

Anna Zoé Wick

The power of reactivations of memory cues, concepts of pre-sleep appraisals, and emotions during sleep



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Anna Zoé Wick  <https://orcid.org/0009-0003-7364-7243>

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The power of reactivations of memory cues, concepts of pre-sleep appraisals, and emotions during sleep

Kumulative Dissertation zur Erlangung der Doktorwürde
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Von

Anna Zoé Wick

Basel, Schweiz

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von Professor Björn Rasch (1. Gutachter), Associate
Professorin Kira Vibe Jespersen (2. Gutachterin) und Dr.
Thomas Schreiner (3. Gutachter)

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Prof. Dr. Dominik Schöbi, Dekan

Thesis examination committee:

Prof. Dr. Björn RASCH, University of Fribourg, examiner

Assoc. Prof. Dr. Kira VIBE JESPERSEN, University of Aarhus, examiner

Dr. Thomas SCHREINER, Ludwig-Maximilians-University, examiner

Abstract

Sleep is important for processing memories and emotions. It is widely assumed that during sleep, particularly during slow-wave sleep (SWS), newly acquired memory traces are spontaneously reactivated, thereby supporting their consolidation and stabilization. Beyond memory traces, the Memories-of-Sleep (MemoSleep-) Hypothesis suggests that cognitive concepts are also reactivated during sleep. The repeated reactivations of these concepts potentially influence sleep quality by either impairing or improving sleep, depending on the particular content of these concepts. However, it remains unclear whether memory reactivations occur primarily during SWS or whether the non-rapid eye movement (NREM) sleep stage N2 is also involved. Additionally, the exact nature of sleep disturbances induced by unfamiliar environments, particularly over non-consecutive nights, has not yet been fully characterized and explained by the MemoSleep-Hypothesis. Finally, the influence of emotions on sleep within the context of the MemoSleep-Hypothesis remains to be clarified.

This dissertation addresses these research gaps through three independent sleep studies. The first study investigated the contribution of memory reactivation during NREM sleep stage N2 compared to SWS. However, no significant difference was found between words that were externally reactivated during N2 and those reactivated during SWS. Moreover, there was no overall memory benefit from targeted memory reactivation (TMR) during sleep. The second study examined sleep disturbances during the first night in an unfamiliar environment, known as the First-Night Effect (FNE), as an example of the reactivation of stressful mental concepts during sleep. The results show that an FNE exists also in non-consecutive nights and even occurs in familiar environments. However, prior familiarization with the recording equipment was found to attenuate the FNE. The third study explored, for the first time, whether musical chords associated

with varying emotional ratings can elicit different brain responses during sleep. The results confirmed that the sleeping brain is capable of differentially processing specific musical chords.

The results of this dissertation challenge the specific role of SWS in memory reactivation during sleep. Additionally, they demonstrate that unfamiliar sleep environments generally impact sleep quality, however, a habituation occurs even over non-consecutive nights. Finally, these findings pave the way for novel approaches to using emotion-associated musical stimuli to influence activated mental concepts during sleep, providing new knowledge and a foundation for further refinements and future research directions within the framework of the MemoSleep-Hypothesis.

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List of Abbreviations

APA	American Psychiatric Association
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ERP	Event-Related Potential
FNE	First Night Effect
Hz	Hertz
IAA	Interhemispheric Asymmetric Activity
MemoSleep (-Hypothesis)	Memories of Sleep Hypothesis
N1	Non-Rapid Eye Movement Sleep Stage 1
N2	Non-Rapid Eye Movement Sleep Stage 2
N3	Non-Rapid Eye Movement Sleep Stage 3
NREM	Non-Rapid Eye Movement
REM	Rapid Eye Movement
SOL	Sleep Onset Latency
SOs	Slow Oscillations
SWA	Slow Wave Activity
SWR	Sharp Wave Ripples
SWS	Slow Wave Sleep
TMR	Targeted Memory Reactivation
TST	Total Sleep Time
WASO	Wake After Sleep Onset
μV	Microvolt

List of included studies

The cumulative dissertation includes the following three studies:

Study 1

Wick, A., & Rasch, B. (2023). Targeted memory reactivation during slow-wave sleep vs. sleep stage N2: no significant differences in a vocabulary task. *Learning & Memory*, 30(9), 192-200. <https://doi.org/10.1101/lm.053683.122>

Study 2

Wick, A. Z., Combertaldi, S. L., & Rasch, B. (2024). The First-Night Effect of sleep occurs over non-consecutive nights in unfamiliar and familiar environments. *SLEEP*, 47(10). <https://doi.org/10.1093/sleep/zsae179>

Study 3

Wick A. Z., & Rasch, B. (2025). *Musical harmony is processed during sleep*. [Unpublished manuscript]. Department of Psychology, University of Fribourg.

1 Introduction

Sleep is fundamentally important for life and health (Lesku & Schmidt, 2022; Vorster et al., 2024) and sleep problems carry serious consequences for cognitive functions, physical health, and well-being (Grandner, 2022). According to the Federal Statistical Office (BFS, 2024), the prevalence of sleep problems in Switzerland has increased by five percent between 1997 and 2022. One third of the Swiss population is affected by sleep problems and is therefore experiencing or at risk of all serious consequences, which result in a loss of healthy years and life quality at the individual level, as well as high economic costs and wider negative implications for the population as a whole (Daley et al., 2009; Hillman & Lack, 2013; Shneerson, 2009). It is therefore in the interest of all parties (e.g., patients, government, economy, etc.) to ensure optimal sleep quality. For these reasons, it is essential to investigate and further understand the relevant processes during sleep, thereby establishing a solid foundation for the development of sleep promoting, risk and side-effect-free interventions.

Although sleep research has produced a large number of studies and a solid body of knowledge over the last century, there remain significant gaps that are under-researched. Therefore, exact mechanisms are not fully understood. This applies to memory research, for example, but also to the precise mechanisms by which cognitions and emotions influence sleep architecture and its quality.

Memory is essential for human cognition, enabling the organism to adapt strategically to changing external environmental conditions (Rasch & Born, 2013). This crucial role of memory formation and consolidation underscores the necessity for a detailed understanding of these processes. The process of memory consolidation is dependent on the interaction of various neural mechanisms that facilitate endogenous reactivations of novel or labile memory traces within the hippocampus (Diekelmann & Born, 2010). A considerable body of research has demonstrated that

these neural mechanisms are located within slow-wave sleep (SWS; see Rasch & Born, 2013). However, although SWS is indispensable for this process, recent analyses indicate that this sleep stage may not be the sole determinant of memory consolidation (Cordi & Rasch, 2021). Especially, the potential contribution of the lighter sleep stage N2 remains to be further elucidated.

The Memory of sleep (MemoSleep-) Hypothesis, proposed by Rasch (2015) posits that not only declarative memories are reactivated endogenously, but also cognitions, formed prior to sleep and thereby influencing subjective and objective sleep quality. Cognitions activate a corresponding semantic representation along with a sensorimotor representation, which becomes subsequently embodied and repeatedly reactivated during the following sleep thereby affecting subjective and objective sleep quality. Cognitions can also be influenced by the appraisal of a situation (Roseman & Smith, 2001). In light of this hypothesis, the question arises of whether appraisals of a novel sleep environment and sleep situation are also embodied and reactivated, which could possibly lead to a First-Night Effect (FNE). The FNE is an intensively studied phenomenon in sleep research, which describes that sleep on the first night in a new place is often characterized by poor sleep quality (Ding et al., 2022). Following this line, it would also be of interest to explore whether this hypothesis and the proposed endogenous reactivations of thoughts affecting sleep can be extended to encompass emotions that are activated by a strong emotion inducer, music (Koelsch, 2014), shortly before sleep.

After identifying three current research gaps within this field of reactivations, the goal of this dissertation seeks to bridge these gaps with three included research studies, thus contributing important insights and further points of consideration to the current state of sleep research.

The following introduction provides a theoretical background including a brief definition of sleep (Chapter 1.1), its structural components and its regulation. Subsequently, the relevance of sleep for memory consolidation will be elaborated (Chapter 1.2), followed by an examination of

two memory consolidation hypotheses and the presentation of the targeted memory reactivation technique. These chapters will lay the foundation to introduce the MemoSleep-Hypothesis (Chapter 1.3). In context of this hypothesis, the necessity to examine the FNE on non-consecutive nights in unfamiliar and familiar environments will then be presented. Furthermore, the question of whether the MemoSleep-Hypothesis can be extended to the reactivation of emotions triggered by music will be investigated. The final chapter of the introduction outlines the central research questions that emerged from the background of this dissertation (Chapter 1.4). These research questions were investigated by three studies (Chapters 2.1, 2.2, and 2.3). In the end, an overall discussion will be provided (Chapter 3).

1.1 Sleep

Sleep is a natural, recurring and reversible modification of consciousness (Tononi et al., 2024). During this state of reduced awareness, the ability to receive and react to external stimuli is diminished (Chokroverty, 2010; Rasch & Born, 2013). The exact function of sleep is still a matter of debate (Krueger et al., 2016). Still, the existing body of theories suggests that sleep is adaptive and has a protective, restorative, energy conservation, and thermoregulating function (Assefa et al., 2021; Chokroverty, 2003; Rattenborg et al., 2017). Moreover, it is an actively regulating process and serves several brain functions such as memory consolidation. In addition, it is essential for the physiological, mental, and social health (Hobson, 2005; Vorster et al., 2024).

Sleep is composed of different sleep stages which are defined by distinct patterns of electrical brain activity, varying in oscillatory frequencies (in Hertz [Hz]) and amplitudes (in microvolts [μ V]) as well as different muscle tones and eye activities (Rechtschaffen & Kales, 1968). These physiological changes of sleep stages can be measured using different components of a polysomnography including the electroencephalogram (EEG), electromyogram (EMG), and

electrooculogram (EOG; Iber et al., 2007). During sleep, the different sleep stages alternate in repetitive cycles of approximately 90-minutes (Carskadon & Dement, 2011), resulting in a typical sleep architecture that can be illustrated using a hypnogram (see Figure 1). This particular sleep architecture with the characteristic features of the different sleep stages will be further described in the following section.

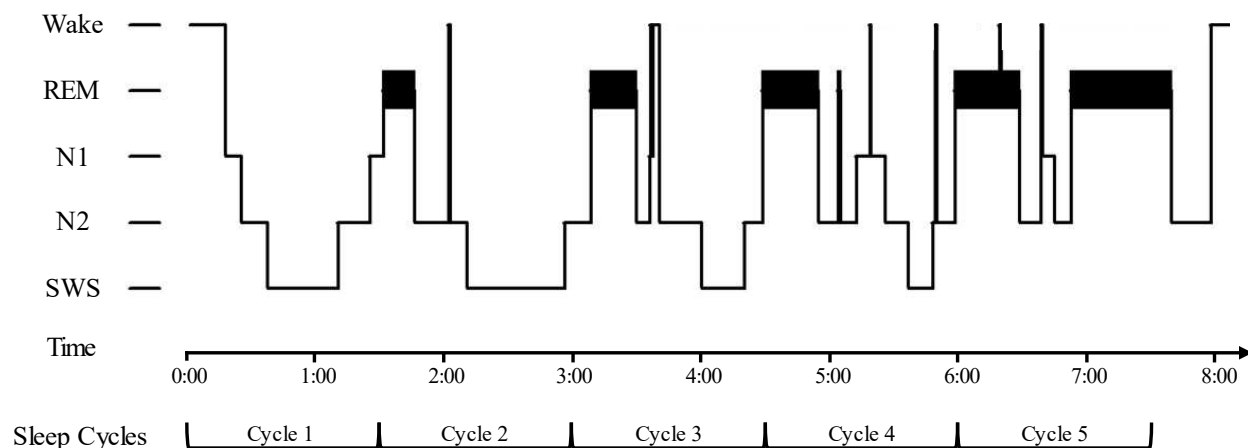


Figure 1. Hypnogram of a nocturnal sleep period of a healthy young adult. A hypnogram is a visual representation of the sleep architecture and shows the sequence and distribution of all sleep stages: Non-Rapid Eye Movement (NREM), stages N1, N2 and N3 (SWS), and Rapid Eye Movement (REM), as well as the time awake after sleep onset. The x-axis represents the time spent in bed, while the y-axis shows the different sleep stages. After a sleep onset latency, sleep is characterized by a repetitive cyclical alternation between NREM sleep stages and REM sleep. Noteworthy, SWS is predominant in the first half of the night, whereas REM sleep is predominant in the second half of the night (Carskadon & Dement, 2011; Rasch & Born, 2013). The 90-minutes sleep cycles are visualized with brackets.

1.1.1 Sleep architecture

The transition time from wakefulness to sleep also known as sleep onset latency (SOL) takes despite fluctuations no longer than 30 minutes (Pollmächer & Lauer, 1992). When asleep, sleep is characterized by a cyclic change between two sleep phases: Rapid Eye Movement (REM)

sleep and Non-Rapid Eye Movement (NREM) sleep. NREM sleep is further subdivided in N1, N2, and N3 (Iber et al., 2007). Usually, sleep is entered with sleep stage N1 (Deatherage et al., 2009). In this stage the eyes roll slowly, the muscle tone decreases, and the occipital 8–12 Hz alpha waves that predominated in the relaxed waking state are slowly replaced by lower frequency 4–6 Hz theta waves (Kumar, 2008; Rama et al., 2006; Rasch & Born, 2013). The deeper N2 stage is reached when sleep spindles and K-complexes appear in the dominant theta waves and the eyes hardly move (Chokroverty, 2003; Hirshkowitz, 2004; Iber et al., 2007). Sleep spindles last from 0.5 to 2 seconds and are characterized by low-amplitude and a high-frequency of 12–14 Hz, whereas K-complexes are biphasic, high-amplitude waves starting with a steep negative deflection immediately followed by a positive peak lasting longer than 0.5 seconds (Purcell et al., 2017; Rechtschaffen & Kales, 1968). Moreover, isolated high-amplitude delta waves also known as slow waves with a frequency of 0.5–4.5 Hz and amplitude of $> 75 \mu\text{V}$ can already be detected in N2. However, as they are the prominent feature of N3, they become particularly dominant when falling into this deep sleep stage, also called slow-wave sleep (SWS; Carskadon & Dement, 2011). The slow oscillating delta waves can be especially found in the frontal brain areas. In this deep sleep stage, there is little eye or body movement (Iber et al., 2007).

REM sleep is characterized by rapid eye movements and muscle atonia. This sleep stage is mostly dominated by a mixture of low-amplitude, high-frequency beta waves (15–25 Hz), slow alpha waves, and waves within the theta range (Chokroverty, 2003).

In total, NREM sleep accounts for approximately 75% to 80 % of total sleep time (TST; Carskadon & Dement, 2011), with SWS being particularly intense and dominant in the first half of sleep and decreasing with sleep duration (Rasch & Born, 2013), whereas REM sleep accounts for approximately 20% to 25% of total sleep time (Chokroverty, 2010). The frequency and duration of REM sleep increases toward the end of the sleep (Rasch & Born, 2013). Less than 5% of the sleep

period is spent awake, in form of short intermittent periods of wakefulness after sleep onset (WASO; Carskadon & Dement, 2011). The composition of sleep, in terms of its sleep stages and duration, varies across the lifespan (Chokroverty, 2010). For healthy young adults, who exclusively participated within the studies included in this dissertation, the recommended duration of TST is seven to nine hours per night (Hirshkowitz et al., 2015).

1.1.2 Sleep regulation

An explanation on how the alternation between sleep and wakefulness is regulated can be found in Borbély's (1982) two-process model of sleep regulation (see Figure 2). This model postulates that the alternating change of sleep and wakefulness is driven by the interplay of a circadian process C and a homeostatic, sleep dependent Process S, which are both separately regulated. The circadian process C refers to a repetitive dynamic within the organism, with a duration of approximately 24 hours scheduling internal life processes e.g., body temperature and the release of the hormone Cortisol (Czeisler & Gooley, 2007). Within these 24 hours, process C fluctuates in a sinusoidal pattern. The controlling pacemaker for this process is located within the thalamus, more precisely, within the supra chiasmatic nucleus (Borbély, 2022; Schmidt et al., 2020). Despite its limited flexibility it is harmonized with external factors such as light (Aschoff, 1965; Czeisler & Gooley, 2007; Lavie, 2001).

In contrast to process C, the homeostatic process S refers to the individual's sleep pressure which increases by the time of wakefulness and decreases during sleep and is lowest after nighttime sleep (Borbély & Achermann, 1992). Sleep pressure is positively correlated to the amount of slow wave activity (SWA; 0.5–4.5 Hz) which indicates the intensity of NREM sleep (Achermann & Borbély, 2003).

The interaction and emerging gaps between these two processes, determine the optimal time for sleep. The lower level of process C and the elevated level of process S during the evening, particularly promote sleep during the night (Borbély, 1982).

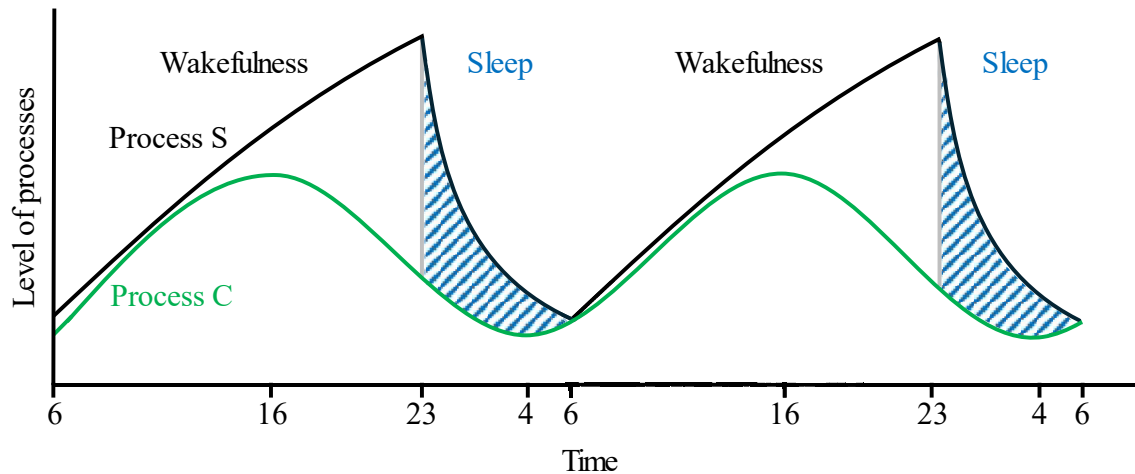


Figure 2. The two-process model of sleep homeostasis. According to Borbély's (1982) model, there are two processes that underlie changes in sleep and wakefulness. Process C (green line; plotted as a negative function) and process S (black line). Process C represents the circadian process and fluctuates during the day. Process S represents the individual sleep pressure, which accumulates during the day and reaches its maximum before sleep onset at around 23:00. Process S then decreases with sleep and is at a minimum during sleep offset. Process S is associated with the amount of slow-wave sleep. This model promotes sleep especially at night. The x-axis represents the time of day, while the y-axis shows the level of processes C and S (adapted from Borbély, 1982).

1.2 Sleep-associated memory consolidation

During sleep, brain activity serves multiple processes and reorganizations, including the process of memory consolidation (Hobson, 2005; Klinzing et al., 2019). Since memory consolidation is important to understand the purpose of this dissertation, the following chapter is dedicated to this topic, providing a broad overview of declarative memory and a theoretical basis for why sleep is so important for this process. This is done by introducing two prominent

hypotheses and presenting supporting evidence from studies. However, a view is also presented that challenges the indispensable and unique role of the SWS in declarative memory consolidation. Finally, the technique of Targeted Memory Reactivation (TMR) is introduced, and a first concrete research gap is identified.

1.2.1 Declarative memory consolidation during sleep

Long-term memory can be subdivided into two principal categories, declarative and non-declarative memories (Squire, 1992). Since this dissertation focuses explicitly on declarative memory, the subsequent sections are specifically about this particular memory category. Declarative memories include the conscious recollection of explicit, verbalizable episodic events and semantic facts (Ackermann & Rasch, 2014; Squire & Zola, 1996). The formation of these memories requires the hippocampus during acquisition. Then, these memories are stored in the medial temporal lobe and neocortex (Squire & Zola, 1996; Squire & Zola-Morgan, 1991; Tulving, 1984). In order to store these newly encoded or labile memory traces in systematic long-term memory networks, the process of memory consolidation is important. This process is characterized by the stabilization, reinforcement or transformation of memories within the brain (Born et al., 2006; Diekelmann & Born, 2010; Eichenbaum, 1999) and mainly manifested during sleep, particularly SWS (Gais & Born, 2004; Maquet, 2001). This has been confirmed by several studies using half-night paradigms, where participants slept only one half of the night after learning declarative material (Plihal & Born, 1999). Results have consistently shown that sleep during the first half of the night, which is dominated by SWS, enhances declarative memory performance compared to the performance after sleep only in the second half of the night, which is dominated by REM sleep (Plihal & Born, 1997; Yaroush et al., 1971), even when controlling for possible confounding circadian effects (Barrett & Ekstrand, 1972).

Why particularly SWS is important for declarative memory consolidation, can be explained by two prominent hypotheses: the active system consolidation hypothesis (Diekelmann & Born, 2010; Rasch & Born, 2013) and the synaptic homeostasis hypothesis (Tononi & Cirelli, 2003). Both hypotheses agree on the critical role of SWS in memory consolidation but diverge in the assumed mechanisms underlying this process, which will be described in the following.

The active system consolidation hypothesis (Figure 3) is based on the two-stage memory system (Marr, 1971; McClelland et al., 1995) and suggests that memory consolidation is an active process, assuming that the newly encoded information is stored within the hippocampus which serves as a temporal store. Then, these memory traces are actively transferred, transformed, and embedded into pre-existent long-term memory networks located in the neocortex and linked to prior knowledge (Diekelmann & Born, 2010). This transfer occurs actively during sleep due to endogenous spontaneous reactivations of the memory traces within the hippocampus (Born & Wilhelm, 2012). These endogenous reactivations arise from an interplay between slow oscillations (SOs) up states (0.5-1 Hz) localizable within the neocortex, thalamo-cortical spindles (12-15 Hz) within the thalamus, and sharp wave ripples (SWR; approx. 80-160 Hz) in the hippocampus (Buzsáki, 2015; Mölle & Born, 2011; Rasch & Born, 2013). In this interplay, SO up states serve as a top-down control and trigger the generation of thalamo-cortical sleep spindles, which in turn act as catalysts for the generation of endogenous reactivation through SWR events within the hippocampus (Born & Wilhelm, 2012; Schreiner et al., 2021). This dialogue is visualized in Figure 3b.

Evidence of these spontaneous memory reactivations by SWR has been most consistently found during SWS in rodents and humans (O'Neill et al., 2010; Wilson & McNaughton, 1994). Moreover, a recent study in humans found supporting evidence that endogenous reactivations are closely timed with the appearance of the SO-spindle coupling (Schreiner et al., 2021).

