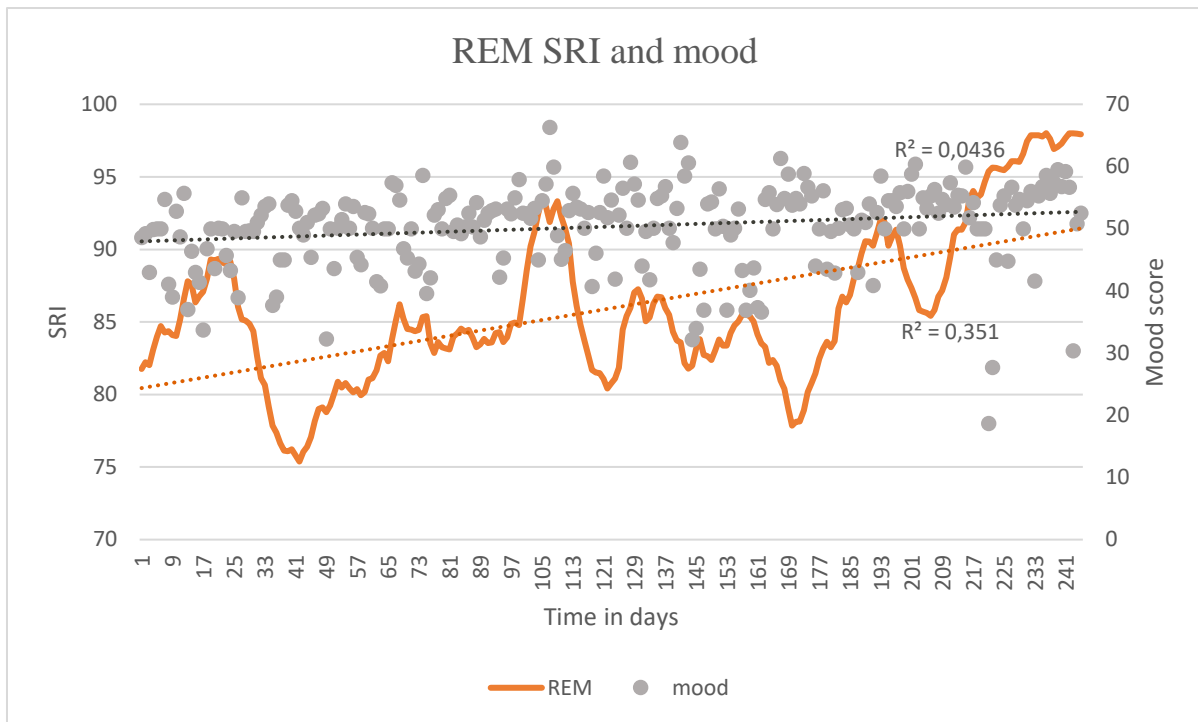


Figure 3: REM sleep SRI and general mood scores on a scale from 0 (sad) to 100 (happy). When we closely look at REM sleep regularity, a slight increase in regularity is seen throughout time with an R^2 of 0,351. Mood on the other hand does not increase and stays around a score of 50 throughout the study.

Next, a sub factor of mood is assessed, but this time with SWS, as sleepiness and tiredness have been associated with SWS. This is another demonstration of the detailed regularity assessment using a specific sleep stage and a parameter with which it has been correlated.