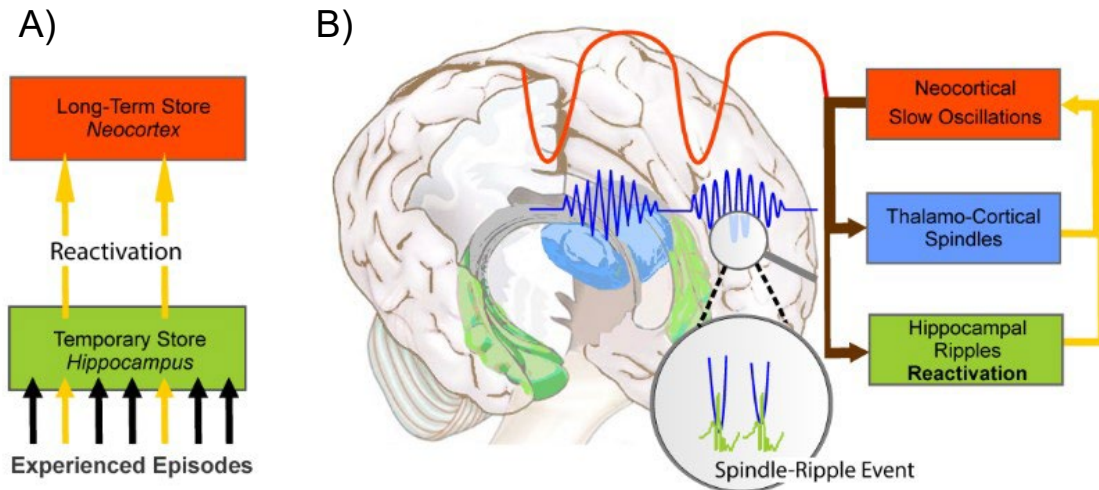


Figure 3. The active system consolidation hypothesis. A) According to this hypothesis, newly declarative information is initially stored in the hippocampus, the temporary memory store. It is then transferred to the neocortex, the long-term memory store, where memory representations are redistributed and integrated into the pre-existing long-term memory system. This particular transfer is dependent upon repeated reactivations. B) Detailed illustration of the precisely timed neural dialogue that facilitates the transfer of memory representations from the hippocampus to the neocortex. The active system consolidation hypothesis posits that the transfer from the hippocampus to the neocortex is under the top-down control of neocortical slow oscillations (SOs). The depolarizing up-phases of SOs (red) synchronously drive the generation of thalamo-cortical spindles (blue) and nested hippocampal ripples (blue), resulting in spindle-ripple events accompanying repeated memory reactivations within the hippocampus. The coordination of these events facilitates the transfer of the memory representation from the hippocampus to the neocortex, where the memory is integrated into long-term networks. Adapted from Born & Wilhelm (2012).

In contrast to the first hypothesis, the second hypothesis, the synaptic homeostasis hypothesis (Figure 4) proposed by Tononi & Cirelli (2003), focuses on a different mechanism. It states that sleep plays a pivotal role in the maintenance of cellular homeostasis and the regulation of synaptic strength and thereby indirectly promoting memory consolidation (Cirelli & Tononi, 2022). The process of acquiring new information during wakefulness, implies that synaptic connections undergo potentiation and strengthening, which results in plastic cortical changes (Tononi & Cirelli, 2003).

The synaptic potentiations result in an unequal distribution between synaptic strengthening and weakening, which requires energy and space, and reach a saturation point (Tononi & Cirelli, 2006). During sleep, particularly SWS, the equilibrium of neural circuits is promoted, whereby irrelevant poorly strengthened connections are further weakened, and essential synaptic connections are further reinforced. This leads to an enhancement of the neural signal-to-noise ratio, which facilitates the integration of important memories into pre-existing memory networks (Tononi & Cirelli, 2003; Tononi & Cirelli, 2014). Furthermore, this synaptic downscaling process, replenishes energy, gives space free, and contributes beneficially to memory consolidation and performance after sleep (Cirelli & Tononi, 2022).

This hypothesis is visualized in Figure 4 and also underscores the significance of SWS, particularly SOs (Tononi & Cirelli, 2006). As both hypotheses are based on different mechanisms, they are not diametrically opposed but can be considered concurrently (Rasch & Born, 2013).

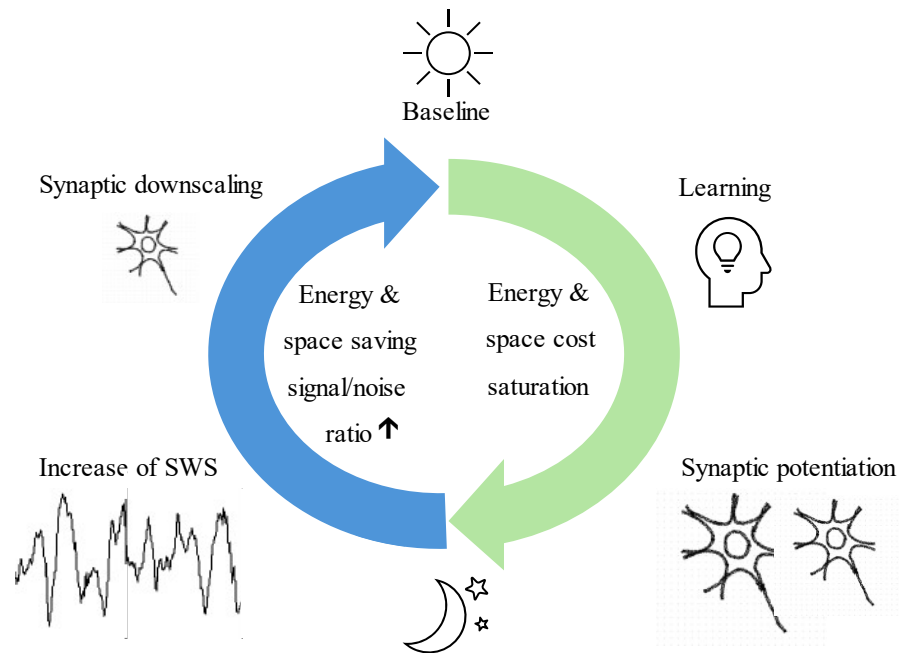


Figure 4. The synaptic homeostasis hypothesis. This hypothesis posits that sleep plays a role in maintaining synaptic balance within the brain, particularly SWS. During wakefulness (green arrow), new information is acquired, which is strengthened and stored through the process of long-term potentiation of synaptic connections. The potentiation of synaptic strength is associated with energy and space requirements and leads to a saturation of learning capacity over time. Then, during sleep (blue arrow), particularly SWS, the brain downscales and weakens synaptic connections made during the day. This serves to restore synaptic balance and increase the overall efficiency. The most important and strongest synaptic connections are selectively preserved, while less important connections are weakened. Adapted from Tononi & Cirelli (2006).

In alignment with these hypotheses and scientific evidence, it appears that SWS represent the primary sleep stage in which declarative memory consolidation occurs. However, an increasing number of recent replication failures of groundbreaking original studies support evidence that the distinctive function of SWS may be systematically overestimated in the context of the memory consolidation and may be less significant than previously assumed (Cordi & Rasch, 2021). Only few researchers consulted systematically the question whether the lighter NREM sleep stage N2

also plays a role in memory consolidation (Lahl et al., 2008; Ruch et al., 2012) since the important features of SOs, sleep spindles, and the coupling between these two features are still present in N2, albeit to a lower amount. These few studies unambiguously show that memory consolidation takes place during N2 too (Lahl et al., 2008; Ruch et al., 2012). To understand why this sleep stage offers also solid conditions for memory consolidation, it is necessary to first introduce a special technique. This technique aims to manipulate and helps further investigate the memory consolidation during sleep also permitting an examination into whether N2 is a contributing sleep stage within the process of declarative memory consolidation.

1.2.2 Targeted memory reactivation

Noteworthy, the memory consolidation process is selective, enhancing explicitly encoded and relevant memories in particular (Diekelmann & Born, 2010). Although, the accumulated evidences are quite weak (Cordi & Rasch, 2021). However, despite this weak evidence, it is of interest to manipulate the salience of a memory trace in order to increase or decrease the likelihood of its consolidation.

Over the past decades, several researchers have shown that the process of consolidation can indeed be externally manipulated by presenting memory cues during sleep which were associated with previously learned material (Hu et al., 2020). This technique takes the advantage of the fact that the brain still perceives stimuli at least on a reduced level (Tononi et al., 2024). Successfully used memory cues are for example words, odors, or tones (Hu et al., 2020). Thereby, reactivations of memory traces are specifically enhanced, and the process of memory consolidation can be further examined (Carbone & Diekelmann, 2024; Oudiette & Paller, 2013).

This prominent technique is known as Targeted Memory Reactivation (TMR) and has been widely used in sleep research (see Hu et al., 2020). Its advantages lay in the direct manipulation of the priority of a specific memory trace to be actively reactivated. This may lead to a higher probability of the integration into long-term networks which is a core assumption of the active system hypothesis (Diekelmann et al., 2009; Lewis & Bendor, 2019). Further, the synaptic downscaling hypothesis specifically argues that TMR-cues further act as protectors for the specific synaptic connections against downscaling, promote gist extraction and integration, while non-reactivated, irrelevant connections are further depressed and weakened (Tononi & Cirelli, 2014). Still, it should be mentioned that researchers point out that it is unclear whether exogenous reactivations lead to qualitatively similar or different neural patterns compared to spontaneous endogenous reactivations (Born & Wilhelm, 2012; Hu et al., 2020).

In 2024, Carbone and Diekelmann synthesized the current state of TMR research results and reviewed that TMR has been successfully applied to enhance procedural, declarative, and emotional memory performances after sleep, providing robust findings (Cordi & Rasch, 2021). Moreover, studies have also been conducted which show that TMR can promote forgetting (Carbone & Diekelmann, 2024). Hu et al. (2020) summarized 91 TMR-studies in a meta-analysis. The authors discovered that TMR significantly impacts the consolidation of memory, with small to medium effect sizes, and declarative memory in particular, with small effects (Hedges' $g = .23$).

1.2.3 Declarative TMR, SWS and N2 sleep

In declarative memory studies, protocols describe the use of TMR as soon as signs of stable NREM sleep appear. This does not always imply only SWS, but also N2 (Cordi & Rasch, 2021; Göldi et al., 2019; Hu et al., 2020; Schreiner & Rasch, 2015). These successfully used protocols

prompt the assumption of an involvement of not only SWS as derived specifically from the two hypotheses above (see Chapter 1.2) but also sleep stage N2.

Indeed, in light of the crucial neural processes underlying optimal memory consolidation, it becomes evident that these neural features are observable during both sleep stages N2 and SWS. As previously mentioned, within this process, SOs were found to be fundamental and most dominant in SWS but they are also present in the lighter NREM sleep stage N2 (Iber et al., 2007). Additionally, in the memory consolidation process, sleep spindles are involved, which are detectable in SWS, but one of the prominent characteristics of N2 (Rasch & Born, 2013). In addition, researchers observed the importance of the coupling of these two features (Antony et al., 2018; Cairney et al., 2018; Schreiner et al., 2021) which has also been concluded as an optimal cue delivering moment by Carbone and Diekelmann (2024), followed by a call for further investigations. Due to more SOs during SWS, this specific coupling seems to be more likely to appear in SWS. More precise EEG-analyses supported these results: A high density of sleep spindles during SWS as well as SOs directly following a TMR-memory cue were positively linked to successful cuing. Moreover, an increase in theta power after a memory cue was delivered also seems to be crucial (Schreiner & Rasch, 2017). Although, all these findings should be considered with caution due to replication failures (Cordi & Rasch, 2021).

However, turning to N2 sleep, this sleep stage is considered as stable sleep stage, in which humans spend about 45 to 55 % of their TST in each night (Carskadon & Dement, 2011) and is in contrast to SWS, equally distributed between night halves (Ackermann & Rasch, 2014). This large proportion gives the experimenter more time to reactivate memory cues. Moreover, it is considered as a light NREM sleep stage (Rasch & Born, 2013) in which vigilance level is higher and arousal level is lower compared to the deeper sleep stage SWS. Studies have shown that during N2, stimuli are more likely to be perceived and processed (Andrillon et al., 2016; Andrillon & Kouider, 2020;

Blume et al., 2017). Accordingly, individual memory cues might be better perceived and processed within N2.

Which sleep stage offers the optimal outcome on memory consolidation following the use of TMR was systematically analyzed by Hu et al. (2020). The authors discovered that TMR is effective in both sleep stages. Notably, they even identified a descriptively slightly higher effect size for TMR during N2 (Hedges' $g = .32$) compared to SWS (Hedges' $g = .27$). However, caution is advised by drawing inferences based on these results due to the presence of several confounding factors, including the fact that not only studies investigating declarative memory consolidation, but other memories were categorized, and heterogeneous experimental designs and memory tasks were used. Furthermore, the number of studies included in the analysis of N2-TMR and SWS-TMR was unbalanced (13 vs. 174 studies). Additionally, the protocolized use of SWS did not always entail solely SWS, but also N2, which further challenges to isolate the specific contributions of the two sleep stages. Surprisingly, although extensive research has been carried out on the use of TMR (Carbone & Diekelmann, 2024; Hu et al., 2020) no direct within-subject comparison of TMR between both sleep stages (N2 vs. SWS vs. control) does exist.

Since research today has not yet provided such a study, the scientific gap remains, as there is no clear answer what role N2 in comparison to SWS has in the process of memory consolidation, because a systematic comparison of declarative memory consolidation during both sleep stages, in a within-subject design during one night is still lacking.

1.3 Memory consolidation: The case of endogenous reactivations

As previously laid out, the consolidation of declarative memory occurs, embedded within other processes, through endogenous reactivations during sleep. These reactivations can be

specifically reinforced and manipulated by the TMR-technique (Diekelmann & Born, 2010; Oudiette & Paller, 2013).

However, the question arose whether these endogenous reactivations are limited to the process of memory consolidation or can be extended to other cognitive processes. Specifically, whether not only newly acquired declarative memories are endogenously reactivated during sleep but also cognitions which have been directly formed before sleep. These are not intended to influence a specific performance directly after sleep, but rather to particularly affect sleep architecture and subjective sleep quality.

From several models of insomnia, it is well known that dysfunctional cognitions such as rumination and worries have the power to affect sleep negatively and are central drivers of insomnia (Beck et al., 2023; Tang et al., 2023; Tousignant et al., 2019; Wuyts et al., 2012).

Within the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association [APA], 2022), central symptoms of insomnia include unsatisfactory sleep quality due to difficulties to fall or stay asleep, as well as early morning awakenings. These symptoms all persist for a minimum of three month and result in significant distress and functional impairment in several life domains.

An efficacious treatment of insomnia is the cognitive behavioral therapy, although this treatment is not equally beneficial for all patients. Therefore, a clear recommendation was suggested to further investigate the underlying mechanisms on how cognitive processes affect sleep to support an optimal treatment success (Tang et al., 2023).

Indeed, the underlying mechanisms on how these cognitive processes in general directly affect sleep architecture not only before sleep but also continuously during sleep are not well understood. In addition, cognitive models of insomnia do not take into account how positive cognitions affect sleep, nor do they focus on healthy populations. Nevertheless, it would be of great

interest and importance to identify the specific mechanisms and further individual factors to design an additional non-pharmacological intervention listing concrete strategies for insomniac patients to improve their sleep, and for healthy population to avoid the escalation of poor sleep quality or transient insomnia into a primary insomnia or other diseases caused by poor sleep (see Vorster et al., 2024).

1.3.1 Memories of Sleep Hypothesis

The Memories of Sleep (MemoSleep)-Hypothesis (Rasch, 2015) addresses this issue. The MemoSleep-Hypothesis (Figure 5) attempts to determine how cognitive processes such as thoughts, rumination, and worries precisely affect sleep architecture in healthy populations. The underlying core premises are that wake/sleep cognitions, also referred to as sleep or wake memories, simultaneously activate a semantic and sensorimotor representation associated with either the sleep (low-arousing) or wake (high-arousing) state. Consequently, these cognitions become embodied. This assumption was derived from existing embodied cognition theories, which fundamentally assume that cognitions are stored in multimodal representations within the brain and are influenced and shaped by the interaction of the body and its environment (Barsalou, 2008; Shapiro & Spaulding, 2024). Based on this assumption, the MemoSleep-Hypothesis further postulates that activated, embodied sleep/wake memories are more likely to be endogenously reactivated during subsequent sleep. As a result, the repetitive reactivation of the embodied memories will influence sleep. Following this hypothesis, the activated cognitions of “wakefulness” before sleep should activate the semantic and sensorimotor body representation and become embodied which leads to an increase in cognitive and physiological arousal. During subsequent sleep, these concepts become repeatedly reactivated and may lead to more sleep disturbances and unrestful sleep. In contrast, the activated concept of “sleep” or “relaxation” should lead to improved sleep.

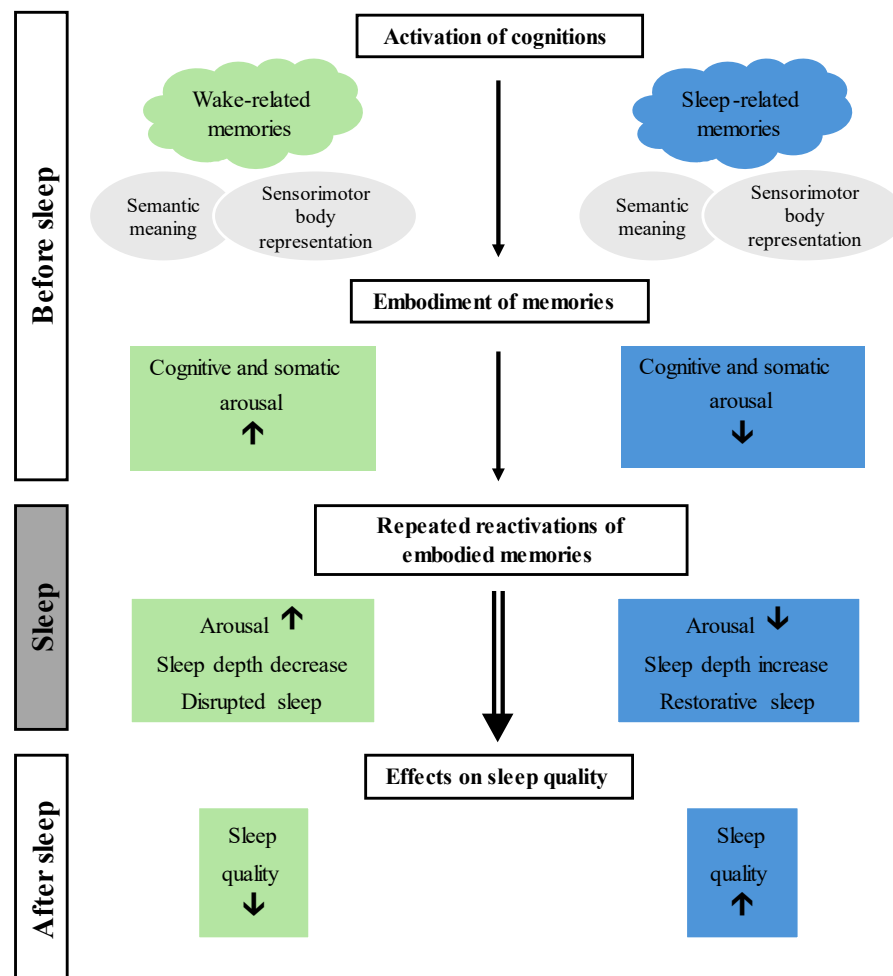


Figure 5. The MemoSleep-Hypothesis (Rasch, 2015). The activation of cognitions associated with wake or sleep states simultaneously activate their semantic meanings and sensorimotor representations. Thus, they are embodied and either increase or decrease cognitive and somatic arousals. These cognitions are termed embodied wake/sleep memories. Embodied wake/sleep memories which were activated prior to sleep are more likely to be endogenously reactivated repeatedly during sleep. During subsequent sleep, the increased endogenous reactivations of embodied wake/sleep memories activate associated somatic responses. This results in an increase or decrease of arousal level, thereby affecting sleep depth and sleep architecture. Depending on the nature of responses, this can either improve or impair sleep quality.

It is still unclear how these reactivations of sleep/wake memories during sleep occur at the neural level. Although memory reactivation has been proposed as an explanation for why thoughts

and cognitions are also actively reactivated during sleep, it is still not entirely clear whether these reactivations are analogous to memory reactivations in the interaction of various neural mechanisms and the hippocampus, particularly during SWS as it was not defined in this hypothesis.

Still, the hippocampus also appears to be involved in the retrieval of declarative memories (Eichenbaum, 1999; Ritchey et al., 2013; Tanaka et al., 2014). Therefore, one possible conclusion is that the hippocampus is also involved in the retrieval, the activation, and the following reactivation of mental concepts of a wake/sleep memory, thereby communicating with the neocortex and simultaneously activating pre-existing long-term memory networks.

On a behavioral level, this hypothesis already found support in results that have shown that sleep can be manipulated by forming an explicit intention (Combertaldi & Rasch, 2020). Subjects instructed themselves before sleep and formed the intention to sleep as good or as bad as possible. Objective and subjective sleep parameters were indeed worse in the bad condition compared to a control night. However, participants could not improve their sleep. In another study, participants were pre-sleep instructed to react to an auditive stimulus during sleep, simulating on-call work. Results show that this instruction significantly impaired subsequent sleep quality even in the absence of any sound delivery (Combertaldi et al., 2022). A recent study by Beck et al. (2023) found that experienced stress negatively modifies sleep depth. The investigators compared two conditions in which participants either directly experienced stress before sleep or anticipated a stressful event before sleep and found that both experienced and anticipated stress had a negative effect on several sleep parameters, including SWS, sleep spindles, other SWS-parameters, and sleep depth. Interestingly, pre-sleep stress particularly affected early sleep and induced physiological arousal, whereas anticipated stress specifically affected late sleep. The authors concluded that the effects on late sleep resulted from repeated reactivations of activated stress concepts (Beck et al., 2023).

The findings of these studies suggest that sleep is modifiable by intentions, pre-sleep and anticipated stress. So far, however, the evidence is accumulating in a negative rather than a positive way. Another perspective is provided by studies of hypnosis on sleep. It has been shown that listening to a relaxing hypnosis before sleep targeting to deepen sleep, subsequently increases SWS and sleep depth, and improves sleep quality at least in highly suggestible participants (Cordi et al., 2014, 2020). One potential mechanism underlying this phenomenon is rather the unconscious activation and subsequent reactivation of the concept of "deep relaxation" during sleep.

1.3.1.1 First-Night Effect

The aforementioned studies support the theory that stressors experienced prior to sleep result in an activation of stress-related cognitions and physiological arousals. These cognitions and physiological arousals subsequently influence sleep quality through the reactivations of these cognitive, embodied concepts of stress (Beck et al., 2023). However, to examine how cognitions, and possible pre-sleep stress has an influence on subsequent sleep, a specific task does not have to be artificially created as in e.g., Beck et al. (2023) or Combertaldi et al. (2022), but can also be seen in a common phenomenon during the first night in an unfamiliar new environment e.g., a sleep laboratory. Typically, sleep during the first night in a new environment is associated with poor sleep quality and altered sleep architecture. This effect is known as the First-Night Effect (FNE) and was first discovered by Agnew et al. in 1966 and is a well-established phenomenon in sleep research (e.g., Le Bon et al., 2001; Newell et al., 2012; Toussaint et al., 1995). Based on 53 studies, Ding et al. (2022) concluded in their meta-analysis that during the first night in a new environment SOL, WASO and REM latency were prolonged, TST, sleep efficiency (SE) and REM duration were decreased, and the portion of N1 was increased. Interestingly, these changes were only observed

during the first night. The general recommendation therefore has emerged to include an adaptation night but exclude the data from further considerations (Lee et al., 2016).

There exist different possible reasons for the occurrence of FNEs such as external factors (the unfamiliar surroundings and situation, including the limited freedom to move and the discomfort of the recording equipment) and internal factors such as stress (Johns & Doré, 1978; Le Bon et al., 2001) which may arise from the appraisal of the situation (Lazarus, 1999). Following the assumptions of the MemoSleep-Hypothesis, the evaluation of all these factors of the new unknown situation and sleep environment could possibly activate the mental concepts “unfamiliar” “unsafe” or “stress” and lead to corresponding embodied representations. These concepts are then repetitively reactivated during sleep, leading to more awakenings and unrestful sleep, all typical signs of an FNE. Nevertheless, it is still unclear to what extent the environment and situation contribute to the disrupted sleep patterns by an FNE.

Noteworthy, FNEs are best studied over two subsequent nights, including one adaptation night, directly followed by an experimental night (Ding et al., 2022). However, the efficacy of non-consecutive adaptation nights as well as the patterns of reoccurrence are less well-understood, despite the fact that in sleep experiments, adaptation nights are typically conducted several days prior to the experimental night.

A neural phenomenon during the FNE has been discovered by Tamaki et al. (2016). The authors systematically investigated the underlying neural mechanisms during the FNE. They discovered besides an FNE, greater SWA power during the SWS in the first sleep cycle in the right hemisphere than in the left hemisphere particularly in the default mode network. During the second night one week later, this interhemispheric asymmetric activity (IAA) was no longer detectable. Furthermore, this IAA appeared to be unique to SWS as it was not observable during the lighter N2 sleep stage. Two other experiments of this research group corroborated the more vigilant right

brain hemisphere during the first night. Based on these data, the researchers concluded that the FNE may act as a protective mechanism in an unfamiliar environment during the first night by keeping one brain hemisphere more alert. In doing so, they drew explicit parallels to the unihemispheric SWS, a solution for certain species colonizing suboptimal habitats to circumvent the dilemma of remaining alert without completely abandoning the important processes within sleep (Lima et al. 2005; Mascetti, 2016). An attempt to replicate these findings with a high-density EEG recording somehow failed since Mayeli et al. (2022) found the opposite pattern in comparison to Tamaki et al. (2016). They were able to detect greater SWA power in the left hemisphere during the occurrence of an FNE.

Interestingly, the co-occurrence of FNE and IAA seems to be relatively new, but the detection of IAAs during sleep was documented already during the 1970s (Armitage et al., 1989; Goldstein et al., 1972; Roth et al., 1999; Sekimoto et al., 2000). Remarkably, when all of the aforementioned studies are considered collectively, no consensus regarding the pattern and appearance of IAAs during sleep exists. However, in alignment with the findings of Tamaki et al. (2016) and the conclusion that SWA-IAA is a protective mechanism during the first night in an unfamiliar environment, asymmetric activity should be absent during a second night or within a familiar environment.

Based on this background, a second scientific gap arises. It remains unclear whether one night in an unfamiliar environment is enough for adaptation and for reducing arousing pre-sleep appraisals, which become embodied and reactivated during sleep, leading to an FNE. More precisely, it is unclear whether the FNE persists when returning to the same unfamiliar environment one week later. Moreover, it is not clear whether a prior familiarization to the recording equipment in a familiar environment helps to attenuate a possible FNE when sleeping in an unfamiliar environment one week later. In addition, it is not yet very clear what role IAAs play in the FNE.

1.3.1.2 The MemoSleep-Hypothesis and its extension to emotions

The MemoSleep-Hypothesis (Rasch, 2015) refers specifically to cognitions and thoughts. However, whether this hypothesis can be extended to emotions is not explicitly defined yet. The embodiment of emotions is also a well-established phenomenon and embodiment theories refer not only to cognitions, but also to emotions (Niedenthal, 2007).

The definition of emotions is a major topic of debate, due to the existence of a large number of divergent theories, focusing on different aspects (Kleinginna & Kleinginna, 1981; Mulligan & Scherer, 2012). However, most theories agree that emotions are very complex phenomena which have an adaptive function and are triggered by a relevant internal or external stimulus. Moreover, emotions are limited to a certain duration whereby their intensity decreases over time (Scherer, 2000).

Emotions and cognitions are closely linked and bi-directionally influenceable (Krizan et al., 2024). Emotions arise from cognitive processes, such as appraisals, and are shaped by cognitions and thoughts (Izard, 1992; Lazarus, 1991). In turn, according to Lazarus (1982, 1991) emotions cannot emerge in the absence of thoughts. By definition, when an emotion is specifically activated, corresponding thoughts should also be activated. However, studies that focus specifically on the activation of emotions and consider cognitive processes as important by-products are still lacking.

Since cognitions have an influence on sleep as laid out in the previous subchapter 1.3.1, but also generate emotions (Lazarus, 1991; Scherrer 2000), it can therefore be reasonably assumed that not only cognitions but also emotions have the power to influence sleep. However, studies concentrating on this phenomenon in context of the MemoSleep-Hypothesis are still pending.

Nevertheless, the influence of emotions on sleep is in accordance with clinical research findings. Impaired sleep or insomnia represent core symptoms of stress or affective

psychopathologies, such as the major depression (APA, 2022). Based on previous research, Krizan and colleagues (2024) reviewed the impact of emotions on sleep in their meta-analysis including 31 studies. Although the underlying mechanisms on how emotions impact sleep are not fully understood, despite the lack of heterogeneous study designs, and a potential publication bias, the authors found that specifically negative emotions prolonged the SOL.

Since emotions affect sleep, it is therefore worthy to focus on the question whether a targeted activation of a specific emotion before sleep can influence sleep architecture and its quality. According to the MemoSleep-Hypothesis, the activated emotion before sleep should lead to embodied associations and become repetitively reactivated during sleep. Concretely, a stimulus or input which activates the emotion “sadness” should lead to an impaired sleep quality, following the features of depressive symptoms (APA, 2022). Diametrically opposed, an activated positive emotion should lead to a restorative, improved sleep quality.

This concept may already be considered as a valid, non-pharmacological approach to influence sleep by the activation of emotions prior to sleep. Nevertheless, in light of the preceding chapters on memory consolidation, it is worth considering whether the TMR-method can be further used to externally reinforce the possible endogenous reactivation of the activated emotion by an emotional stimulus during sleep, thereby influencing sleep quality to a greater extent. The advantage of the TMR-method, the targeted reactivation of a particular information, has already been the central object of investigation, supporting the MemoSleep-Hypothesis. Beck and colleagues (2021) externally reactivated relaxing words during sleep, selected from a hypnosis which subjects listened prior to sleep. The findings indicated that the reactivation of these words resulted in alterations of the sleep architecture, as shown by an increase in SWA, and an improvement in sleep quality.

Reflecting on the preceding subchapter 1.2.1, Carbone and Diekelmann (2024) presented findings from studies which utilized TMR to effectively enhance emotional memories (Hutchison et al., 2021; Xia et al., 2023). To operationalize the emotional memory strength, an emotional stimulus, such as a picture, is typically paired with neutral words (Lehmann et al., 2016), pseudowords (Xia et al., 2023), neutral sounds and tones (Legendre et al., 2019; Sterpenich et al., 2014), or emotional sounds (Ashton et al., 2018; Cairney et al., 2018; Pereira et al., 2022). During subsequent sleep, the associated cue is presented again following the main goal to improve the emotional memory retrieval after sleep. However, the focal statistical meta-analysis by Hu et al. (2020), which included 12 emotional TMR studies, demonstrated that TMR did not yield a statistically significant overall benefit for emotional memories (Hedges' $g = .10$). But, to answer the question of whether the assumptions of the MemoSleep-Hypothesis can be extended to include and be applied to emotions, a stimulus is needed that allows both a strong activation and reactivation of emotions during sleep and not a special association of two items as done in studies on emotional memory consolidation.

1.3.1.3 Music: Powerful to evoke emotions and influence sleep

A powerful stimulant to evoke emotions is music (Koelsch, 2014). “Music represents ...[and] creates real, felt emotions” (Scherer & Coutinho, 2013, p.121). Depending on the type and characteristics of music, it can activate different emotions (Hallam et al., 2011; Koelsch, 2014). Music helps to alleviate anxiety and pain, as well as promoting a down-regulating effect on physiological parameters, including heart rate and blood pressure (Nilsson, 2008). Given its powerful influence on emotions, music represents an efficacious therapeutic intervention for many psychological conditions such as stress reduction (de Witte et al., 2022) and depression (Aalbers et al., 2017; Tang et al., 2020). In addition, listening to music before sleep is an effective non-invasive

technique for facilitating sleep (Dickson & Schubert, 2020, 2022). Pre-sleep music listening may suppress negative thoughts, thereby establishing a healthy sleep-promoting routine when done on a regular basis (Dickson & Schubert, 2020). As reviewed by Dickson and Schubert (2019), music improves sleep quality both subjectively and objectively by masking other disturbing sounds. Furthermore, the relaxation induced by music listening, the enjoyment of listening to preferred music, the distraction from stressful thoughts, the expectation of music, and the biological synchronization of musical features seem to influence sleep with varying support degrees (De Niet et al., 2009; Dickson & Schubert, 2019). Moreover, subjective and objective sleep quality ratings improve, when using music as a sleep aid (Cordi, 2021). Nevertheless, all of the aforementioned studies on the effects of pre-sleep music listening, which suggest a beneficial impact on sleep quality, have in common that the duration of music exposure is limited until sleep onset. Still, it remains unclear whether music presented during sleep has also a beneficial impact on sleep quality.

Previous research has shown that the sleeping brain is capable of processing stimuli with emotional salience during sleep. Chen and colleagues (2016) presented either happy or fearful spoken syllables to 12 participants during different stages of sleep and found that event related potentials (ERPs) showed a typical pattern of emotional processing across all sleep stages. Similarly, Wielek et al. (2021) investigated whether the sleeping brain is able to distinguish between familiar and unfamiliar voices and names. The results showed that the brain is able to discriminate the familiarity of voices in N2 and SWS with an identical neural pattern in both sleep stages. However, the authors did not find a difference between familiar and unfamiliar names during sleep, nor did they find the same neural pattern during wakefulness. Moreover, a study conducted by Xia et al. (2023) updated the emotional tone of aversive memories using TMR. During the night, positive words were paired with the aversive memories from a pre-sleep learning paradigm and repeatedly presented. In the morning the aversiveness of these memories was lower

rated. These results show that the sleeping brain is even able to update the emotionality of certain memories through an external stimulus.

Turning back to the designs of TMR studies, single tones and musical pieces have effectively been used as memory cues to externally reactivate memories (Fabbri et al., 2024; Gao et al., 2020; Hu et al., 2020; Rudoy et al., 2009). The simultaneous play of multiple single tones forms a musical chord (Piston, 1950) which represent the smallest musical element that conveys emotional information. In Western culture, music is predominantly composed by consonant major and minor chords (Bakker & Martin, 2014). Relatively stable, major chords are associated with positive feelings, whereas minor chords are linked to negative emotions (Parncutt, 2014). In contrast, dissonant chords have been found to trigger unpleasant feelings (Pallesen et al., 2005). However, all these conclusions are drawn upon studies during wakefulness. Therefore, it is currently unknown whether musical elements containing emotional content are processed and capable of reactivating a specific emotion during sleep, thereby influencing sleep quality.

Based on this background the third research gap can be summarized as follows: In light of the MemoSleep-Hypothesis, an investigation into whether it is possible to activate an emotion by musical major, minor, and dissonant chords before sleep, which in turn activates an embodied representation of the corresponding emotion, would be of interest. Further, it would be interesting to see whether during subsequent sleep it is possible to externally reinforce a particular reactivation with these chords following the procedures of TMR studies. However, since it is unclear whether the human brain is capable of perceiving musical harmony during sleep, this issue needs to be addressed as part of a first proof-of-concept study. Consequently, this study will provide the basis for future investigations examining the targeted activation and reactivating of a specific emotion during one night, thereby influencing subjective and objective sleep quality.

1.4 Research questions and aims

In consideration of the aforementioned state of the art and the three identified scientific gaps, this dissertation aims to provide a deeper understanding of the following through three studies: Despite extensive investigations on memory consolidation, the isolated contribution of sleep stage N2 within this process has hardly been investigated before. While studies have underscored the importance of SWS, the role of N2 remains unclear. Furthermore, it is unclear whether the mechanism of endogenous reactivations of memory traces can only be observed exclusively within the declarative memory consolidation process or whether reactivations assumed by the MemoSleep-Hypothesis can also explain the FNE. More precisely, the question is whether pre-sleep appraisals of the environments are embodied and repeatedly reactivated during sleep, leading to an FNE. Additionally, it is unclear whether the MemoSleep-Hypothesis can be extended to emotions and if a targeted activation of an emotion can be specifically reactivated during sleep, potentially influencing sleep quality. These gaps will be examined in greater detail in the three research studies included in this dissertation.

Study 1 aims to provide more data and a broader insight into the differences and the contributions of the two sleep stages N2 and SWS within the declarative memory consolidation process. This will be operationalized by applying TMR during a single night within these two sleep stages versus a control condition.

The second study (Study 2) investigates the influence of pre-sleep evaluation of situational and environmental factors on sleep. To address this issue, the phenomenon of the FNE is employed. Specifically, the study examines whether one adaptation night in a novel environment and situation is sufficient to improve pre-sleep appraisal and thereby a potential FNE one week later. To further elucidate the contribution of environment and situation, first night's sleep in a new unfamiliar

environment is compared to a familiar home environment. This is operationalized by conducting a study that compares the adaptation night to a second night one week apart.

The third study (Study 3) investigates the possibility of specifically activating an emotion before sleep and reactivating this emotion through TMR during the night. This is operationalized using musical chords with varying harmonic degree. As this type of emotion reactivation is novel and there is currently no evidence as to whether this approach is effective, this project is rather a proof-of-concept study, laying the foundation for further studies.

2 Included Studies

2.1 Targeted memory reactivation during slow wave sleep vs. sleep stage N2: No significant differences in a vocabulary task

Anna Wick¹, Björn Rasch^{1 *}

¹ Department of Psychology, University of Fribourg, Fribourg, Switzerland

*Corresponding author:

Björn Rasch, Department of Psychology, University of Fribourg, Fribourg, Switzerland, Rue P.-A-de-Faucigny 2, CH-1700 Fribourg. Email: bjoern.rasch@unifr.ch

Abstract

Sleep supports memory consolidation, and slow-wave sleep (SWS) in particular is assumed to benefit the consolidation of verbal learning material. Re-exposure to previously learned words during SWS consistently benefits memory, with a technique known as targeted memory reactivation (TMR). However, TMR has also been successfully applied during sleep stage N2, while a direct comparison between words selectively reactivated during SWS vs. N2 is still missing.

Here, we directly compared the effects of N2-TMR and SWS-TMR on memory performance in a vocabulary learning task in a within-subject-design. 21 healthy young participants (main sample) and 13 healthy young participants (additional sample) learned 120 Dutch-German word pairs before sleep. Participants in the main sample slept for ca. 8 hours during the night, while participants in the additional sample slept ca. 3 hours. We reactivated the Dutch words selectively during N2 and SWS, in one single night. 40 words were not cued. Participants recalled the German translations of the Dutch words after sleep in the morning (main sample) or at 2 am (additional sample).

As expected, we observed no differences in recall performance between words reactivated during N2 and SWS. However, we failed to find an overall memory benefit of reactivated over non-reactivated words. Detailed time-frequency analyses showed that words played during N2 elicited stronger characteristic oscillatory responses in several frequency bands, including spindle and theta frequencies, compared to SWS. These oscillatory responses did not vary with the memory strengths of individual words.

Our results question the robustness and replicability of the TMR benefit on memory using our Dutch vocabulary learning task. We discuss potential boundary conditions for vocabulary reactivation paradigms, and most importantly, see the need for further replication studies, ideally including multiple laboratories and larger sample sizes.

Introduction

Slow wave sleep (SWS) is characterized by slow-wave activity (0.5 – 4.5 Hz), occurs mainly in the first part of the night and is assumed to play an important role for sleep-associated memory processes (Walker and Stickgold 2004). The synaptic down-selection hypothesis, for example, postulates that selected synaptic weights are scaled down by slow oscillations during SWS, affecting signal-to-noise ratios and retrieval access after sleep. In this notion, spontaneous or induced reactivations of memory networks can bias downscaling, protecting memory traces from being forgotten (Tononi and Cirelli 2020). According to the active system consolidation hypothesis, memory traces are spontaneously reactivated during SWS, leading to a memory trace reinforcement in different memory systems, including cortical long-term memory networks. This process of system consolidation occurs mainly during SWS and depends on a fine-tuned interaction between hippocampal sharp-wave ripple, thalamo-cortical sleep spindles and cortical slow oscillations (Diekelmann and Born 2010). While an 8-hour night of sleep typically consists of 90 minutes of SWS, we spent 4-5 hours in the stable sleep stage N2 (Carskadon and Dement 2011). Also, in N2, slow waves occur but this sleep stage is dominantly characterized by single K-complexes and sleep spindles, suggesting that at least some slow waves/spindle related memory functions might be retained during sleep, albeit to a lesser extent than during SWS. However, most sleep and memory models do not explicitly address the role of N2 in memory processes during sleep.

Empirically, both SWS and N2 sleep are involved in memory processes during sleep (Ackermann and Rasch 2014). SWS is most consistently related to processes of declarative memory consolidation e.g., consolidation of verbal or spatial information (Diekelmann et al. 2009). Several night-half studies consistently showed that early, SWS-rich sleep favors the consolidation of declarative memories as compared to the second half of the night. For example, in the study of

Plihal and Born (1997), 10 subjects learned a declarative memory task and a procedural memory task before the retention interval. On two nights, the sleep group learned the tasks either before a 3-hour sleep period or after a 3-hour sleep period during the night before going back to sleep for 3 hours. The authors found that declarative memory consolidation was better after the first SWS-rich half of the night, while procedural memory consolidation benefited more from the second half of REM-rich sleep. Importantly, the amount of N2 sleep was equal between the two night-halves, suggesting that N2 sleep in the second night-half is not sufficient to promote declarative memory consolidation during sleep (Gais and Born 2004). Note that theoretically, forgetting processes in REM sleep might have counteracted positive effects of N2 sleep on memory in the second night half (Crick and Mitchison 1983). Furthermore, the coupling between slow waves and sleep spindles appears to be essential for successful memory consolidation during sleep (Antony et al. 2018; Cairney et al. 2018), which may occur more frequently during SWS due to the higher rate of slow waves.

In contrast to SWS, N2 sleep has been related to the consolidation of procedural and motor skills (Smith et al. 2004; Walker et al. 2002). However, evidence for an involvement of N2 sleep in the consolidation of verbal information also exists: Lahl et al. (2008) found that an ultrashort 6-min nap only containing N2, already promoted memory performance after sleep. Moreover, Ruch et al. (2012) found that the rate of sleep spindles, delta, and slow oscillations during N2 promoted recall performance.

In recent years, targeted memory reactivation (TMR) has become an established method to investigate memory processes during sleep. TMR assesses memory processes by presenting reminder cues (e.g., scents, clicks, tones, words) during sleep which were coupled to previously learned material before sleep (Cordi & Rasch, 2021; Hu et al., 2020). Thereby, memory

consolidation can be externally manipulated, and reactivations of memory traces are specifically reinforced and their effect on post-sleep memory performance can be directly measured (Oudiette and Paller 2013). TMR typically improves memory measures after sleep, and successful reactivation during sleep is associated with event-related increase in theta and spindle oscillations, which are more pronounced for later remembered vs. non-remembered words (Schreiner and Rasch 2017). This was found in a study by Schreiner et al. (2015a). In this particular study, participants learned 120 Dutch-German word pairs in the evening and recall was tested immediately afterwards. Participants then slept for 3 hours. During sleep, half of the words were reactivated, and half of the words were not reactivated. After 3 hours, the memory performance of subjects was tested again. Based on their performance, the words were divided into remembered and non-remembered words and accordingly analyzed in the time frequency dimensions.

In a meta-analysis on TMR during sleep, Hu et al. (2020) identified a small to medium effect size on behavioral memory performance in over 73 TMR studies. A considerable number of these studies presented reminder cues selectively during SWS, providing substantial evidence that induced memory reactivations during SWS promote memory formation. Another subset of studies presented reminder cues during both SWS and N2 sleep, with a similar positive effect on memory performance after sleep. While extensive TMR research has been conducted on SWS alone and N2 & SWS combined, there is limited data on declarative memory cues exclusively presented during N2. Tilley (1979) delivered TMR cues in either N2 or REM sleep and found that the declarative memory performance improved in subjects assigned to the N2 but not to the REM condition. Furthermore, Sterpenich and colleagues (2014) reactivated pre-sleep learned sound-image associations in either REM or N2 sleep and found that only subjects in the REM condition benefited from the reactivations, but not subjects in the N2 condition.

Interestingly, stimuli are more likely to be perceived and processed during stage N2 sleep as compared to SWS (Andrillon and Kouider 2020), which might lead to a facilitated reactivation of associated memory representations. However, the unique contribution of N2 sleep on reactivated memories and sleep-associated memory consolidation processes is still unclear, as a direct comparison of TMR cues presented selectively during N2 and SWS has never been conducted before.

To investigate this important research question, in this TMR study, we presented reminder cues in the same night selectively during N2 or SWS. Success of sleep-stage specific TMR was compared to stimuli not presented during sleep in a within-subject design. We used a Dutch vocabulary task, which has been used in our laboratory to induce increased memory performance after reactivation during sleep (Schreiner and Rasch 2015; Schreiner et al. 2015a, 2015b; Göldi et al. 2019). Following these studies, we also controlled for the number of recalled and non-recalled word pairs within each condition for each subject individually. We hypothesized that reactivation of word pairs during N2 would have a similar memory-enhancing effect as the application of TMR during SWS. In addition, we predicted that theta and spindle activity is induced during successful memory reactivation in both N2 and SWS.

Results

To test our hypothesis, 21 participants spent one night in the sleep laboratory (see materials and methods section for more details). Prior to sleep, participants learned 120 Dutch-German word pairs. During nighttime sleep, we reactivated a separate list of Dutch words selectively during N2 and another list of Dutch words during SWS. 40 control words were not cued. Each condition consisted of the same amount of remembered and not remembered words. In the morning, we asked participants to recall the German translations of the Dutch words again. The procedure is visualized in Figure 1a. Due to technical problems in some test runs, we excluded one word pair from the 120-word list and performed all analyses based on 119 word pairs. Then, we analyzed the effects of N2-TMR vs. SWS-TMR vs. control words. Within the result section, we report mean $\pm$ SEM.