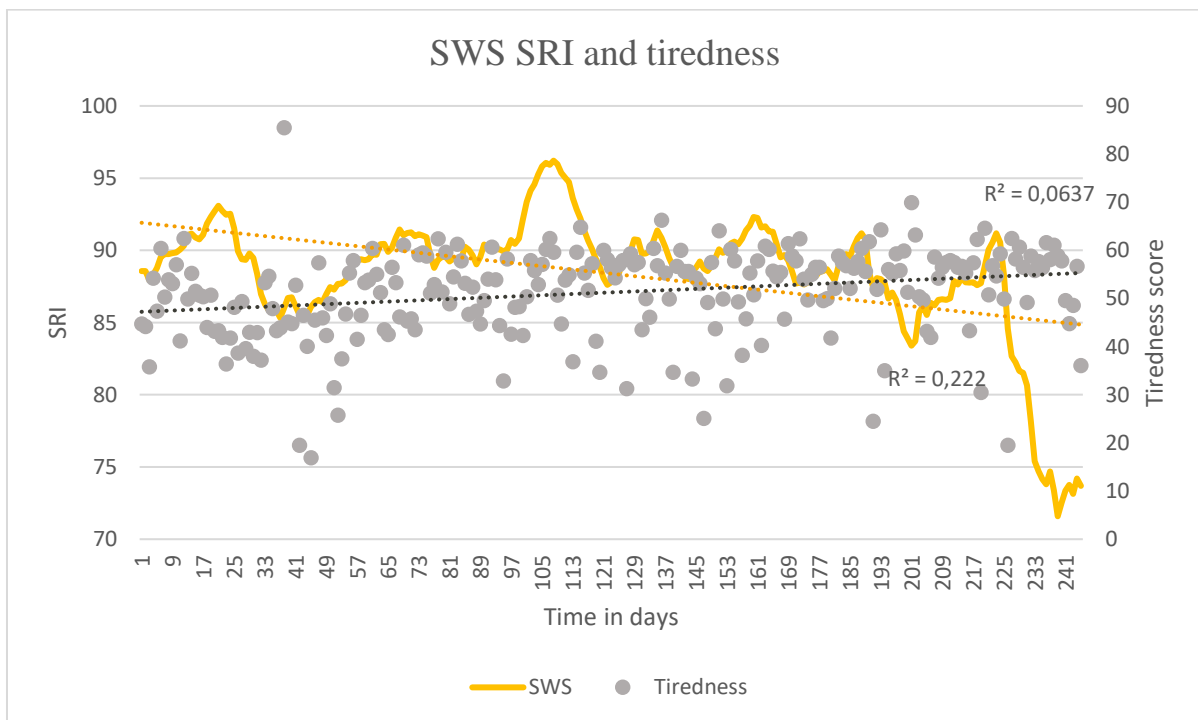


Figure 4: Slow wave sleep regularity throughout time together with a general tiredness score. SWS is highly regular and floats around an SRI score of 90, with a decrease starting at approximately day 217. Tiredness score is, like SWS regularity, very stable throughout time.

Discussion:

The Quantified Self Project assesses a single healthy human being. The stability in mood and tiredness is reflected by a generally high SRI score throughout the study. This study aimed at creating a method to investigate sleep regularity in a highly accurate and detailed manner, based on but different from existing measures. Sleep regularity needs further research as it has been shown to significantly affect sleep quality (Gooley, 2016). Actigraphy is a good tool and has been widely used to assess regularity yet has its limitations. It is not suitable for people with any kind of motor disorder, sleep apnea or any sleep disorder that might interfere with the signal actigraphy uses to assess sleep (Sadeh, Hauri, Kripke, & Lavie, 1995). The use of the ZMax or any other verified sleep wearable, overcomes this issue and increases the detail of the regularity assessment significantly. They can accurately distinguish sleep from wakefulness and can recognize specific sleep stages. This might be important as different sleep stages, namely REM sleep and NREM sleep are functionally very different. Studying their specific regularity might uncover correlates within a broad spectrum of healthy functions.

General sleep is made up of two states: REM and NREM sleep. The fact that general sleep and NREM sleep seem to follow the same negative trajectory throughout time might be explained by the relatively large amount of NREM sleep versus REM sleep. As is known, approximately 20-25% of sleep is comprised of REM sleep whereas 75-80% is NREM sleep (Deatherage, Roden, & Zouhary, 2009; McCarley, 2007). When looking more specifically into NREM sleep, the variability in regularity is almost the same as in LS. This can be explained by the fact that LS is made up more than half of the total sleep time with N1 (2-5%) and N2 (45-55%). SWS sleep fills another 13-23%. As can be seen in figure 2, the variability in N2 sleep shows the highest resemblance to general sleep regularity and this explains most of the variability in the general sleep regularity. The REM regularity stability is accompanied by stability in mood. This makes sense as REM sleep is the sleep stage most intertwined with the experience of stress and emotion (Vandekerckhove & Cluydts, 2010; Walker, 2009). As REM sleep and mood have an intricate relationship, a high REM sleep regularity might be beneficial for stable mood. Additionally, good mood, and especially long term stable mood might, in its turn be beneficial for REM sleep regularity. Any clear causal relationship cannot be determined from the data but a cycle in which the one benefits the other is highly likely. There is plenty of evidence suggesting mood and REM sleep are part of a cycle that can become vicious, even pathological. This cycle is very likely to also work in a positive manner, in which the mood might help stabilize REM sleep regularity in addition to other REM sleep parameters (Vandekerckhove & Wang, 2017) and REM sleep regularity might stabilize or even increase general mood. SWS regularity is very stable throughout the study, as is reflected by a very stable tiredness score. As SWS has been correlated to a feeling of sleepiness (Carskadon & Dement, 1977; Fröberg, 1977), it makes sense that these two factors coincide. The dip at the end of the SWS regularity trajectory is not reflected in any kind of increase in feeling tired. The feeling of tiredness or being rested might not solely be based on the regularity of SWS alone. NREM sleep regularity does not contain this dip and thus might lift the general regularity that might cause one to feel more rested and less tired. It could also be that feeling tired depends more on other SWS variables such as duration.