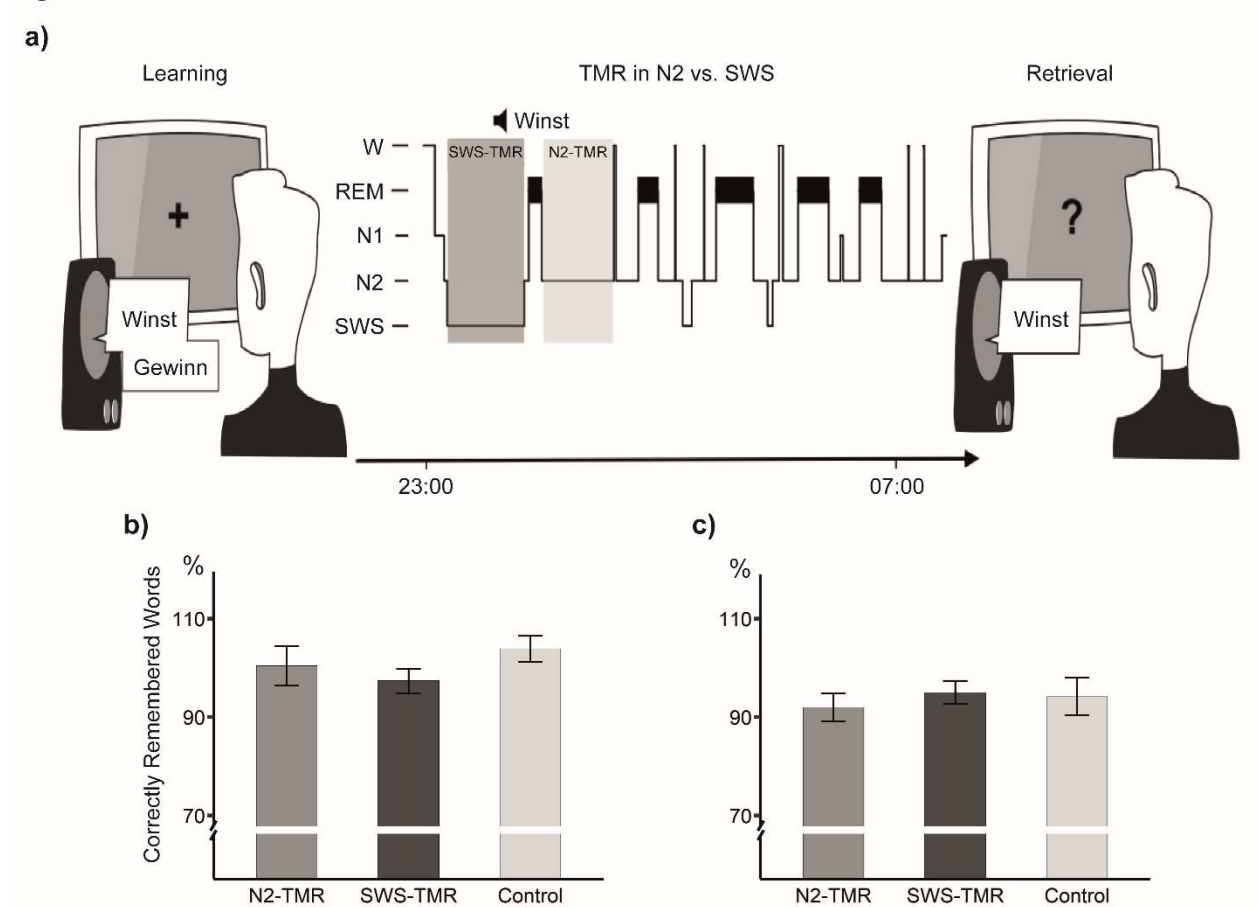
Figure 1

Figure 1. Experimental procedure and behavioral results. **a)** Experimental procedure of the main study. After preparation, participants studied 120 Dutch–German word pairs in the evening. Afterwards, participants went to bed and slept for 8 hours. During stable N2 and SWS, we presented two separate lists of 40 Dutch words. 40 words were not presented. In the morning, participants were tested on the German translation of the Dutch words again. **b)** Behavioral results of the main study. We did not detect any memory differences between selective reactivation during N2 sleep (N2-TMR) and slow-wave sleep (SWS-TMR). In addition, we did not observe a general memory benefit for reactivated vs. not reactivated words (Control). In addition, retrieval performance is reported as a percentage of correctly retrieved German translations, with performance set to 100% before sleep. Values are mean $\pm$ SEM. **c)** Behavioral results of the additional study (n = 13, identical

design except 3 hours of sleep instead of 8 hours). Similar to our main study, we were not able to find any memory differences between selective reactivation during N2 sleep (N2-TMR) and slow-wave sleep (SWS-TMR). Analogously, we did not observe a general memory benefit for reactivated vs. not reactivated words (Control). Retrieval performance is reported as a percentage of correctly retrieved German translations, with performance set to 100% before sleep. Values are mean $\pm$ SEM.

Effects of sleep-stage specific TMR on memory performance

Consistent with our hypothesis, sleep-stage specific reactivation of word-pairs during N2 or SWS did not result in a significant difference in memory performance tested after sleep. Participants remembered 100.4 ± 4.0 % of the translations to the Dutch words in the morning after TMR during N2 (with performance during encoding in the evening set to 100%). When words were presented during SWS, participants recalled 97.3 ± 2.5 % of the translations they had recalled before sleep. The difference between TMR during N2 and SWS was not significant ($t(20) = 0.59, p > 0.50$, see Figure 1b). However, contrary to our prediction, N2-TMR or SWS-TMR did not lead to an improved memory performance compared to words that were not presented during sleep (uncued control word pairs: 103.9 ± 2.6 %). The overall ANOVA including the within-subject factor ‘Condition’ (N2-TMR, SWS-TMR, Control) was not significant ($F(1.64, 32.80) = 0.98, p = .37, \eta^2_G = .04$). Thus, we were unable to replicate the overall beneficial effect of reactivating words during sleep, irrespective of the sleep stage. Table 1 provides a detailed overview of the recall performances during the learning and retrieval phases for each TMR category. The post-hoc calculated statistical power to detect a medium effect size of $f = 0.25$ was 34% ($\alpha = 0.05, n = 21$). This particularly low statistical power in spite of the within-subject design and $n = 21$ is due

to the low and on average negative correlation between the three measurements (i.e., N2-TMR, N3-TMR, control; average $\rho = -0.15$).

Table 1. Recall performance in learning and retrieval phases (Mean $\pm$ SEM)

Recall	N2			SWS			Control			F	p-value
Evening	16.9	$\pm$	0.5	16.24	$\pm$	0.62	16.43	$\pm$	0.53	2.83	0.74
Morning	17.05	$\pm$	0.79	15.76	$\pm$	0.69	17.05	$\pm$	0.65	2.27	0.13
Change	0.05	$\pm$	0.63	-0.48	$\pm$	0.37	0.62	$\pm$	0.41	1.2	0.31
Change %	100.42	$\pm$	4.0	97.34	$\pm$	2.49	103.86	$\pm$	2.6	0.98	0.37

Note. Data are means $\pm$ SEM. Numbers indicate absolute or relative values of correctly recalled words that were presented during N2 or SWS (40 words for N2-TMR and 40 words for SWS-TMR) or not (control words, 40 in total). Absolute number of correctly recalled words of the learning phase in the evening and the retrieval phase in the morning after the presentation during the night are indicated. Change (Change %) refers to the absolute (relative) difference in performance between learning and retrieval phases.

Our failure to find an enhancing effect of TMR on memory cannot be due to memory performance during encoding: Participants recalled 41.7 ± 1.3 % German translations of the 119 word-pairs (49.7 ± 1.6 words, word range 37- 64). Thus, the encoding level in our study group was on a medium encoding level which is considered optimal for detecting sleep-associated memory effects (Groch et al. 2017). Furthermore, we did not detect a significant difference in encoding levels between the three conditions (N2-TMR: 16.9 ± 0.5 words; SWS-TMR: 16.2 ± 0.6 words, Control: 16.4 ± 0.5 words; $F(1.90, 37.90) = 2.83, p = .074, \eta_G^2 = .01$). To further ensure that encoding levels did not affect our measure of overnight memory consolidation, we inspected possible

correlations between encoding performances and overnight memory consolidation. Overall, we observed no significant correlation, $r(61) = -.075, p > .50$. We also did not find any significant correlation within each condition, excluding possible confounding influences of different encoding levels on our main results (N2-TMR: $r(19) = -.058, p > .80$; SWS-TMR: $r(19) = -.15., p > .50$; Control: $r(19) = -.057, p > .80$). In addition, we controlled for the number of word repetitions within N2 (9.21 ± 0.23) and SWS (9.09 ± 0.42), by introducing them as covariates. However, we did not find a significant difference in memory performance ($p > .05$).

Next, we analyzed the influence of TMR during SWS or N2 sleep on behavioral performance in more detail by separating between gained words (words remembered during recall after sleep, but not during the encoding before sleep), maintained words (words remembered during encoding and post-sleep recall), lost words (words remembered during encoding, but not during post-sleep recall) and never recalled words (words remembered neither during encoding nor recall). TMR during SWS resulted in a significant higher number of lost words (3.52 ± 0.31) compared to TMR during N2 (2.71 ± 0.38) and control words ($2.10 \pm 0.30, F(1.57, 31.34) = 5.59, p = .013, \eta_G^2 = .13$). Also the number of maintained words was lower after TMR during SWS (12.71 ± 0.72) compared with TMR during N2 (14.29 ± 0.66) and the no-TMR control condition ($14.33 \pm 0.69, (F(1.53, 30.56) = 8.52, p = .002, \eta_G^2 = .06)$). No significant difference occurred between the three conditions for gained words ($p > .738$) and never recalled words ($p > .785$). This detailed analysis showed that in our study, TMR during SWS appeared to have an interfering effect on memory consolidation, increasing the number of lost words and decreasing the number of maintained words. These results are presented in Table 2.

Table 2. Recall performance within different word categories (Absolute numbers; Mean $\pm$ SEM)

Word Category	N2	SWS	Control	F	p-value
Maintained	14.29 $\pm$ 0.66	12.71 $\pm$ 0.72	14.33 $\pm$ 0.69	8.52	0.002
Gained	2.76 $\pm$ 0.59	3.05 $\pm$ 0.32	2.71 $\pm$ 0.37	0.26	0.738
Lost	2.71 $\pm$ 0.38	3.52 $\pm$ 0.31	2.1 $\pm$ 0.3	5.59	0.013
Never Recalled	20.1 $\pm$ 0.71	20.29 $\pm$ 0.65	20.43 $\pm$ 0.52	0.19	0.785

Note. Retrieval performance within the different word categories. Numbers indicate absolute values and are presented as means $\pm$ SEM. 4 different categories are separated by the TMR-condition: N2-TMR SWS-TMR, and not reactivated control words (40 words each). Maintained: words remembered during encoding and post-sleep recall; Gained: words remembered during recall after sleep, but not during the encoding before sleep; Lost: words remembered while encoding, but not during post-sleep recall; Never recalled: words not remembered during either encoding or recall.

Additional data

To strengthen our conclusion and partly overcome the low statistical power in the current study, we also analyzed data from a small study conducted during the pilot phase of the current study. 13 healthy young subjects took part in this study (mean age $M=22.14$ $SD = 2.87$). The TMR paradigm and experimental design were identical to the main study, except that participants slept only 3 hours between encoding and recall.

The analysis of this study showed no sleep-stage specific differences in the TMR-effect on memory consolidation over three hours of sleep: participants recalled 91.97 ± 2.81 % words reactivated during N2 (N2-TMR condition), 94.99 ± 2.36 % of words after SWS-TMR and 94.14 ± 3.83 % of control words (with memory performance during encoding set to 100%). The differences were not significant ($p > 0.70$, see Figure 1c).

In a next step, we combined the data from the pilot and the main study and performed the analyses with all 34 participants. After N2-TMR N2 subjects recalled $96.1 \pm 2.6\%$ of the translations to the Dutch words. When the words were presented during SWS, participants recalled $98.3 \pm 2.8\%$ of the translations they had remembered before sleep. The difference between TMR during N2 and SWS was not significant ($t(36) = -0.49, p > 0.63$). In addition, neither N2-TMR nor SWS-TMR did result in improved memory performance compared to control words not presented during sleep (control word pairs: $101 \pm 2.2\%$). The overall ANOVA was not significant ($F(1.95, 70.35) = 0.83, p = .437, \eta_G^2 = .02$). By combining the two data sets, we were able to increase the observed statistical power to detect a medium effect of $f = 0.25$ to ca. 55% (average correlation between condition $\rho = -0.08, n = 34, 3$ measurements, $\alpha = 0.05$).

Oscillatory correlates of reminder presentation and successful reaction during sleep

Participants slept on average 455.90 ± 4.32 min (please refer Table 3 for general sleep characteristics). Presenting words during sleep evoked characteristic responses in the sleep including K-complexes and spindle oscillations. This well-known pattern is reflected in the time-frequency spectrum as increases in the SWA band (1 - 4.5 Hz), theta band (5-7 Hz) and alpha band (8-12 Hz), followed by increases in responses in the spindle band (slow spindles 11-13 Hz; fast spindles 13-15 Hz) and beta activity (15-25 Hz) (see a, for word-evoked response during N2 and SWS combined, Figure 2b for responses during N2 only, Figure 2c for responses during SWS only). Focusing our analyses on a cluster of frontal electrodes (F3, F4, Fz, F7, F8), responses in all these different bands were more pronounced after word presentations during N2 than in with SWS (all $p < 0.028$, see Figure 2d).

Table 3. Overview of times spent in the different sleep stages

Sleep parameter	Mean	±	SEM
SOL [min]	22.07	±	3.97
WASO [min]	19.74	±	2.84
N1 [min]	19.74	±	1.89
N2 [min]	228.81	±	6.34
SWS [min]	93.29	±	5.16
REM [min]	94.33	±	4.87
WASO [%]	4.30	±	0.62
N1 [%]	4.31	±	0.40
N2 [%]	50.30	±	1.52
SWS [%]	20.45	±	1.10
REM [%]	20.60	±	0.97
TST [min]	436.17	±	4.81
SWS latency [min]	21.5		2.24
REM latency [min]	108.19		8.89
Total [min]	455.90	±	4.32

Note. Times in the different sleep stages. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow wave sleep; REM: rapid-eye movement sleep; TST: Total sleep time without WASO; Total: total sleep time including WASO. Numbers are means ± SEM (in minutes or %).

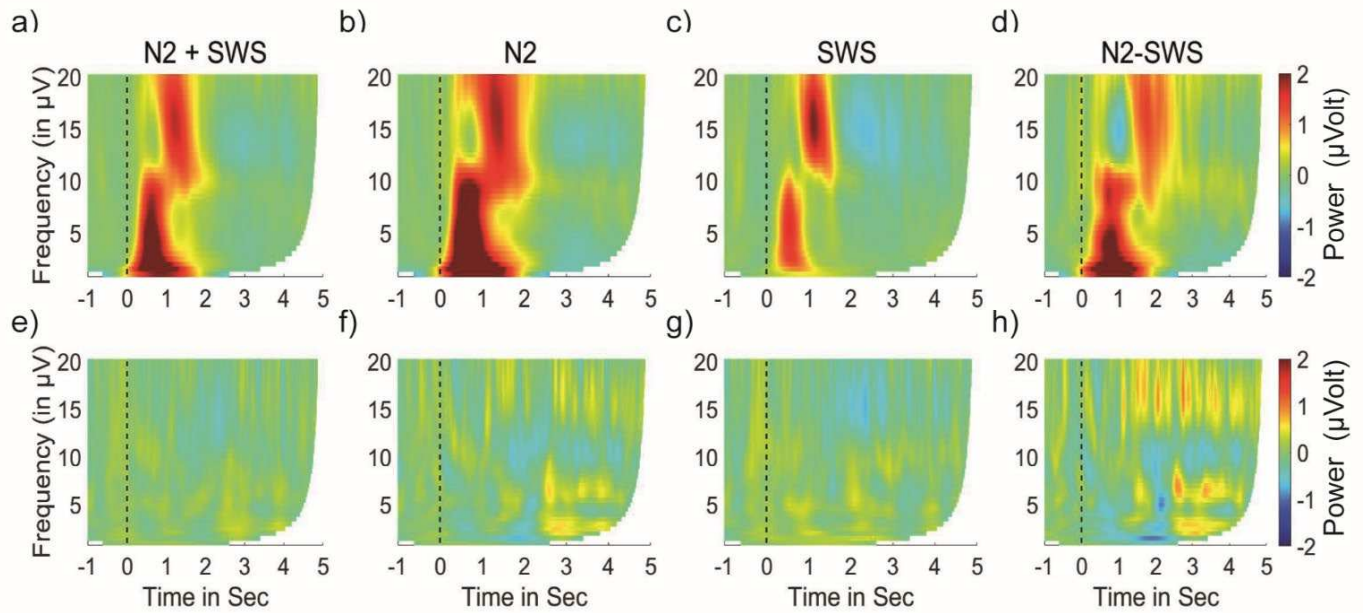
Figure 2

Figure 2: Averaged oscillatory responses to words presented during N2 and SWS in the time frequency spectrum recorded at all frontal channels (F3, F4, Fz, F7, F8) for memory-independent and memory-dependent processes. **a)** Oscillatory power changes to all words presented during N2 and SWS show characteristic increases in the delta, theta, and alpha band, followed by increases in the spindle and beta band **b)** Oscillatory responses to all words presented in N2 **c)** Oscillatory responses to all words presented during SWS **d)** Difference between the neural responses of all words in N2 and SWS. Responses in all different frequency bands were more pronounced after word presentations during N2 than in SWS (see text, for significant clusters). **e)** For memory-dependent oscillatory processes, we did not observe any significant cluster when comparing oscillatory responses for all remembered words, irrespective of the sleep stages when words were presented. **f)** Similarly, no difference between the oscillatory responses of all remembered and non-remembered words during N2. **g)** Also, no significant difference between the neural responses of all remembered and non-remembered words during SWS. **h)** Consistently, we could not detect any

significant increase or decrease between memory-dependent oscillatory processes after reactivation in N2 vs. SWS.

In a next step, we categorized the words into “Remembered” and “Non-Remembered” based on morning retrieval to measure neural correlates associated to successful memory reactivation. Differences in this measure have been linked to memory processes during sleep (Schreiner & Rasch, 2017). Higher values on this comparison indicate increased oscillatory responses for later remembered vs. non-remembered words. Because theta power has been repeatedly associated with successful memory reactivation during sleep (Osipova et al. 2006; Nyhus and Curran 2010), we examined theta-power (5-7 Hz) in the time window of 500 – 800 ms after cue onset as described by Schreiner et al. (2015a). In contrast to previous findings, we were not able to detect significant clusters within this particular time window independent of the sleep stage ($p > 0.05$, see Figure 2e, f and g). When contrasting oscillatory correlates of successful memory reactivation during N2 and SWS, we observed a mild increase in theta power in a later time window (2500 ms to 3000 ms, see Figure 2h). Nevertheless, this cluster also did not reach significance.

Discussion

In the current study, we specifically compared the influences of reactivating words selectively during stage N2 sleep and slow-wave sleep (SWS). While targeted memory reactivation (TMR) did not differ during N2 and SWS, we found no beneficial effect of TMR on memory compared to words not reactivated during sleep. We observed this pattern of results in both our main study sample (8 hours sleep duration) and our additional sample (3 hours sleep duration). Also, combining the two sample did not alter our results. On a neurophysiological level, words presented during sleep elicited the well-known responses, including K-complexes and increases in spindle oscillations, with significantly higher responses after reactivation during N2. However, we observed no memory-specific increases in theta or spindle oscillations for successfully remembered vs. non-remembered words.

The fact that we could not replicate the memory-enhancing effect of TMR independently of sleep stages was unexpected. We used exactly the same task and procedures as reported in our previous studies. For example, we reported a memory-enhancing effect in a sample of healthy young adults applying TMR during N2 and SWS using the identical Dutch vocabulary task (Schreiner and Rasch 2015). In addition, we replicated the memory benefits of TMR (again N2 and SWS combined) in three separate groups in a subsequent study using the same task (Schreiner and Rasch 2015). While the experimental and task procedures, the stimuli, the sleep laboratory and the sample characteristics were highly comparable and the sample size even higher than in the previous studies, we can only speculate on possible reasons for our failure to replicate the TMR benefits on memory consolidation during sleep: First, one procedural difference between former study is words were reactivated selectively during N2 and SWS, and not during SWS only or SWS and N2 sleep combined as in previous studies

(e.g., Schreiner and Rasch 2015). Thus, it could also be that reactivation in both sleep stages is necessary to induce memory benefits by TMR. However, we also observed non-significant findings in previous studies reactivating in both sleep stages N2 and SWS together (e.g., Wilhelm et al. 2020; Cordi et al. 2018). Conversely, some studies reported memory-enhancing effects of TMR after selective reactivation during N2 sleep (see meta-analysis in Hu et al. 2020). Sleep duration between encoding and recall does not appear to be critical, as we did not find sleep-stage specific memory benefits after 8 hours or 3 hours of sleep. Moreover, also in the meta-analysis, the TMR benefit was not dependent on the sleep duration and occurred equally for nighttime and nap studies (Hu et al. 2020). Another problem may be that we did not control for the influence of REM sleep. Recent studies suggest that the integration of TMR-triggered information depends on the occurrence of REM sleep, and thereby influences the strength of memory consolidation (Tamminen et al. 2017). However, this does still not explain our pattern of results.

Another difference between the current study relative to former studies is that a larger portion of learned words was reactivated. In the current study, 67 % were reactivated and not 50 % as in studies before. This may have increased the probability of the reactivation generalizing to the non-cued words. However, Schreiner et al. (2015b) also reactivated 67% of the items and reported positive TMR effects on memory consolidation during sleep.

Additionally, we conducted a within-subject comparison for one night. Therefore, we cannot exclude a possible competition in reactivation between stages resulting in a lack of effect.

Another critical point is that we started to reactivate during N2 (but not SWS) in all our participants, as N2 sleep typically occurs before SWS. Therefore, we cannot exclude an effect of sequence on sleep-stage specific TMR benefits on memory. However, participants reached SWS already after 21.5 ± 2.24 min, thus many N2 words were also played after the first SWS period

assuring some counterbalance between TMR during N2 and SWS. Finally, the sample could have been different in basic characteristics compared to former studies.

Another important explanation of our failure to find a memory-enhancing effect of TMR may lie in our low statistical power. Although the effects of TMR on memory were statistically significant in the meta-analysis (Hu et al. 2020), the effect size was in the small to medium range. Importantly, within-subject comparisons typically have a higher statistical power than between-subject experiments because fewer participants are usually required. However, the actual power of within-subject comparisons is strongly dependent on the correlation between measurement points. In our combined sample, the average correlation between measurement points was small and negative ($\rho = -0.08$, statistical power ca. 55% with $n = 34$, 3 measurements, medium effect $f = 0.25$, $\alpha = 0.05$), which greatly reduces statistical power compared with plausible positive and medium sized correlations in similar designs (e.g., with a typically assumed $\rho = 0.5$, the statistical power would reach ca. 89% in our study). It might be worth collecting average ρ values from existing TMR studies that have used within-subject designs to obtain a better estimate of plausible ρ values, which may facilitate the sample size planning in the future (e.g., average ρ values vary from -0.15 to 0.53 in our recent verbal TMR studies (Schreiner and Rasch 2015; Schreiner et al. 2015b; Göldi et al. 2019)).

Improving the quality of our study planning (including sample size estimation, pre-registration of hypotheses etc.) is also an important issue in TMR research, as Hu et al. (2020) reported a publication bias in their meta-analysis: more positive studies and fewer negative studies seem to have been published in this area. Generally, larger sample sizes and studies involving collaborations with multiple laboratories are indispensable to improve reproducibility in the field, together with the need for the publication of all available negative or zero findings. Our recent call for replications and larger sample size in the field of sleep and memory (see Cordi and Rasch 2021)

has already stimulated the publication of some studies with large samples (see e.g., Denis et al. 2022).

Since we were unable to observe a memory-enhancing effect of TMR compared to non-reactivated words in our current study, a clear interpretation of the sleep-stage specific TMR results is not possible. Nevertheless, it is interesting that we did not find a significant difference between words reactivated in N2 and in SWS. Additionally, in the TFA, we observed that words presented during N2 elicited stronger responses in all frequency ranges including theta and spindle oscillations. The increased neurophysiological responses are consistent with the assumption that sounds presented during N2 sleep are more likely to be processed compared to SWS (Andrillon and Kouider 2020). As spindle oscillations have been functionally implicated in memory processes during sleep (Fogel and Smith 2011), one might predict that enhanced processing associated with increased spindle oscillations should also lead to better memory reactivation/consolidation during sleep. A similar conclusion could be drawn for theta oscillations. However, increases in theta oscillations following TMR also occur independently of the memory-enhancing effect of TMR, suggesting that increases in theta oscillations might reflect successful reactivation rather than successful consolidation after stimulus presentation during sleep (see working model in Schreiner and Rasch 2017). Only increased theta followed by increased spindle activity could be beneficial for consolidation of reactivated memories during sleep. However, this pattern was actually more pronounced in N2 than in SWS, which did not lead to a better memory after TMR during N2. Importantly, the overall increase in oscillatory power after stimulus presentation in N2 compared with SWS was independent of memory, i.e., it occurred for both remembered and non-remembered words. In contrast to previous reports, we were not able to observe memory-specific increases in theta and spindle oscillations in our study. However, this could be explained by the missing behavioral effect of TMR in our study. Additionally, when comparing oscillatory power changes

between words presented in N2 and SWS, our results may be biased by differences in baseline activity between the two sleep stages. In our analyses we applied a baseline correction from -1 to 0 seconds before the word presentation. This might have limited the extent of power enhancement by words in the lower frequency bands during SWS compared with N2 sleep, because e.g., SWA in the baseline period is higher in SWS than in N2 sleep. However, in an exploratory analysis without baseline correction, the large difference in SWA power overshadowed any event-related power changes of word presentation during sleep for this comparison. Thus, we believe that a baseline correction is necessary to describe event-related power changes in different sleep stages. Furthermore, we have successfully used baseline corrected time frequency data to detect TMR related power changes in N2 and SWS (see the supplementary information of Schreiner and Rasch (2015)).

In sum, we were not able to replicate the memory-enhancing effect of TMR in the Dutch vocabulary task and are therefore unable to answer the question whether N2- or SWS-TMR contributes to reactivation-induced memory benefits during sleep. However, the topic should not decrease in relevance due to our non-existing significances. Overall, there is a need to investigate the boundary conditions for TMR, as they are of great importance. Future studies could use the same experimental design to test the still important question with a different memory task, as we cannot draw a meaningful conclusion because our task seem to not have worked properly. In addition, pre-sleep learning strength might have affected the benefits of TMR during sleep, as the general effects of sleep on memory also depend strongly on memory strength and prior knowledge (see for example Cordi et al. 2023). Furthermore, it could be interesting to examine whether incorrect answers given during encoding before sleep are maintained and consolidated during sleep. Moreover, next studies could consider the two halves of the night. Since Rasch and Born (2013) have suggested that it is not a quantitative but a qualitative difference of the N2 sleep during the

two night-halves, it would be interesting to reactivate different sets of items during SWS in the first half of the night and in N2 in the second half of the night. This could provide deeper insights into whether or to what extent the memory processes during N2 within the first half of the night depend on the processes of the SWS. In addition, a following study could even compare the memory consolidation process during N2 of the first and second night-half.

Materials and Methods

Participants

The sample consisted of 24 young and healthy participants (14 females) aged 18 to 30 years ($M = 23.38$; $SD = 3.63$). All subjects were German speakers, had no prior knowledge of the Dutch language, were free of any physical and mental disease and reported a healthy wake-sleep-cycle. Due to errors in list generation (see Reactivation of vocabulary for details), we had to exclude 3 participants from all analyses. Therefore, the final sample consisted of 21 individuals (12 women) aged 18 to 30 years ($M = 23.29$; $SD = 3.52$).

We conducted an a priori power analysis using G*Power version 3.1.9.6 (Faul et al. 2007) to determine an adequate sample size for ANOVAs including 3 repeated measures. To achieve 80 % power to detect a medium effect ($f = 0.25$) at a significance level of $\alpha = .05$ and a correlation among measurements of $\rho = 0.6$, the required sample size was $n = 23$. Subjects were recruited via a newsletter sent to psychology students and advertisements on various internet platforms. Two days before each session, subjects received a reminder-e-mail containing the instruction to refrain from consuming alcohol for two days prior the experiment. Additionally, they were asked to get up at least at 7:00 a.m. in the morning of the experimental day and to stop consuming caffeine from 2 p.m. on.

The local ethics committee approved the study, and all subjects gave written informed consent in the beginning of the experimental night. Moreover, subjects received an expense allowance of 50 CHF for participation.

Design and procedure

The study took place in one experimental night. Subjects arrived at 08:30 p.m. in the sleep laboratory of the University of Fribourg, filled out various questionnaires, and prepared for the

night. Once the experimenter attached the electrodes for polysomnographic recordings, subjects performed the Dutch–German word pairs task (details in Vocabulary learning task). At approximately 11:00 p.m., the subjects went to bed and lights were turned off for eight hours. After sleep onset and entering NREM sleep, the experimenter manually started the reactivation of previously learned Dutch words. For each of the two sleep stages, N2 and SWS, a separate list of 40 Dutch words was played (cued words, see Reactivation of vocabulary for details). After approximately 400 words were played in each sleep stage (N2-TMR: $M = 369.32$ $SE = 8.99$; SWS-TMR: $M = 364.86$, $SE = 16.02$, no significant difference detected, $t(20) = 1.09$, $p = 0.29$), the experimenter stopped the reactivation procedure, and the subject slept for the remaining time. After eight hours, the experimenter turned on the light and woke up the subject. Again, subjects completed questionnaires and recalled the German translations of the Dutch words (see Cued recall testing for details). In the end, the experimenter detached the electrodes, and subjects left the laboratory between 7:00 and 8:00 a.m.. The procedure is illustrated in Figure 1a.

Questionnaires

Prior to the experimental session, subjects filled out various questionnaires to obtain information about demographics, general health. We used the Edinburgh Handedness Inventory to identify the handedness of the subjects (Oldfield 1971). Moreover, we used the (Buysse et al. 1989) to gain information about the subjective sleep quality and habits of the last four weeks.

After sleep, subjects filled out the SF-A/R questionnaire (Görtelmeyer 2011) to gauge the subjective sleep quality (general sleep characteristic; ASC) of the previous night. The scores of these individual questionnaires are shown in Table 4.

Table 4. Overview of questionnaire data

	Mean	SD
Age [in years]	23.29	3.52
EHI [in %]	69.52	49.95
PSQI [index]	6.15	1.56
ASC [index]	3.48	0.75

Note. Overview of questionnaire data. Age of participants is indicated in years; EHI: Edinburgh Handedness Inventory, indicated by questionnaire index; PSQI: Pittsburgh Sleep Questionnaire Inventory, indicated by questionnaire index; ASC: General sleep characteristic, scale of the SF-A/R, indicated by questionnaire index. Numbers are means $\pm$ standard deviation (SD).

Vocabulary learning task

The vocabulary learning task was created and used in a previous work by Schreiner and Rasch (2015) using E-Prime software 2.0.10 (Psychology Software Tools Inc., Pittsburgh). It contains 120 Dutch - German word pairs and consists of three parts in the learning phase before sleep: 1. Passive encoding, 2. Immediate retrieval with feedback and 3. Immediate retrieval without feedback. In all parts, words are presented acoustically via loudspeaker (range of word duration: 450–700 ms) in a randomized order (word pairs and lists (Tables S1, S2, and S3) in the supplementary material). Due to technical problems in some test runs, we excluded one word pair of the word list. During the first part (passive encoding), each Dutch word is presented followed by its German translation. An inserted affixation cross between the Dutch and German translation of 200 ms and an interval of 1000-3000 ms between each word pair reduced presentation speed of words. Within this phase, subjects try to memorize as many word pairs as possible. In the second phase (immediate retrieval with feedback), the subjects only hear the Dutch word again, and speak out the German translation or indicate that they do not know it. Irrespective of whether it was

remembered correctly or incorrectly, the correct German translation is presented again. During the third part (immediate retrieval without feedback), the subjects hear the Dutch words one last time but contrary to the second phase, no feedback is given about the correct German translation. The experimenter manually codes the correctness of each answer with '1' for correct and '2' as incorrect. The performance level of the final part built the baseline of memory performance before sleep.

Reactivation of vocabulary during the night

Based on the individual final memory performance during the evening, a MATLAB (Mathworks, Natick) algorithm generated a separate 40-word list consisting of prior known and unknown words for each sleep stage N2 and SWS. 40 Dutch words were not presented during sleep (uncued control words). In each word list, the number of previously known and unknown words was equally distributed. On average, the range of known words in all three categories was 11 to 22 words.

We used EPrime 2.0.10 (Psychology Software Tools Inc., Pittsburgh), to acoustically play the words from both lists at a volume of 50 dB via loudspeakers and presented them in a random order at the appropriate sleep stage. Cues were separated by an interstimulus interval of 5000–7000 ms.

During the night, an experimenter monitored the sleep of the subject. As soon as signs of stable N2 or SWS appeared (as given by the American Association of Sleep Medicine (AASM; Iber et al. 2007)), the experimenter manually started the reactivation of the corresponding word list and paused immediately when signs of arousals, awakenings, or transitions to N1 or REM sleep were detectable. Due to the typical pattern of sleep architecture, TMR of N2 words was started

earlier than TMR with SWS words. As soon as the SWS became apparent by a higher occurrence of delta waves, the experimenter switched to the SWS list.

Once 400 words had been played in each sleep stage (each word was played $9.01 + 13.58$ times), the experimenter terminated the reactivation procedure. This was the case after approximately 2 or 3 sleep cycles.

Cued recall testing after sleep

Following eight hours of sleep, we confronted the subject with the third phase of the vocabulary task (retrieval without feedback) again. After listening to the Dutch word, subjects spoke out the German translation, without any feedback being given.

Polysomnographic recordings

We collected electrophysical data during sleep with different polysomnographic components (PSG): For the electroencephalogram (EEG), we used 18 single gold-cups electrodes which we positioned in accordance with the international 10-20 system (C3, C4, Cz, F3, F4, F7, F8, Fz, Fpz, P3, P4, Pz, M1, M2, O1, O2, T5, T6; Chatrian et al. 1985). Moreover, we affixed the electromyogram (EMG), the electrooculogram (EOG) and the electrocardiogram (ECG) according to the international recommendation by the AASM (Iber et al. 2007). The EEG was derived referentially, whereas the EMG, EOG, and ECG were derived bipolar. However, we set all low and high frequency recording filters of each component to the recommended level of the AASM (EEG: 0.3 Hz / 35 Hz; EOG: 0.3 Hz / 35 Hz; EMG: 10 Hz / 100 Hz; ECG: 0.3 Hz / 70 Hz; Iber et al. 2007) and kept all impedances below 5 k Ω .

Sleep scoring

The electrophysiological data was first re-referenced to the contralateral mastoid and filtered as recommended by the AASM (Iber et al. 2007), using the software BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) Then, we segmented the eight hours of bed time (from ‘Lights off’ to ‘Lights on’) into 30-seconds-epochs and two independent sleep scorers visually classified the epochs with the different stages ‘Wake’, ‘REM’, ‘N1’, ‘N2’ or ‘SWS’. In case of disagreements, we consulted a third expert scorer.

Time frequency analyses

To gain further insights of the oscillatory activity of TMR during N2 and SWS, we conducted a time frequency analysis (TFA). For this purpose, we first preprocessed EEG data using BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) and removed artifacts from the data. In the beginning of this process, we imported sleep stage markers to serve as segmentation markers. Once, cues were separated into equally sized segments with borders set to 3 seconds before and 5 seconds after a cue, the following steps were done according to the procedure described by Ackermann et al. (2015). A high-pass filter was set to 0.1 Hz, a low-pass filter to 40 Hz and a notch filter to 50 Hz. Finally, data were re-referenced to the averaged value of both mastoids. Based on the sleep stages, equally sized sections of 2048 data points of 4 sec each with a 100-point overlap were created. Ensuring to analyze only artifact-free sections, an automatic artifact rejection excluded segments, if the maximal difference in EMG activity was over 150 μ V and the maximal difference in each EEG channel was over 500 μ V. Then, artifact free segments were exported and further analyzed with the Fieldtrip toolbox (Oostenveld et al. 2011). The TFA was done by adapting the procedure of Beck et al. (2021). Similarly, baseline was normalized with

a period of -1 to 0 s before stimulus onset. In a next step, we averaged overall data, per subject, per sleep stage and per morning performance, to compare oscillatory power in different frequencies (1-20 Hz) in a time window of 0 to 4.5 seconds after cue onset averaged across all frontal channels (F3, F4, Fz, F7, F8). Results were compared using cluster-based permutation tests for dependent samples as implemented in the FieldTrip toolbox (Oostenveld et al. 2011). For the cluster-level statistic, we used the maximum sum of t-values within every cluster. The cluster-level statistic was calculated for each of 1000 randomly drawn data partitions, which exceed the actually observed test statistic, resulting in a Monte Carlo p-value, controlling for multiple comparisons. The alpha level was set to .05 and corrected for two-sided testing.

We compared words played during N2 and during SWS. We also compared remembered and non-remembered words based on morning recall. We did this for all words overall, but also separately for each sleep stage.

Statistical analyses

We performed all analyses based on 119 words using R Studio software 4.3.1 (<https://posit.co/>). In order to determine the effects of TMR in N2 and SWS, several sets of mixed-design analyses of variances (ANOVA) were run. Effect patterns were further explored by post hoc t-tests. For all analyses, the significance level was set to $p \leq 0.05$. When Mauchly's tests revealed a violation of sphericity, the correction proposed by Greenhouse-Geisser was used. Within the result section, we report mean $\pm$ SEM.

Additional data

During the piloting phase of the main study, we conducted a small study with 13 subjects (mean age $M=22.14$ $SD = 2.87$). The TMR paradigm and the experimental design was identical to

our main study except for the sleep duration. In this study, subjects slept only 3 hours in total and TMR stimuli were delivered in the first 90 min (N2: 303.70 ± 34.68 , SWS: 376.54 ± 79.93 words did not differ $p > .35$). The recall of the words took place between 2 - 3 a.m..

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Disclosure Statement

The authors declare no conflicts of interest.

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2.2 The First-Night Effect of sleep occurs over non-consecutive nights in unfamiliar and familiar environments

Anna Zoé Wick¹, Selina Ladina Combertaldi¹ and Björn Rasch^{1 *}

¹ Department of Psychology, University of Fribourg, Fribourg, Switzerland

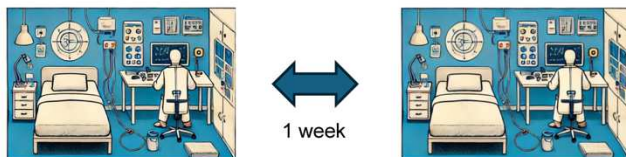
*Corresponding

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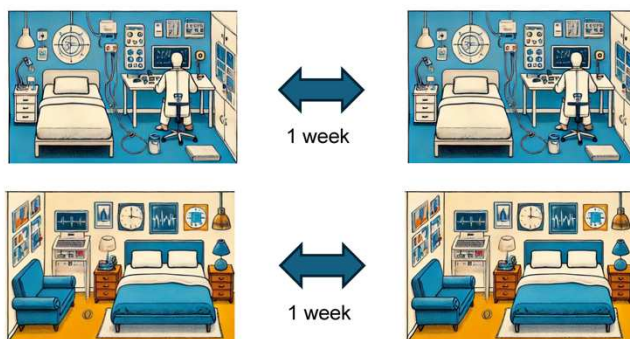
Björn Rasch, Department of Psychology, University of Fribourg, Rue P.-A.-de-Faucigny 2, CH-1700 Fribourg, Switzerland. Email: bjoern.rasch@unifr.ch

What are the First-night effects of two nights one week apart?

Study 1: Sleep Laboratory



Study 2: Sleep Lab and at Home



Results

First night Second night

↑	Sleep onset latency	↓
↑	Wake after sleep onset	↓
↓	Total sleep time	↑
=	Slow Wave Sleep	=
≈	Interhemispheric asymmetry	≈

In both environments

Conclusions

First-night effects occur also
when nights are one week apart

In Home and Lab environment

**Adaptation night needed in
sleep research studies**

Abstract

The first night in an unfamiliar environment is marked by reduced sleep quality and changes in sleep architecture. This so-called First-Night Effect (FNE) is well established for two consecutive nights and lays the foundation for including an adaptation night in sleep research to counteract FNEs. However, adaptation nights rarely happen immediately before experimental nights, which raises the question of how sleep adapts over non-consecutive nights. Furthermore, it is yet unclear, how environmental familiarity and hemispheric asymmetry of slow-wave sleep (SWS) contribute to the explanation of FNEs. To address this gap, 45 healthy participants spent two weekly separated nights in the sleep laboratory. In a separate study, we investigated the influence of environmental familiarity on 30 participants who spent two non-consecutive nights in the sleep laboratory and two nights at home. Sleep was recorded by polysomnography. Results of both studies show that FNEs also occur in non-consecutive nights, particularly affecting wake after sleep onset, sleep onset latency, and total sleep time. Sleep disturbances in the first night happen in both familiar and unfamiliar environments. The degree of asymmetric SWS was not correlated with the FNE but rather tended to vary over the course of several nights. Our findings suggest that non-consecutive adaptation nights are effective in controlling for FNEs, justifying the current practice in basic sleep research. Further research should focus on trait- and fluctuating state-like components explaining interhemispheric asymmetries.

Keywords

First-Night Effect, Environment, Sleep Quality, Polysomnography, Asymmetry, Sleep/Wake Cognition, EEG analysis, Electrophysiology

Statement of Significance

Sleep studies aim to investigate the nature of sleep to provide appropriate treatments or interventions to improve its quality. However, the sleep quality during the first night of sleep studies in unfamiliar environments seems to be confounded by a First-Night Effect. Here, we provide evidence that the current practice in sleep research of using adaptation nights several days before the actual experiment is effective in controlling for sleep impairments on the first night. These adaptation nights remain important in both unfamiliar (e.g. sleep lab) and familiar (e.g. home recording) environments.

Introduction

A considerable body of literature describes that sleep during the first night in a new, unfamiliar surrounding differs from sleep in a familiar environment. This phenomenon is known as the First-Night Effect (FNE) of sleep and was first described by Agnew and colleagues¹ in 1966. In 2022, Ding et al.² conducted a meta-analysis of 53 studies on the FNE over consecutive nights and found that indeed sleep quality and quantity were generally reduced in the first night compared to the second night: Particularly, objective sleep onset latency (SOL), Wake after Sleep Onset (WASO), the duration spent in non-rapid eye movement (NREM) sleep N1, and rapid eye movement (REM) latency were all longer on the first night. Additionally, compared to the second night, there was a decrease in Total Sleep Time (TST), Sleep efficiency (SE) and REM sleep. However, the meta-analysis did not find any significant effect on Slow-wave sleep (SWS) or SWS latency, nor any effects on N2 sleep. Based on the known changes in sleep architecture during the first night in an unfamiliar environment, it is recommended for sleep studies to include one adaptation night prior to the subsequent experimental night, but to disregard its data for further analyses³. Although this procedure is associated with a high investment of effort, time and money for researchers³, it is generally accepted in the field of sleep research.

However, this common practice has several weaknesses. First, the relative importance of adaptation nights for all sleep studies is controversial, depending on whether primary sleep variables are a central object of the investigation or not⁴. Second, although Ding et al.² concluded in their meta-analysis that no significant differences were observed in most sleep parameters between the second and the following nights, it remains unclear whether an unfamiliar environment influences the sleep architecture only in the first night or whether the adaptation process continues onto subsequent nights (see ^{1,2,5-7}). Third, the FNE is influenced by several factors, such as sleep patterns in the past week³ or age (i.e., milder FNEs in young participants compared to older

participants²). Finally, and most importantly, most data on the FNE are derived from studies conducted on consecutive nights, meaning that participants spent two nights in a row in the sleep lab². This procedure differs from the common practice in sleep research, which typically includes an adaptation night several days or even weeks before the actual experimental night. Thus, to establish a strong foundation for integrating adaptation nights in sleep research, data on the FNE and adaptation effects of sleep in an unfamiliar environment over several non-consecutive nights in healthy young participants are required. So far, only very few studies have systematically examined adaptation processes across non-consecutive nights. One study by Lorenzo and Barbanoj⁸ recorded sleep in healthy young participants in three sessions over the course of four consecutive nights each. The interval between the three sessions was one month. They observed reductions in objective sleep quality, particularly significant changes in REM-related sleep variables indicative of an FNE only in the first night of the first session. No FNE was observed in the first nights of the second or third session.

A similar finding is reported by Thornby⁹ who studied healthy young participants for four nights each separated by a few days. An FNE was also observed, especially in variables related to REM sleep. In a long-term study over 10 weeks, patients with insomnia slept in the sleep laboratory for two consecutive nights each week. The authors did not report any reoccurrence of the FNE. However, Scharf et al.¹¹ also carried out a long-term sleep study with patients that suffered from insomnia. As opposed to Stepanski et al.¹⁰ they reported that a reduction in sleep quality indicative of FNE occurred when insomnia patients returned to the sleep laboratory. Thus, although some findings suggest that adaptation to the new environment may also be observed in non-consecutive sleep recordings, the data are not fully consistent.

In addition, it remains unclear whether FNEs in non-consecutive nights only occur in unfamiliar environments, or whether they also occur in a familiar environment (e.g. at home)⁵. For

consecutive nights, impairments of sleep in the first night also occur in familiar home settings, possibly due to the unfamiliarity of the recording situation and the polysomnographic equipment (e.g. electrodes, etc., see meta-analysis²). However, it is still unknown whether FNEs also occur in a home environment when recording nights are spaced apart by several days.

Finally, the underlying mechanisms generating FNEs remain unclear. In recent years, an interesting hypothesis has been proposed linking changes in sleep architecture during the first night to asymmetric sleep behavior: Tamaki and coworkers¹² proposed that the FNE may be related to increased monitoring demands of the new, unfamiliar environment, reflected in a decrease in one hemisphere's depth of sleep. In their study, the left hemisphere showed reduced power in the delta-activity range (1 - 4 Hz) during SWS in the first night, but not in a second night recorded one week later. This interhemispheric asymmetry of delta activity during SWS predicted increases in objective SOL during the first night. Follow-up studies confirmed that the left hemisphere reacted more vigilantly than the right hemisphere in the first sessions. From these data, the researchers concluded that the FNE might act as a protective mechanism in an unfamiliar environment during the first night by keeping one brain hemisphere more alert. Contrary to this idea, multiple earlier studies examining interhemispheric asymmetries have found no consistent relationship between hemispheric asymmetry during SWS and FNEs^{13,14}. Furthermore, recent studies rather suggest stable and trait-like components for hemispheric asymmetries during sleep, possibly linking the degree of asymmetries to inter-individual difference in the anatomy of the corpus callosum¹⁵. In light of these contradicting findings, we also analyzed whether or not the hemispheric asymmetry of delta oscillations during SWS was larger during the first night compared with subsequent nights and whether the degree of asymmetry was correlated with an FNE of sleep.