As mentioned in the Sleep Regularity part of this study, sleep regularity has been often investigated using measures such as total sleep time, midpoint of sleep, sleep onset, or morning awakening time, all targeting one single nighttime sleep episode (Manber et al., 1996; Medeiros et al., 2001). However, this poses problems for individuals who do not have regular nighttime sleep episodes. May it be because they have polyphasic sleep, shift work and therefore irregular sleep schedules or any other reason that prevents individuals from having a single nighttime sleep episode. Traditional polysomnography is not a perfect solution for this problem as applying PSG takes time and should be done by the researcher. However with the use of the ZMax, one could apply EEG by themselves when going to sleep, whether that be a single nighttime episode, or any other sleep episode. Actigraphy is also suitable for participants without a single sleep episode. Unfortunately, with actigraphy, the level of detail EEG enables cannot be

replicated. It is worth noting that while this method can overcome the aforementioned issue by applying EEG during every sleep episode, our participant only wore the ZMax during a single nighttime sleep episode. Any naps that occurred during the day were not recorded. While this is unfortunate for 24 hour regularity assessment, this dataset is a great source to start the development of a PSG based sleep regularity indexing method. Until now, it has not been possible to achieve such detail on a longitudinal scale.

The high level of detail this project has been able to achieve also comes with its challenges. One might differentiate between relative and absolute regularity. This study has measured absolute regularity. However, absolute regularity cannot handle well a case where someone's sleep architecture is perfectly regular, only shifted by some minutes here and there. This shifting sleep effect can be illustrated by the following scenario. Say someone has a weird sleep pattern of sleeping alternately one minute and then being awake for one minute. If sleep always starts exactly at the same time, this person would have a perfectly regular sleep as all epochs match. If sleep starts only one minute late, sleep would be considered super irregular, as not two epochs match. Biologically these two shouldn't be treated differently though, but because of the absolute regularity, they seem completely different. In the real world, this is less of an issue, as sleep stages tend to cluster together and thus slight movement of the entire sleep period will not mess too much with sleep regularity as most epochs will still match. Only the epochs at beginning and end of the sleep will differ. The problem with slightly shifted sleep will likely be worse for more fine-grained measures of sleep, i.e. when not a binary sleep/wake measure is used, but several sleep stages. For each of the sleep stages, the epochs at the beginning and end will not match, making it seem as though sleep is more irregular than it probably is. This study used a univariate measure for all sleep stages separately. This means that for general sleep, the shifting sleep effect will affect the absolute regularity in the same way it will for any other sleep stage. If the regularity would be calculated using the original values 0 (wake), 1 (N1), 2(N2), 3 (SWS) and 5 (REM), the shifting sleep effect would be much greater as with each sleep stage transition, the epochs at the beginning and end would not match. However by sticking to binary calculations on each sleep stage separately, this effect is minimized. With a univariate approach, the sleep shift effect is minimized, however a univariate approach is not able to map the total sleep structure regularity which might also be meaningful. A multivariate approach can ultimately be developed, incorporating all sleep stages, keeping intact the entire sleep structure, while at the same time overcoming the sleep shift problem.

Sleep regularity assessment with the use of EEG is a promising approach that has the potential to uncover specific health benefits related to the regularity of specific sleep stages, whereas assessment using actigraphy has only been able to distinguish wakefulness and sleep. As this field of sleep research is relatively new and literature is scarce, there is much more exploration needed. Not only research on the method itself, but also on the application of this method. Tackling sleep regularity problems and improving it are in the future, but how does one influence sleep regularity more than just going to bed in time each night and avoid sleep jetlag, when the problem involves the regularity of a specific sleep stage? Little is known about this except that a positive attitude towards an intervention developed for increasing sleep regularity is correlated with increased sleep regularity (Windred, Stone, McGlashan, Cain, & Phillips, 2021). Unfortunately the interventions are what's often still missing. More research on the theory, the method as well as the interventions will help to continue the investigation on sleep regularity.

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