Thus, the aim of our study was to investigate whether an FNE reoccurs in sleep studies with non-consecutive weekly nights, and whether or not FNEs in a familiar environment differ from

those in an unfamiliar environment. In addition, we examined the degree of interhemispheric asymmetric activity (IAA) over the course of the different nights and in the different environments. To generate more data on this equivocal matter, we studied the adaptation processes over two, weekly separated, non-consecutive nights. In Study 1, 45 participants spent two nights in the sleep laboratory. In Study 2, 30 participants spent two nights in the sleep laboratory, and two nights at home, in a balanced sequence. Sleep was recorded using polysomnography. We show that an FNE occurs in non-consecutive nights mainly affecting SOL, WASO, and TST. In addition, we report that FNEs occur in non-consecutive nights in both familiar and unfamiliar environments. Finally, we find that the degree of IAA of delta oscillations during SWS is not related to the FNE, but that the left-hemispheric reduction in sleep depth is rather stable over the course of the non-consecutive nights.

Methods

Participants

Study 1 is a re-analysis of data sets drawn from two independent experiments (published in^{16,17}; A more detailed description of the two subsamples is provided in the supplementary information). We collapsed the data of both experiments into one single data set, as the two experimental designs were basically identical (see Design and procedure for further details). Study 1 included 45 young and healthy participants (32 females), ages 18 to 31 ($M = 22.27$; $SD = 2.85$) in the analysis of sleep parameters. In the frontal asymmetry analysis, we included only 35 participants due to the loss of the essential frontal EEG electrodes during one night of the two recorded nights.

Study 2 was specifically designed to investigate the adaptation process between an unfamiliar and a familiar sleeping environment. A total of 31 healthy young participants (22 female, 1 diverse) were included, aged 19 to 31 ($M = 22.81$; $SD = 3.28$). Due to the loss of EEG electrodes during the night, the data from one participant had to be excluded from the analysis of sleep architecture and another data set had to be excluded from the frontal asymmetry analysis. As a result, data from 30 participants were taken into account in each analysis.

All subjects were either German-, French-, or Italian-speaking, in good general health (as indicated by the absence of any medical conditions, physical or mental diseases as assessed by a pre-screening questionnaire) and reported a healthy wake-sleep cycle with no sleep problems. In addition, the subjects were not involved in shift work and did not suffer from jet lag. We recruited subjects via a newsletter sent to psychology students and advertisements on several internet platforms. Two days before each session, subjects received a reminder e-mail containing the instruction to refrain from consuming caffeine and alcohol for two days prior to the experiment. Additionally, we asked subjects to get up no later than 7:00 a.m. on the day of the experiment. Noteworthy, for Study 2, an additional eligibility requirement was that participants generally did

not share a bedroom.

The studies were approved by the local ethics committee and all subjects gave written informed consent in the beginning of the adaptation night. The study was conducted in accordance with the declaration of Helsinki. Subjects received a compensation of 160 CHF for their participation. In case of an early abandonment, we paid subjects proportionally.

Design and procedure

In both studies, we recorded sleep using polysomnography (see Figure 1, for a summary of our design and procedure). In Study 1, subjects spent all nights in the sleep laboratory at the University of Fribourg, with exactly one week between both nights (Figure 1a). Nights were undisturbed but differed with respect to pre-sleep instructions and interventions which were counterbalanced intra-individually (see ^{16,17} and supplementary information). Thus, it is possible to rule out the impacts of these interventions on order and habituation during the nights. Subjects arrived at the sleep laboratory every night between 08:15 and 08:30 p.m. After filling out various questionnaires, subjects had time to get prepared for the night. Next, the experimenter attached the electrodes for the polysomnographic recordings and the participants performed a cognitive task. Then, the subjects went to bed and lights were turned off for eight hours. In the morning, the experimenter turned on the light and woke up the subject. Participants immediately filled out questionnaires and performed several cognitive tasks. Afterwards, the experimenter detached the electrodes, and the subjects left the laboratory between 7:00 and 8:00 a.m.

In Study 2, the subjects spent two nights in the sleep laboratory and two nights in their usual familiar environment, in a balanced order (see Figure 1b). We considered the sleep laboratory as the “unfamiliar” sleep environment and sleeping at home as the “familiar” sleep environment. After

the experimenter attached all electrodes, subjects either went home or spent the night in the sleep laboratory.

Before subjects left the laboratory to sleep at home, the experimenter instructed them to sleep according to their individual sleep habits. In contrast, we strictly enforced a bedtime between 10:30 and 11:00 p.m. in the sleep laboratory, and the subjects were woken up after exactly eight hours.

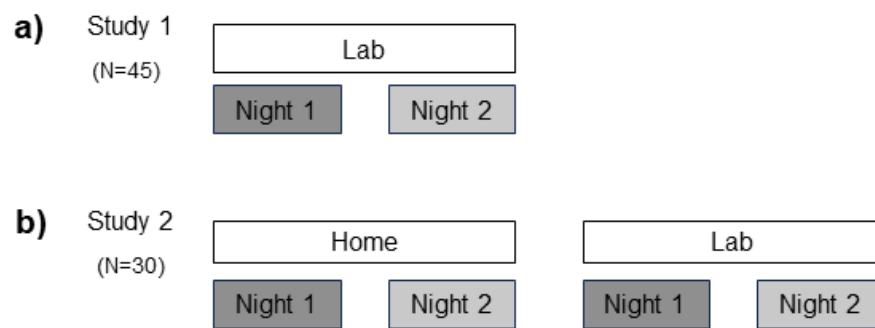


Figure 1. a) Study design of Study 1: The study consisted of two nights, each separated by 1 week, conducted in the sleep laboratory. In all nights, participants slept in the sleep laboratory. **b)** Study design of Experiment 2: The study consisted of four nights, each separated by a one-week interval. Half of the participants slept first in the sleep laboratory for two nights and then two nights at home or vice versa. The order was randomized and counterbalanced between the subjects.

Questionnaires

Prior to the first session, subjects filled out various questionnaires to obtain information about demographics, general health, handedness, drug consumption, and personality. We used the Morningness-Eveningness-Questionnaire¹⁸ and Pittsburgh Sleep Questionnaire Inventory¹⁹ to gain information about the chronotype, subjective sleep quality and sleep habits during the last

four weeks. Throughout each session, subjects filled out short questionnaires before they went to bed and after they woke up. They rated their sleep quality of the preceding night. They were also asked about any alcohol, nicotine, caffeine, and other drug consumption during the day. Finally, in order to determine the present mood, they used a Likert scale to rate several items (MDBF²⁰). The following morning, we operationalized the subjective sleep quality from the previous night using the SFAR questionnaire²¹, and once more, we collected data on the subjects' moods using the MDBF²⁰.

Polysomnographic recordings

We collected electrophysical data during sleep using different polysomnographic components: The electroencephalogram (EEG) consisted of twelve single gold-cups electrodes which we positioned in accordance with the international 10-20 system (C3, C4, Cz, F3, F4, Fpz, P3, P4, M1, M2, O1, O2)²². Moreover, we attached the electromyogram (EMG), the electrooculogram (EOG) and the electrocardiogram (ECG) according to the international recommendation by the American Academy of Sleep Medicine (AASM²³). We derived the EEG referentially, whereas the EMG, EOG and ECG were generated bipolar. However, we maintained all impedances below 5 k Ω and set the sampling rate to 500 Hz, along with the low and high frequency recording filters of each component set to the suggested level of the AASM (EEG: 0.3 Hz / 35 Hz; EOG: 0.3 Hz / 35 Hz; EMG: 10 Hz / 100 Hz; ECG: 0.3 Hz / 70 Hz)²³.

In Study 2, we used a mobile polysomnographic device (SOMNOtouchTM RESP, SOMNOmedics), for electrophysiological recordings with 10 single gold-cup electrodes. We positioned the six EEG electrodes at F3, F4, Fpz, Cz, M1, M2²². The two EOG and two EMG electrodes we attached following the standards of the AASM²³.

Sleep scoring

Prior to sleep scoring, we used the program BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) to prepare and filter the polysomnographic data as recommended by the AASM²³. Then, we segmented the eight hours of bedtime (from ‘Lights Off’ to ‘Lights On’) into 30-seconds-epochs, which were visually scored and classified into the different stages ‘Wake’, ‘REM’, ‘N1’, ‘N2’, or ‘SWS’ by two independent sleep research PhD students, who are highly trained and experienced in sleep scoring. Agreement rate of the two sleep scorers was on average 86%. In case of a disagreement, we consulted a third expert sleep scorer.

Power analysis

We used the BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) for EEG data management and frequency analyses. In the beginning, we imported sleep scorings as segmentation markers. For the following steps of performing a Fast Fourier Transformation (FFT), we used the procedure described by Ackermann et al.²⁴ with small exceptions. Likewise, we set a high-pass filter (0.1 Hz) and a low-pass filter (40 Hz) and re-referenced the data to the averaged power of both mastoids. Then, we used the SleepCycles package for R²⁵ to segment the sleep into its sleep cycles. Following the procedure of Tamaki et al.¹² we also inspected only the SWS of the first sleep cycle.

After performing these steps, within the SWS of the first sleep cycle, we created equally sized sections of 2048 data points respectively 4 seconds with a 100-point overlap. Making sure that only segments free of artifacts were analyzed, an automatic artifact rejection excluded segments, if the maximal difference in EMG activity was over 150 μ V and the maximal difference in each EEG channel was over 500 μ V. Finally, an FFT with a 10% Hanning window and a resolution of 0.25 Hz was performed for every EEG channel to calculate the power (in μ Volt) of the delta (1 - 4.5 Hz),

theta (4.5-8 Hz), alpha (8-11 Hz) sigma (11-15 Hz) and beta (15-25 Hz) frequency bands. Importantly, due to the fact that only frontal electrodes (F3, F4) were available in Study 2, it was only possible to compare the frontal power of the different frequency bands in both Study 1 and Study 2.

Asymmetric Index

The asymmetry index (AI) corresponds to the interhemispheric slow-wave activity (SWA) in the frontal regions during SWS and it is calculated following the formula $[(\text{left SWA} - \text{right SWA}) / (\text{left SWA} + \text{right SWA})]^{12}$. The more the final value (given in μVolt) differs from 0 the more asymmetric activity was present.

Statistical analysis

We carried out all analyses using the R Studio software 4.3.1²⁶. In order to determine the existence and appearance of an FNE and asymmetric activity, we ran several sets of analyses of variances (ANOVAs). Effect patterns were further explored by post hoc t-tests and Helmert contrasts. For all analyses, the significance level was set to $p \leq 0.05$, and a level of $p < 0.1$ was considered to indicate a statistical trend. When Mauchly's tests revealed a violation of sphericity, the correction proposed by Greenhouse-Geisser was used. Prior to any analyses, objective data was checked for outliers. When a value for each individual sleep metric throughout the course of the two nights together exceeded the range of ± 3 SD of the mean formed, that value was conservatively designated as an outlier. In this case, the participant was excluded for the ANOVA considering the respective sleep parameter. This was done separately for Study 1 and 2.

We used no correction for multiple comparisons. We deliberately chose a liberal statistical threshold to reduce the chance of false negatives and to increase the statistical power of our study.

This allows us to detect also medium-sized FNEs on sleep parameters. With this strategy, we minimized the chance of falsely concluding that some parameters do not show FNEs when they actually do. Thus, we were more conservative in rejecting the need for an adaptation night. Conversely, if we do not find significant differences for certain sleep parameters even with our liberal threshold, we can be fairly certain that no medium-sized adaptation effect exists for these parameters. This means that an adaptation night is probably not necessary when these sleep parameters (e.g. SWS) are the focus of investigation. We believe that our liberal statistical strategy is well justified given the main aim of our study. Please note that our strategy implies that some of our reported FNEs may be false-positives and therefore require independent replication.

Results

In a first analysis step, we tested adaptation effects across the two first nights in Study 1. Then, we report the impact of the factor “Environment” on the adaptation process in Study 2. In the end, we present the results concerning the interhemispheric asymmetric activity (IAA) within the delta band during SWS.

Study 1: Adaptation processes over four non-consecutive nights

In Study 1, we detected evidence for a First-Night Effect (FNE) for the following sleep parameters: Objective sleep onset latency (SOL), total sleep time (TST) and total time between sleep onset and lights on (TOTAL), and trends for wake after sleep onset (WASO) and slow-wave sleep latency (SWS latency; see Table 1 for descriptive values).

Table 1

Sleep parameters of Study 1

Sleep parameter	Night 1			Night 2			N	Statistics ANOVA
	Mean	SEM		Mean	SEM			
SOL [in min]^a	20.37	± 2.05		14.01	± 2.19		45	$F(1,44) = 8.33, p = .006, \eta^2 = .05$
WASO [in %]^c	3.5	± 0.58		2.26	± 0.39		43	$F(1,42) = 3.33, p = .075, \eta^2 = .04$
N1 [in %]	5.85	± 0.34		6.14	± 0.36		43	$F(1,42) = 0.59, p = .448, \eta^2 < .01$
N2 [in %]	46.25	± 1.1		47.66	± 1.01		45	$F(1,44) = 1.20, p = .279, \eta^2 = .01$
SWS [in %]	21.64	± 1.18		20.69	± 0.8		44	$F(1,43) = 0.66, p = .422, \eta^2 < .01$
REM [in %]	19.48	± 0.74		20.34	± 0.6		45	$F(1,44) = 1.19, p = .281, \eta^2 < .01$
SWS latency [in min]^c	15.69	± 0.97		14.14	± 0.89		45	$F(1,44) = 3.03, p = .089, \eta^2 = .02$
REM latency [in min]	103.07	± 5.98		90.83	± 5.98		44	$F(1,43) = 2.82, p = .100, \eta^2 = .02$
TST [in min]^a	438.05	± 5.05		450.65	± 4.14		44	$F(1,43) = 4.26, p = .045, \eta^2 = .04$
Total [in min]^a	457.99	± 3.2		465.95	± 2.57		42	$F(1,41) = 4.60, p = .038, \eta^2 = .04$
Subjective SOL [in min]	19.22	± 2.34		15.12	± 2.7		45	$F(1,44) = 2.00, p = .165, \eta^2 = .01$
Subjective WASO [in min]	14.63	± 3.13		13.56	± 3.47		45	$F(1,44) = 0.09, p = .771, \eta^2 < .01$
Subjective SQ [index]	26.36	± 0.68		26.16	± 0.75		45	$F(1,44) = 0.05, p = .818, \eta^2 < .01$

Note: Time spent in the different sleep stages in Study 1 during Night 1 and Night 2. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow-wave sleep; REM: rapid eye movement sleep; TST: Total sleep time; Total: Total time between sleep onset and 'Lights On'; Subjective SQ: Subjective sleep quality. Numbers are means $\pm$ SEM (in minutes or percentage). **a)** Average of the first night differed significantly from the second night ($p < .05$). **c)** Average of the first night differed from the second night marked with a trend ($p < .1$).

For example, in the adaptation night, participants took an average 20.37 ± 2.05 minutes to fall asleep, compared to 14.01 ± 2.19 minutes in Nights 2, $F(1, 44) = 8.33, p = .006, \eta^2 = .05$; see Figure 2a, for pair-wise comparisons). Moreover, TST was significantly shorter in the first night (438.05 ± 5.05 min) compared to the second night (450.65 ± 4.14 min; $F(1, 43) = 4.26, p = .045$,

$\eta_G^2 = .04$; Figure 2e) as well as TOTAL, which was shorter in the first night (457.99 ± 3.20 min) than in the second night (465.95 ± 2.56 min; $F(1, 41) = 4.60, p = .038, \eta_G^2 = .04$).

We also found that during the first night, participants reached the stage of SWS (indicated by the SWS latency) later in the first night (15.69 ± 0.97 min) relative to the second night (14.14 ± 0.89 min). This sleep parameter was marked with a trend ($F(1, 44) = 3.03, p = .089, \eta_G^2 = .02$). In the same vein, we found another trend for WASO, as participants were more awake in the first night than the second night (3.50 ± 0.58 % vs. 2.26 ± 0.39 %; $F(1, 42) = 3.33, p = .075, \eta_G^2 = .04$).

Interestingly, no other objective sleep parameters (including the duration of N2, SWS or REM sleep) showed a significant FNE (Figure 2b and c), For subjective sleep parameters (i.e., subjective SOL, WASO and sleep quality (SQ)), we also found no significant main effects (all $p > .165$, see Table 1).

It is possible that the pre-sleep activity in this Study 1 may have had an impact on the participants' sleep quality. To exclude this potential bias, we conducted an additional analysis comparing only the adaptation night versus the neutral night of participants who slept in the second night in the neutral condition. This sample consisted of 16 participants. Even in this smaller subsample we continued to find FNE-affected sleep parameters. We still observe statistical trends for TST ($F(1, 14) = 4.14, p = .061, \eta_G^2 = .11$), SOL ($F(1, 15) = 3.14, p = .097, \eta_G^2 = .06$), SWS latency ($F(1, 15) = 4.36, p = .054, \eta_G^2 = .03$) and a significant difference for WASO ($F(1, 14) = 5.29, p = .037, \eta_G^2 = .14$). In addition, participants spent significantly less time in the sleep stage N2 during the first night than in the second neutral night, $F(1, 15) = 5.58, p = .032, \eta_G^2 = .06$. For further details (including means $\pm$ SEMs), please refer to Table S1 in the supplementary information.

In summary, adaptation nights seem to be beneficial for some sleep stages since SOL, TST, Total, SWS latency, WASO but also N2 sleep appear to be sensitive to FNEs but adapt during a

subsequent, non-consecutive night spent in the sleep laboratory, whereas time spent in SWS appear to be rather unaffected by FNEs.

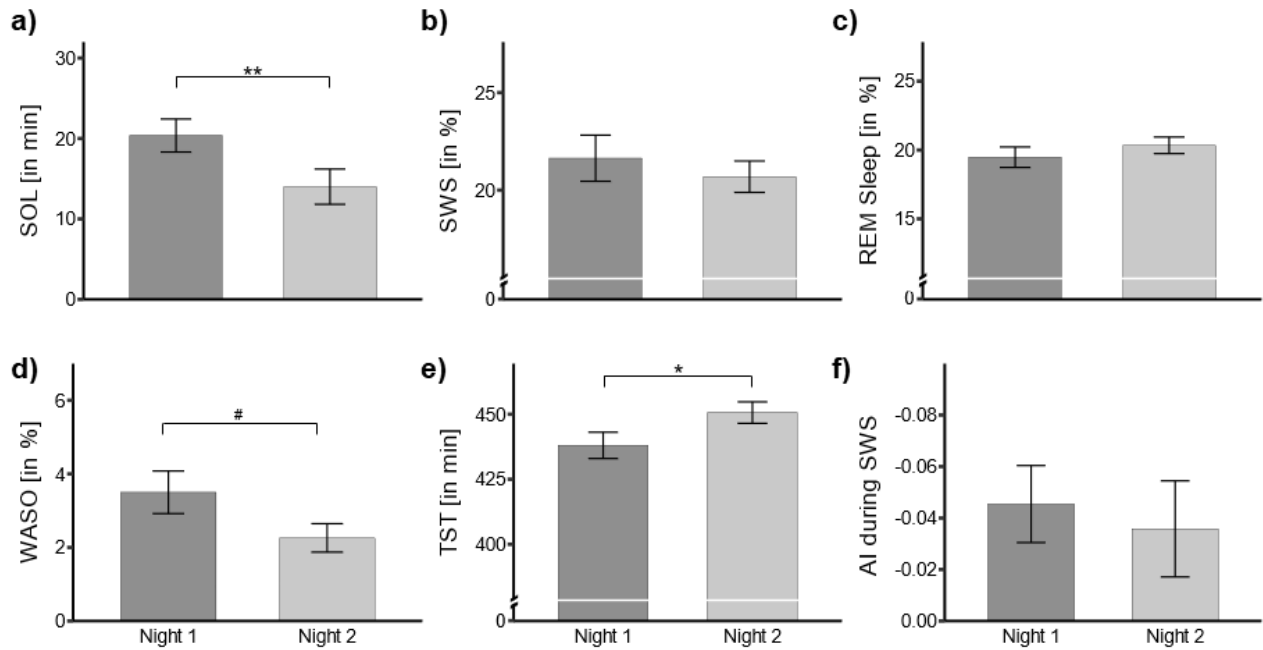


Figure 2. Sleep parameters during both nights of Study 1 in the sleep laboratory. **a)** Sleep onset latency (SOL). **b)** Slow-wave sleep (SWS). **c)** Rapid eye movement (REM) sleep. **d)** Wake after sleep onset (WASO). **e)** Total sleep time (TST). **f)** Asymmetry index (AI) during SWS within the first sleep cycle. Data are means $\pm$ SEM. Numbers indicate absolute or relative values.

Study 2

Study 2: Better sleep at home than in the sleep laboratory

In Study 2, we examined the impact of the environment (home vs. sleep laboratory) on sleep and FNEs. Participants spent two non-consecutive nights in their own home environment and two non-consecutive nights in the sleep laboratory, with the order of home vs. laboratory environment counterbalanced among participants. The mobile recording devices were identical in both sleeping environments. For these analyses, we used ANOVAs including the within factors “Environment” (Home vs. Laboratory) and “Environment Night” (First vs. Second). Table 2 presents an overview of all sleep parameters and significant main effects.

Table 2

Sleep parameters of Study 2 separated by environment.

Sleep parameter	Home						Lab					
	Night 1			Night 2			Night 1			Night 2		
	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM
SOL [in min]	22.86	±	3.5	20.1	±	3.11	27.52	±	2.9	25.62	±	3.24^b
WASO [in %] ^a	4.35	±	0.54	3.63	±	0.58	5.65	±	0.82	4.21	±	0.58
N1 [in %] ^c	4.81	±	0.34	4.57	±	0.39	5.09	±	0.39	4.44	±	0.35
N2 [in %]	42.59	±	1.2	43.28	±	1.28	42.73	±	1.28	43.71	±	1.28
SWS [in %]	24.98	±	1.01	24.19	±	1.19	25.22	±	1.36	25.03	±	1.17
REM [in %]	22.87	±	0.64	23.33	±	0.91	20.26	±	0.72	21.62	±	0.64^b
SWS Latency [in min]	12.63	±	0.91	12.21	±	0.77	13.71	±	0.66	12.46	±	0.57
REM Latency [in min]	82.66	±	5.28	78.97	±	6.26	86.78	±	5.02	91.03	±	6.15
TST [in min]	456.5	±	7.69	456.7	±	8.32	428.14	±	4.73	432.14	±	5.5^b
Total [in min] ^c	473.25	±	6.81	482.95	±	6.79	451.14	±	3.19	453.71	±	3.34^b
TIB [in min]	492.32	±	6.43	494.23	±	7.77	481.05	±	0.33	480.63	±	0.17^b
SE [in %]	90.9	±	0.9	89.9	±	1.23	88.78	±	0.96	89.74	±	1.12
Subjective SOL [in min] ^c	18.22	±	1.75	13.87	±	1.6	20.13	±	1.73	20.27	±	1.58^b
Subjective WASO [in min]	9.73	±	1.72	8.98	±	1.6	12.72	±	1.86	10.47	±	1.44
Subjective SQ [index]	22.83	±	1.04	24.2	±	1.2	22.37	±	1.01	23.07	±	1.01

Note: Time spent in the different sleep stages during Study 2 presented by the environment condition and number of nights spent in this specific environment. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow-wave sleep; REM: rapid eye movement sleep; TST: Total sleep time; Total: Total time between sleep onset and 'Lights On'; SE: Sleep efficiency; TIB: Time in bed; Subjective SQ: Subjective sleep quality. Numbers are means ± SEM (in minutes or percentage). **a)** Significant FNEs in both environments (main effect, $p < .05$). **b)** Significant main effect of the factor Environment ($p < .05$). **c)** FNEs marked with a trend in both environments ($p < .1$).

Overall, participants slept better in their home environment than in the sleep laboratory. For example, SOL was significantly shorter when participants slept at home (21.48 ± 2.33 min) compared with the laboratory (26.57 ± 2.16 min, $F(1, 28) = 6.47$, $p = .017$, $\eta_G^2 = .02$, see Figure 3a). Furthermore, TST and TOTAL was ca. 25 – 26 minutes longer at home compared to the laboratory (both main effects $p < .001$). The time in bed (TIB) was also significantly different in the two environments ($F(1, 27) = 5.25$, $p = .030$, $\eta_G^2 = .05$). It should be noted, however, that the duration of bedtime in the sleep laboratory was restricted to eight hours, whereas no such restrictions were applied at home. Because participants slept longer, the percentage of REM sleep was also generally higher when participants slept at home (23.10 ± 0.55 %) as opposed to in the sleep laboratory (20.94 ± 0.63 %; $F(1, 27) = 8.58$, $p = .007$, $\eta_G^2 = .07$).

We found no further significant influence of the factor Environment on any other objective sleep parameters (all $p > .129$, see Figure 3b and Table 2). Considering the subjective sleep parameters, we observed that participants reported falling asleep faster at home (16.04 ± 1.21 min) than in the sleep laboratory (20.20 ± 1.64 min; $F(1, 29) = 5.68$, $p = .024$, $\eta_G^2 = .05$). Nonetheless, subjectively reported WASO and subjectively reported sleep quality (SQ) showed no significant main effects of the environment ($p > .173$).

Are First-Night Effects modulated by sleeping in a different environment?

In addition to the main effects of the environment reported above, we were interested in the question whether the general increase in sleep quality between the first and second night in a specific environment would be modulated by the type of environment (home vs. laboratory). Thus, we were specifically interested in the interaction between the factors Environment and Environment night (first vs. second night). However, we were not able to find a significant interaction, neither of the objective nor of the subjective sleep parameters (all $p > .236$). We only

observed one statistical trend for an interaction between the two factors Environment and Environment Night for subjective SOL ($F(1, 29) = 3.82, p = .060, \eta_G^2 = .02$): at home, participants indicated that they fell asleep later in the first night (18.22 ± 1.75 min) compared with the second night (13.87 ± 1.60 min). In the laboratory, subjective SOL judgements were highly comparable (20.13 ± 1.73 min and 20.27 ± 1.58 min).

As we were not able to observe any significant interaction, FNEs appear to be comparable across different environments. In support of this conclusion, we found several significant main effects of the factor “Experimental nights” (first vs. second night), independent of the actual environment: For example, we observed a significant main effect for WASO ($F(1, 26) = 4.32, p = .048, \eta_G^2 = .03$): Participants were more awake in the first night (5.00 ± 0.50 %) than in the second night, independent of the familiar or unfamiliar sleeping environment (3.92 ± 0.41 %, Figure 3c). In addition, the portion of N1 sleep was larger in the first night (4.95 ± 0.26 %) than the second night across both environments (4.51 ± 0.26 % ($F(1, 29) = 3.14, p = .087, \eta_G^2 = .01$). Moreover, we observed a trend for shorter TOTAL time in the first night (462.20 ± 4.01 min) than in the second night (468.33 ± 4.24 min; $F(1, 27) = 3.15, p = .087, \eta_G^2 = .01$). Finally, subjective SOL tended to be experienced shorter during the second night than during the first night ($F(1, 29) = 3.42, p = .075, \eta_G^2 = .01$). Other sleep parameters, including objective SOL, TST and SWS latency reported in Study 1, did not reveal significant main effects for FNEs (all $p > .131$).

In summary, these results indicate that FNEs do not appear to be modulated by different settings as they occur in both unfamiliar and familiar environments. Instead, these analyses reveal that sleep in the second night is generally better than sleep during the first night, irrespective of the environment. This suggests that there is a habituation effect to the polysomnographic setup during the night and that this situational factor plays a crucial role in the development of the FNE.

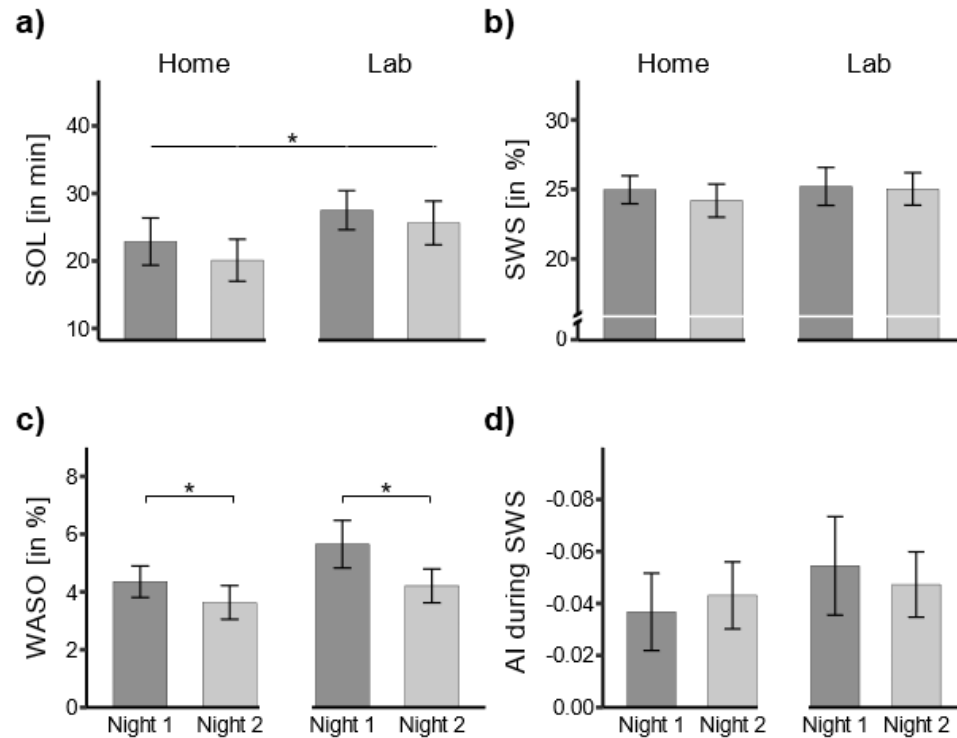


Figure 3. Sleep parameters in familiar (Home) vs. unfamiliar (Lab) environment of Study 2. **a)** Sleep onset latency (SOL). **b)** Slow-wave sleep (SWS). **c)** Wake after sleep onset (WASO). **d)** Asymmetry index (AI) during SWS within the first sleep cycle. Data are means $\pm$ SEM. Numbers indicate absolute or relative values.

Does sleeping at home with PSG reduce the First-Night Effects in the sleep laboratory?

In the next analyses, we specifically addressed the question of whether two nights spent at home with a mobile recording device can reduce FNEs in the sleep laboratory. For this analysis, we only inspected nights spent in the sleep laboratory. We compared two groups of participants: The “Home adaptation” group spent two nights at home using the mobile recording device prior to their first night in the sleep laboratory. The other group slept directly in the lab, without any adaptation at home (“No home adaptation” group). If sleeping at home prior to the two

experimental nights would reduce FNEs, we would expect a significant interaction between the factors “Experimental night” (First vs. Second) and the factor “Group” (Home adaptation vs. No home adaptation). However, we observed no evidence for such an interaction (all $p > .155$). Instead, we observed a main effect marked with a trend for the first vs. the second night in the lab in both groups for REM sleep: Participants spent less time in REM sleep in the first night in the lab ($20.76 \pm 0.86 \%$) compared with the second night ($22.06 \pm 0.75 \%$), $F(1, 27) = 3.14$, $p = .088$, $\eta_G^2 = .03$ (Figure 4c). For N1 we also observed a trend for more N1 sleep in Night 1 vs. Night 2 ($5.09 \pm 0.39 \%$ vs. $4.44 \pm 0.35 \%$; $F(1, 28) = 3.17$, $p = .086$, $\eta_G^2 = .03$). Thus, FNEs for REM and N1 persisted (at least marked with a trend) regardless of whether two adaptation nights were spent at home or not. Still, we observed a general benefit of spending two adaptation nights at home: Participants with home adaptation generally spent more time in REM sleep in the sleep laboratory ($23.40 \pm 0.80 \%$) than participants without home adaptation ($19.55 \pm 0.66 \%$, $F(1, 27) = 9.13$, $p = .005$, $\eta_G^2 = .20$, Figure 4c). Moreover, participants with home adaptation had a greater TIB in the sleep lab (481.05 ± 0.22 min) than participants without home adaptation (480.48 ± 1.52 min, $F(1, 27) = 5.21$, $p = .031$, $\eta_G^2 = .08$). Besides that, participants rated the subjective SOL in the sleep laboratory as generally shorter after home adaptation (17.28 ± 1.71 min) than after no home adaptation (23.12 ± 1.41 min; $F(1, 28) = 4.59$, $p = .041$, $\eta_G^2 = .11$). Additionally, we observed some statistical trends for generally improved sleep in the lab after home adaptation e.g., participants of the Home adaptation group objectively took less time to fall asleep (21.88 ± 2.66 min) than the No home adaptation group (33.15 ± 3.37 min; $F(1, 28) = 4.10$, $p = .052$, $\eta_G^2 = .11$). Finally, TOTAL was longer for participants of the Home adaptation group (457.08 ± 2.90 min) than for those of the No home adaptation group (446.55 ± 3.40 min; $F(1, 28) = 3.37$, $p = .077$, $\eta_G^2 = .09$). Table 3 provides all values of the sleep architecture.

In conclusion, spending two nights at home tends to improve some sleep parameters for subsequent nights in the sleep laboratory, indicating that some adaptation to the recording equipment occurs. However, home adaptation is not sufficient to eliminate all indices for FNEs in the laboratory.

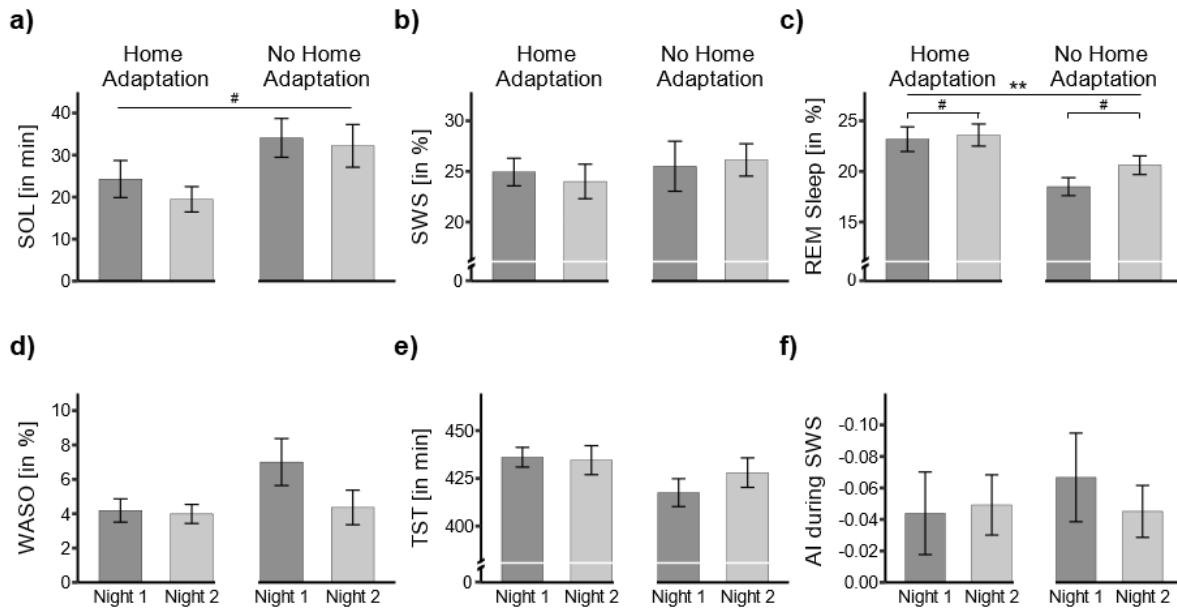


Figure 4. Sleep parameters in the unfamiliar (Lab) environment of Study 2, separated by Home Adaptation vs. No Home Adaptation groups. **a)** Sleep onset latency (SOL). **b)** Slow-wave sleep (SWS). **c)** Rapid eye movement (REM) sleep. **d)** Wake after sleep onset (WASO). **e)** Total sleep time (TST). **f)** Asymmetry index (AI) during SWS within the first sleep cycle. Data are means $\pm$ SEM. Numbers indicate absolute or relative values.

Table 3

Sleep parameters of laboratory nights separated by groups in Study 2

Sleep parameter	No Home Adaptation						Home Adaptation					
	Lab Night 1			Lab Night 2			Lab Night 1			Lab Night 2		
	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM
SOL [in min]	24.30	±	4.40	19.47	±	3.02	34.10	±	4.62	32.20	±	5.08^d
WASO [in %]	4.19	±	0.68	3.99	±	0.55	7.01	±	1.37	4.36	±	1.01
N1 [in %]^c	4.73	±	0.55	4.41	±	0.55	5.45	±	0.55	4.48	±	0.45
N2 [in %]	43.46	±	1.85	43.83	±	1.89	41.94	±	1.80	43.58	±	1.79
SWS [in %]	24.94	±	1.36	24.01	±	1.71	25.51	±	2.48	26.14	±	1.60
REM [in %]^c	23.19	±	1.22	23.60	±	1.09	18.49	±	0.89	20.61	±	0.92^b
SWS latency [in min]	14.36	±	0.93	13.43	±	0.95	12.75	±	0.82	12.04	±	0.65
REM latency [in min]	81.18	±	7.40	87.32	±	6.87	92.00	±	6.79	94.50	±	10.17
Total [in min]	455.30	±	4.36	458.87	±	3.92	445.80	±	4.65	447.30	±	5.13
TST [in min]	436.07	±	5.17	434.53	±	7.61	417.54	±	7.29	428.00	±	7.73
TIB [in min]	481.29	±	0.36	480.82	±	0.24	480.43	±	0.21	480.53	±	0.23^b
SE [in %]	90.53	±	1.06	90.38	±	1.59	86.90	±	1.51	89.06	±	1.61
SOL subjective [in min]	16.87	±	2.47	17.70	±	2.46	23.40	±	2.20	22.83	±	1.84^b
WASO subjective [in min]	11.37	±	2.63	9.23	±	2.08	14.07	±	2.66	11.70	±	2.03
Sleep Quality subjective	23.93	±	1.58	23.60	±	1.67	20.80	±	1.18	22.53	±	1.19

Note: Time spent in the different sleep stages in Study 2 during the laboratory nights only. For the No Home Adaptation group, the nights in the laboratory are the absolute first and second night within the study. For the Home Adaptation group, the laboratory nights follow after the two nights they already spend at home to get familiar with the device. The absolute night number is Night 3 and Night 4. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow-wave sleep; REM: rapid eye movement sleep; TST: Total sleep time; Total: Total time between sleep onset and 'Lights On'; SE: Sleep efficiency; TIB: Time in bed; Subjective SQ: Subjective sleep quality. Numbers are means ± SEM (in minutes or in percentage).

b) Significant main effect of the factor Group ($p < .05$). **c)** FNEs marked with a trend in both groups ($p < .1$). **d)** Difference marked with a trend for the factor Group ($p < .1$).

EEG power spectrum and Interhemispheric Asymmetry during SWS

In addition to the sleep architecture, we examined the interhemispheric asymmetry activity (IAA) of the delta band (1 – 4.5 Hz) within SWS of the first sleep cycle throughout the nights. This was done against the background of Tamaki et al.¹², who reported that the IAA in the delta band during SWS is a neural correlate of a “Night Watch System” during sleep and therefore a correlated and potential mechanisms of the FNE. We first examined the factor “Night” in Study 1, to see whether a difference of the asymmetry index (AI) across the different nights existed or not. Then, we focused our attention to the factor ‘Environment’ of Study 2. Finally, we examined the relationship between the AI and the FNE, as previously investigated in the key study by Tamaki et al.¹², who observed a negative correlation between the AI and the SOL.

We first analyzed the average frontal power (in μVolt) of the delta (1 - 4.5 Hz), theta (4.5-8 Hz), alpha (8-11 Hz) sigma (11-15 Hz) and beta (15-25 Hz) bands during SWS within the first sleep cycle of both brain hemispheres. We compared the power of all frontal frequency band activities across all nights for both studies. We also compared occipital delta activity in the first study, as it has been suggested that a reduced SWA power may be involved in the FNE²⁷. However, we found no significant differences between any of the nights or environments for the frontal power in any frequency bands for both studies (all $p > .132$, see Tables 4-6 for Means $\pm$ SEMs) and not for the occipital delta power in Study 1 ($p > .369$). We only observed a trend for frontal sigma power in Study 1 (adaptation night: $0.33 \pm 0.02 \mu\text{Volt}$; second night: $0.30 \pm 0.02 \mu\text{Volt}$, $F(1, 33) = 3.52$, $p = .069$, $\eta_G^2 = .11$), whereas no such difference occurred in Study 2 ($p > .161$, see Tables 5-6).

In Study 1, we were also unable to detect a significant main effect of the factor “Night” on the interhemispheric asymmetry ($p > .572$). Interestingly enough, however, we found a significant intercept ($F(1, 34) = 7.70$, $p = .009$, $\eta_G^2 = .15$), providing evidence for the existence of IAAs in both nights. We found a negative AI, indicating higher SWA power in the right frontal hemisphere

compared to the left hemisphere. In Study 1, an AI value of -0.045 ± 0.015 μVolt was recorded during Night 1, which then decreased to -0.036 ± 0.019 μVolt in Night 2. We also used one-sample t-test to determine whether the AIs were significantly different from 0. This was the case for Night 1 ($t(34) = -3.04, p = .005, d = -0.51$), and for Night 2 we detected a trend, $t(34) = -1.92, p = .064, d = -0.32$, (Figure 2f).

In Study 2, we analyzed the factors “Environment” (Home vs. Laboratory) and “Environment Night” (First and Second) on IAAs of delta oscillations during SWS. In the sleep laboratory, the AI value was -0.054 ± 0.019 μVolt on the first night and on the second night at -0.047 ± 0.013 μVolt . At home, the AI was at -0.037 ± 0.015 μVolt and on the second night at -0.043 ± 0.013 μVolt . Again, except the significant intercept ($F(1, 27) = 14.4, p = .001, \eta_G^2 = .25$), no main effect or interaction reached significance (all $p > .4376$). In Study 2, all AIs significantly differed from 0 (Sleep laboratory night 1: $t(27) = -2.87, p = .008, d = -0.54$; Sleep laboratory night 2: $t(27) = -3.77, p < .001, d = -0.71$; Home night 1: $t(27) = -2.47, p = .020, d = -0.47$) except Home night 2: ($t(27) = -3.35, p = .002, d = -0.63$; see Figure 3d).

We also examined whether there was a group difference in IAAs during the nights within the sleep laboratory, but no main effect or interaction became significant (all $p > .375$), except for a significant intercept indicating a stable presence of asymmetric sleep depth ($F(1, 26) = 12.39, p = .002, \eta_G^2 = .27$; see Figure 4f).

To more accurately describe the stability of asymmetric sleep depth throughout the different nights, we calculated the intraclass coefficient (ICC) to assess the reliability of AIs across all nights for each study separately. For Study 1, a moderate average ICC of .504 was found over the course of the two nights within a 95% confidence interval from .208 to .715 ($F(34, 34.4) = 2.99, p < .001$). For Study 2, we also observed a moderate degree of reliability between the four nights. The average measure ICC was .516 with a 95% confidence interval from .329 to .7 ($F(27, 83.5) = 5.23, p < .001$).

Between the familiar and unfamiliar sleeping environments we also observed a moderate degree of reliability: ICC = .59 with a 95% confidence interval from .288 to .787 ($F(27, 27.8) = 3.86, p < .001$). Lastly, looking at the degree of reliability within the environments, both ICC were moderate (Home: ICC = .626, ($F(27, 27.4) = 4.26, p < .001$); Lab: (ICC=.583), $F(27, 27.3) = 3.72, p < .001$)). Thus, the IAA may be a partially established trait feature with additional state influences.

Finally, we calculated a Pearson's correlation coefficient to evaluate the linear relationship between the SOL and the interhemispheric asymmetry in the delta band as reported by Tamaki et al.¹². However, neither in Study 1 ($r(68) = -.00, p = .977$) nor in Study 2 ($r(102) = .01, p = .949$) did we find such a correlation.

Overall, we found no association between frontal or occipital power activity during SWS of the first sleep cycle and any particular night. Moreover, we were able to detect IAAs in the delta band during SWS both in Study 1 and 2, with a higher SWA power in the right brain hemisphere compared to the left hemisphere. This asymmetry was moderately stable across all non-consecutive nights and across environments in Study 2. Nevertheless, we were not able to find any link between this interhemispheric asymmetry in sleep depth and the FNEs of sleep.

Table 4

Frontal frequency power (in μV) in SWS of the first sleep cycle for Study 1

Study 1	Night 1			Night 2		
	Mean	$\pm$	SEM	Mean	$\pm$	SEM
Frontal Delta	38.49	$\pm$	3.89	38.38	$\pm$	3.57
Frontal Theta	2.21	$\pm$	0.18	2.16	$\pm$	0.18
Frontal Alpha	0.74	$\pm$	0.06	0.69	$\pm$	0.06
Frontal Sigma	0.33	$\pm$	0.02	0.30	$\pm$	0.02
Frontal Beta	0.03	$\pm$	0.00	0.03	$\pm$	0.00
Occipital Delta	12.70	$\pm$	1.05	13.72	$\pm$	1.09

Note: The extracted mean power (in μV) of the delta (1–4.5 Hz), theta (4.5–8 Hz), alpha (8–11 Hz), sigma (11–15 Hz), and the beta band (15–25 Hz) during SWS in the first sleep cycle for each experimental night. We extracted the mean frontal and also occipital delta power during SWS in the first sleep cycle for the first two nights. Numbers are means $\pm$ SEM (in μV).

Table 5

Frontal frequency power (in μV) in SWS of the first sleep cycle for Study 2, separated by environment

Study 2	Home						Lab					
	Night 1			Night 2			Night 1			Night 2		
	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM
Frontal Delta	67.65	±	4.52	67.66	±	4.74	66.90	±	4.95	70.10	±	5.07
Frontal Theta	3.09	±	0.21	3.07	±	0.18	3.09	±	0.21	3.16	±	0.20
Frontal Alpha	1.50	±	0.18	1.55	±	0.17	1.52	±	0.18	1.61	±	0.19
Frontal Sigma	0.87	±	0.08	0.93	±	0.09	0.93	±	0.08	0.94	±	0.08
Frontal Beta	0.09	±	0.01	0.09	±	0.01	0.09	±	0.01	0.09	±	0.01

The extracted mean power (in μV) of the delta (1–4.5 Hz), theta (4.5–8 Hz), alpha (8–11 Hz), sigma (11–15 Hz), and the beta band (15–25 Hz) during SWS in the first sleep cycle for each experimental night. We extracted the averaged frontal power during SWS of the first sleep cycle separated by Environment (Home and Lab). Occipital delta was not extracted in Study 2 as no occipital electrodes were available in this study. Numbers are means $\pm$ SEM (in μV).

Table 6

Frontal frequency power (in μV) in SWS of the first sleep cycle for Study 2, separated by group

	No Home Adaptation			Home Adaptation		
	Lab Night 1		Lab Night 2	Lab Night 1		Lab Night 2
	Mean	$\pm$ SEM	Mean $\pm$ SEM	Mean	$\pm$ SEM	Mean $\pm$ SEM
Frontal Delta	69.32	$\pm$ 8.55	71.34 $\pm$ 9.97	64.64	$\pm$ 8.42	68.95 $\pm$ 8.20
Frontal Theta	3.30	$\pm$ 0.35	3.36 $\pm$ 0.34	2.91	$\pm$ 0.26	2.98 $\pm$ 0.24
Frontal Alpha	1.53	$\pm$ 0.25	1.56 $\pm$ 0.23	1.51	$\pm$ 0.26	1.66 $\pm$ 0.30
Frontal Sigma	0.96	$\pm$ 0.11	0.99 $\pm$ 0.12	0.90	$\pm$ 0.12	0.88 $\pm$ 0.11
Frontal Beta	0.10	$\pm$ 0.01	0.09 $\pm$ 0.01	0.08	$\pm$ 0.01	0.08 $\pm$ 0.01

Note: The extracted mean power (in μV) of the delta (1–4.5 Hz), theta (4.5–8 Hz), alpha (8–11 Hz), sigma (11–15 Hz), and the beta band (15–25 Hz) during SWS in the first sleep cycle for each experimental night. We extracted the averaged frontal power during SWS of the first sleep cycle separated by Group (Home adaptation and No home adaptation). Occipital delta was not extracted in Study 2 as no occipital electrodes were available in this study. Numbers are means $\pm$ SEM (in μV).

Discussion

In our studies, we examined the nature of First-Night Effects (FNEs) during non-consecutive nights. Additionally, we also investigated the role of a familiar versus an unfamiliar environment, as well as the potential relationship between FNEs and different settings in regard to the interhemispheric asymmetric activity (IAA) of delta oscillations during slow-wave sleep (SWS):

Our analyses of Study 1 revealed that several sleep parameters of the first night significantly differed from the following night indicating the presence of an FNE, including objective sleep onset latency (SOL), total sleep time (TST), total time between sleep onset and lights on (TOTAL). To a lesser extent, the FNE also affected wake after sleep onset (WASO) and SWS latency. However, the sleep stage SWS was not affected by an FNE. In Study 2, we also found significant non-consecutive FNEs for WASO and a weak FNE for sleep stage N1, REM sleep, TOTAL, and subjective SOL in both familiar and unfamiliar recording environments, with overall greater sleep quality at home than in the sleep laboratory. Analyses of the delta power showed no significant difference between the nights but the environment and also that the IAA within the delta band (1 - 4.5 Hz) during SWS revealed a general difference in the presence of IAAs but this was not exclusively associated with a specific night or environment.

Our results are consistent with the meta-analytic findings of Ding et al.² for consecutive nights: They report consistent FNEs for SOL, WASO, TST and other sleep parameters in the first rather than subsequent nights. Generally, more sleep parameters showed FNEs in consecutive nights (as reported in the meta-analysis) compared to our study with non-consecutive nights. A possible explanation is the age of our participants: Ding et al.² recognized that young participants had only modest FNEs, which is consistent with our findings in young participants. A second explanation for the greater FNEs on consecutive nights as compared to non-consecutive nights may be due to direct rebound effects that occur on a second night immediately following a first night of

impaired sleep due to an unfamiliar environment². Thus, non-consecutive adaptation nights may even be helpful in obtaining more habitual sleep patterns in the sleep laboratory. The meta-analysis by Ding et al.² also detected no differences in the degree of FNEs between home and lab studies. This fits well with our findings in Study 2 in familiar and unfamiliar environments, suggesting that an adaptation night is still necessary even when the study is conducted in a familiar environment. Thus, the best option to minimize FNEs is still to adapt to the same recording environment as the actual sleep study is taking place. Nevertheless, adaptation nights at home resulted in a more general improvement in sleep parameters during the first and second night of recording in the laboratory, irrespective of the FNE in the lab. Therefore, adaptation nights at home may improve subsequent sleep quality in a more general way in the sleep laboratory, possibly allowing for a general adaptation to the recording situation with electrodes, cables, and other equipment.

Interestingly, in our two studies, some sleep parameters (e.g. SWS) were not affected by FNE and remained relatively stable over the nights. Also in consecutive nights, Ding and colleagues² reported no FNEs for SWS and N2. If sleep studies have a focus only on SWS and do not focus on sleep quality per se, an adaptation night may be omitted in these particular sleep studies.

Although many sleep parameters showed the expected effects of the first night, we were unable to show that these adaptation processes were correlated with changes in specific frequency band power or IAAs in the delta band during SWS of the first sleep cycle. Our analyses showed a general difference in the presence of IAAs in both studies over several nights and also between familiar and unfamiliar environments, which is incompatible with the findings and hypothesis reported by Tamaki et al.¹². However, please note that Tamaki et al.¹² detected IAAs using magnetoencephalography to localize IAAs and focused only on brain networks including the default mode network. Furthermore, the medium stability (as indicated by the ICC) of the IAA across nights, suggests that a few stable trait components may underlie IAAs in the delta band

during SWS. Interestingly, some researchers have suggested that structural differences such as the integrity of the corpus callosum may underlie interhemispheric asymmetries in slow wave activity (SWA)^{14,15}. In addition to these trait influences, the moderate ICCs in our study indicate that some state aspects also have an influence on the IAA, but these state aspects do not appear to be related to concepts of “familiarity” or FNEs.

Our study has some limitations and drawbacks. As mentioned in the Methods section, we obtained the data of Experiment 1 from two independent sleep studies which had an identical design, but differed in aim, research questions and experimental conditions (more details about conditions provided in the supplementary information and in^{16,17}). However, we consider this limitation to be minor, as the results of a subgroup analysis including 16 participants who all had only neutral nights (without intervention) after the adaptation night revealed relatively comparable results (see supplementary information). A limitation of Study 2 is that the bedtime restriction of eight hours in the sleep lab was not applied in the home environment. Consequently, the significant effects of TST, TOTAL, and Time in Bed (TIB) may be due to this restriction. Moreover, we cannot exclude the possibility that the other sleep parameters were also affected by this free choice of sleep opportunity within the home environment. Additionally, the sex ratio in our samples was unbalanced, which casts doubt on how broadly applicable the findings are. Furthermore, the negative finding that the environment did not moderate FNEs, together with some non-significant interactions, may be attributed to the relatively small sample size. Moreover, we used only a minimal set of two electrodes, which makes it difficult to pinpoint the location of asymmetric activity given the already poor spatial resolution of the EEG. Finally, we used a very liberal and conservative testing strategy to analyze our data. While we minimize the risk of excluding false-negative cases, our strategy also carries the potential for an increased number of acceptances of

more false-positives. Therefore, general comparisons between the studies should be interpreted with caution.

Taken together, the results of our two experiments highlight the importance of including an adaptation night in sleep studies with non-consecutive nights, ideally in the same environment as the later experimental nights. In addition, our findings indicate that familiarity with the environment may not be sufficient to attenuate an FNE, as FNEs also occur in a home environment. Based on our data, it seems unlikely that home adaptation nights can completely replace sleep lab adaptation nights. Nevertheless, additional adaptation nights at home may be beneficial to improve sleep quality in the laboratory. To provide a complete clarification of this question, future studies would need to directly compare two to three experimental nights with an adaptation night at home or in the laboratory.

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Disclosure Statement

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Data availability

Datasets analyzed in this article are available online in Open Science Framework (OSF) at <https://osf.io/5fmzp/>.

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Supplementary information
for
The First-Night Effect of sleep occurs over non-consecutive nights in unfamiliar and
familiar environments

Anna Zoé Wick¹, Selina Ladina Combertaldi¹ and Björn Rasch^{1*}

² Department of Psychology, University of Fribourg, Fribourg, Switzerland

*Corresponding

author:

Björn Rasch, Department of Psychology, University of Fribourg, Rue P.-A-de-Faucigny 2, CH-1700 Fribourg, Switzerland. Email: bjoern.rasch@unifr.ch

Supplementary information of Study 1

Study 1 is a re-analysis of data sets drawn from two independent experiments (published in ^{16,17})

In order to gain a more in-depth understanding of both experiments, the participant samples and experimental conditions are described in greater detail.

Experiment 1

Sample:

The first sample was gathered between October 2016 and April 2017 and included 15 subjects (11 females and 4 males; $n_1=15$), aged 18 to 26 years ($M_1 = 21.45$; $SD_1 = 2.33$). All subjects were students. Thirteen subjects were right-handed. The subjects were not engaged in night shifts and were instructed to maintain a regular sleep rhythm throughout the study period. They reported a high subjective sleep quality and did not indicate any sleep disorders. They were also instructed to abstain from alcoholic and caffeinated beverages on experimental days as well as the day before the experiment. The local ethics committee of the University of Fribourg approved the study, and all subjects provided written informed consent prior to participating. This study was conducted in accordance with the Declaration of Helsinki. Subjects received either university course credits or financial compensation of at least 180 CHF for participating in the experiment. In the event of an early dropout, the payment was provided proportionately.

Experimental conditions:

The subjects were told to talk themselves into either good or bad sleep. Immediately after this instruction, the light was switched off and the task of the subjects was to convince themselves

to sleep as good, as bad, or as neutral as possible. The subjects were asked to try to follow this instruction using only willpower. They were not allowed to get out of bed or use any external aids (e.g., reading) to stay awake. Still, the subjects were free to choose the methods they wanted to use. No further intervention was conducted during the night. A neutral condition served as a as control condition where participants tried to sleep as normal as possible.

Experiment 2

Sample

The second sample was collected between October 2016 and April 2017 and consisted of 21 female and nine male subjects ($n_2=30$) aged 18 to 29 years ($M_2 = 22.67$; $SD_2 = 3.03$). The majority of subjects were students at the University of Fribourg. Twenty-five subjects were right-handed. All subjects were highly motivated, German-speaking, free of any physical and mental disease, and in possession of a healthy wake-sleep cycle. Moreover, all subjects participated voluntarily. Due to a participation in former sleep studies, seven subjects already spent a night in a sleep laboratory at the University of Fribourg. Nevertheless, the polysomnographic derivation with single electrodes was new to all subjects. Subjects were recruited via a newsletter sent to psychology students and advertisements on several internet platforms. Two days prior to each session, subjects received a reminder email containing instructions to refrain from consuming caffeine and alcohol for two days before the experiment. Additionally, they were asked to get up at least at 7:00 a.m. on the experimental day.

Experimental conditions

Subjects were either called to spend actively 30 minutes on a prior chosen social messenger app or followed the instruction of a 30-minutes long progressive muscle relaxation presented via audiotape. In the neutral condition the light was switched off without any task. In both studies, after eight hours, the light was switched on, again and subjects were woken up. No further intervention was conducted during the night.

Supplementary table

Supplementary Table S1. Sleep parameters in the adaptation and second (neutral) night

Sleep Parameter	Night							Statistic ANOVA
	Adaptation			Neutral				
	Mean	±	SEM	Mean	±	SEM	N	
SOL (in min) ^c	21.53	±	3.80	14.84	±	2.90	16	$F(1, 15) = 3.14, p = .097, \eta_G^2 = .06$
WASO [in %] ^a	3.40	±	0.88	1.45	±	0.25	15	$F(1, 14) = 5.29, p = .037, \eta_G^2 = .14$
N1 [in %]	5.98	±	0.56	6.31	±	0.62	16	$F(1, 15) = 0.34, p = .567, \eta_G^2 < .01$
N2 [in %] ^a	44.89	±	1.98	48.71	±	2.10	16	$F(1, 15) = 5.58, p = .032, \eta_G^2 = .06$
SWS [in %]	23.63	±	2.37	22.77	±	2.02	16	$F(1, 15) = 0.26, p = .618, \eta_G^2 < .01$
REM [in %]	19.30	±	1.18	19.38	±	0.87	16	$F(1, 15) = 0.00, p = .951, \eta_G^2 < .01$
SWS latency [in min] ^c	16.59	±	2.02	14.03	±	1.48	16	$F(1, 15) = 4.36, p = .054, \eta_G^2 = .03$
REM latency [in min]	94.50	±	8.48	93.19	±	10.04	16	$F(1, 15) = 0.01, p = .918, \eta_G^2 < .01$
TST [in min] ^c	439.27	±	8.57	457.13	±	4.06	15	$F(1, 14) = 4.14, p = .061, \eta_G^2 = .11$
Total [in min]	458.8	±	5.46	462.8	±	4.03	15	$F(1, 14) = 0.40, p = .537, \eta_G^2 = .01$
Subjective SOL [in min]	18.59	±	4.10	11.88	±	2.28	16	$F(1, 15) = 2.69, p = .122, \eta_G^2 = .06$
Subjective WASO [in min]	11.97	±	5.58	7.28	±	1.75	16	$F(1, 15) = 0.65, p = .432, \eta_G^2 = .02$
Subjective SQ [index]	27.25	±	1.08	27.06	±	1.25	16	$F(1, 15) = 0.02, p = .887, \eta_G^2 < .01$

Note: Time spent in the different sleep stages in Study 1 during the first (adaptation) night and the second neutral (where no intervention took place) night. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow-wave sleep; REM: rapid eye movement sleep; TST: Total sleep time; Total: Total time between sleep onset and 'Lights On'; Subjective SQ: Subjective sleep quality. Numbers are means $\pm$ SEM (in minutes or percentage). **a)** Average of the first night differed significantly from the second night ($p < .05$). **c)** Average of the first night differed from the second night marked with a trend ($p < .1$).

2.3 Musical harmony is processed during sleep

Anna Wick¹ and Björn Rasch^{1*}

¹ Department of Psychology, University of Fribourg, Fribourg, Switzerland

*Corresponding author:

Björn Rasch, Department of Psychology, University of Fribourg, Fribourg, Switzerland, Rue P.-A-de-Faucigny 2, CH-1700 Fribourg. Email: bjoern.rasch@unifr.ch

Abstract

Musical chords represent the most basic musical elements conveying emotional information. During wakefulness, different musical chord categories elicit distinct neuronal correlates and emotions, with major chords typically inducing more positive and minor chords with negative ones. However, it remains unclear whether the brain continues to process musical chords differently when presented during sleep.

To address this question we presented musical major, minor, and dissonant chords to 47 healthy participants during nocturnal non-rapid eye movement (NREM) sleep. Prior to sleep, participants rated the chords in valence and arousal. Sleep was recorded using polysomnography.

Our analysis of the event-related responses (ERPs) during sleep revealed significant differences between the three musical chord categories. Major chords induced the strongest negative amplitude approximately 800 ms after chord onset, indicated as peak-to-peak (PTP) amplitude from the earlier positive peak. Minor chords showed intermediate PTP amplitudes, while dissonant chords elicited the lowest PTP amplitudes. In the time-frequency domain, these differences were also apparent, including differences in slow-wave, theta, alpha and sleep spindle bands across chord categories. Notably, experience in playing a music instrument induced stronger differentiation of musical harmony during sleep compared with participants who never played a music instrument.

In conclusion, our findings suggest that the different processing of single musical chords persists during sleep, influenced by harmonic features and musical expertise in the context of Western musical conventions. Future research should explore whether also longer and more complex harmonic features (e.g. chord sequences or musical pieces) are differentially processed by the sleeping brain.

Introduction

A musical chord can be considered as the smallest musical element that conveys emotional information (Bakker & Martin, 2014; Marin et al., 2015). It consists of the simultaneous play of more than two tones and encompasses both consonant and dissonant intervals (Piston, 1950; Von Helmholtz, 1875). Consonant intervals that form major and minor chords sound stable and complete, whereas dissonant intervals are restless and seek resolution in consonant intervals (Piston, 1950; Von Helmholtz, 1875).

Consonant and dissonant chords are fundamental elements to Western music (Virtala & Tervaniemi, 2017), eliciting distinct emotional responses in listeners (Bakker & Martin, 2014; Virtala & Tervaniemi, 2017). Minor chords are less harmonious than major chords and research has shown that minor chords are generally perceived more negatively than major chords, which tend to connote more positive emotions (Heinlein, 1928; Kolchinsky et al., 2017; Von Helmholtz, 1875). Dissonant chords have been found to induce unpleasant feelings (Maslennikova et al., 2015; Pallesen et al., 2005). The association between major and minor tonalities and their respective positive and negative emotional valences has been found to be psychologically robust (Parncutt, 2014).

This emotional perception appears to be, at least partially, independent of formal musical training (Maslennikova et al., 2015; Pallesen et al., 2005; Roberts, 1986; Virtala et al., 2014), as it may be rooted in low-level sensory processing (Bidelman & Krishnan, 2009). However, the affective response to musical stimuli seems to involve a complex interplay of factors, potentially including learned associations between musical elements and emotional states, prior musical experience, and psychoacoustic properties of the auditory stimulus (Smit et al., 2019). For example, musical expertise seems to enhance the sensitivity to harmonic structures and the consonance-dissonant perception (Arthurs et al., 2018).

Several neuroimaging studies have investigated the perception of musical chords during wakefulness (Minati et al., 2009; Nemoto et al., 2010; Pallesen et al., 2005; Suzuki et al., 2008). All these studies consistently show that consonant major, minor, and dissonant chords can elicit distinct neural correlates and activate different brain areas.

For example, Maslennikova et al. (2013) found higher event related potentials (ERPs) elicited by consonant than dissonant chords in early ERP components (P100 and N200). In addition, differences in the mismatch activity were observed between harmonic and dissonant chords (Quiroga-Martinez et al., 2022; Virtala et al., 2011).

When comparing musicians and non-musicians, ERP amplitudes of early components of dissonant and consonant chords were significantly smaller in non-musicians (Maslennikova et al., 2015). To our knowledge, the brain response to isolated musical chords during sleep has not yet been systematically examined.

Generally, it is now widely accepted that the sleeping brain is capable of processing and distinguishing auditory stimuli. For example, sleep studies have confirmed that a person's own name, but also affective qualities, such as the emotional prosody or familiarity of voices or the "roughness" of shouts, can be distinguished during sleep (Ameen et al., 2022; Blume et al., 2017; Legendre et al., 2022; Oswald et al., 1960; Perrin et al., 1999; Wielek et al., 2021). In sleep and memory research, the capability of the sleeping brain to process auditory stimuli is used to reactivate and strengthen associated memories in targeted memory reactivation (TMR) studies (Hu et al., 2020; Rasch & Born, 2013). While some TMR studies have used musical stimuli as reactivation cues during sleep successfully (Antony et al., 2012; Gao et al., 2020; Schönauer et al., 2014), it has not yet been examined to what extent music itself can be processed during sleep. One recent study started to fill this gap and investigated the rhythm perception during sleep and found that it is only partially possible during sleep (Sifuentes-Ortega et al., 2022).

Therefore, the aim of our study is to explore the question whether musical chords as smallest musical elements are perceived during sleep. In particular, we examined whether different types of chords elicit distinguishable ERPs in the sleeping brain.

We conducted an experiment including 47 young and healthy participants who spent one experimental night in the sleep laboratory. We presented different isolated chord types with no harmonic context (major chords, minor chords, and dissonant triads including whole tone and half tone intervals) in a randomized order during NREM sleep stages N2 and SWS. We hypothesized that different chord types elicit distinct ERPs and oscillatory activity in both N2 and SWS sleep stages.

Methods

Participants

Our final sample consists of 47 healthy young participants (ages from 19 to 25; $M = 21.26$; $SD = 1.57$; 35 females). The final sample encompasses data from our pilot study with 12 young and healthy participants (8 females) ages 21 to 25 ($M = 22.00$; $SD = 1.28$). After our pilot study, we preregistered our study (osf.io/yq7zw) and conducted our main study including 35 young and healthy participants (27 females) ages 19 to 25 years ($M = 21.00$; $SD = 1.59$). As the procedure of the pilot and main study are identical and the results turned out to be highly comparable, we combined both data sets to improve statistical power.

All subjects were German or French speakers, were free of any physical and mental disease and reported a healthy wake-sleep-cycle. We recruited subjects via a newsletter sent to psychology students and advertisements on several internet platforms. Two days before each session, subjects received a reminder e-mail containing the instruction to refrain from consuming caffeine and alcohol for two days prior to the experiment. Additionally, we asked subjects to get up no later than 7:00 a.m. on the day of the experiment.

The studies were approved by the local ethics committee and all subjects gave written informed consent in the beginning of the adaptation night. The study was conducted in accordance with the declaration of Helsinki. Subjects received a compensation of 80 CHF for their participation. In case of an early abandonment, we paid subjects proportionally.

Design and procedure

The study consisted of an adaptation and one experimental night in the sleep laboratory at the University of Fribourg. The nights were separated by a minimum of three and a maximum of 28 nights. During the experimental night, subjects arrived at the sleep laboratory at 8:15 p.m., filled

out various questionnaires, and prepared for the night. Next, the experimenter attached the electrodes for the polysomnographic recordings and the subjects listened to the musical chords while playing a simple puzzle game (Block Game) for 45 minutes. Before and after this game, participants rated the different chords by valence and arousal. At approximately 11:00 p.m., the subjects went to bed and the lights were turned off for eight hours. After sleep onset and entering NREM sleep, the experimenter manually started to play the musical chords using Eprime 2.0.10. After approximately 3.5 hours of sleep the experimenter stopped the manual reactivation program and initiated an automatic presentation of the chords for the remaining sleeping time. In the morning, the experimenter turned on the light and woke up the subject. Participants immediately filled out questionnaires, listened to the musical chords while playing the puzzle game and rated the different chords by valence and arousal before and after this morning task. Afterwards, the experimenter detached the electrodes, and the subjects left the laboratory between 9:00 and 9:30 a.m.

Questionnaires

Prior to the experimental session, participants completed several questionnaires to obtain information about demographics, handedness, drug consumption and personality. We used the Pittsburgh Sleep Questionnaire Inventory (Buysse et al., 1989) to gain information about the subjective sleep quality and sleep habits during the last four weeks. We also evaluated the musical expertise of the participants using the MUSE questionnaire (Chin & Rickard, 2012). This questionnaire explores a variety of aspects of musical engagement, including the question of whether participants have ever played or currently play a musical instrument, the amount of time spent listening to music during the week, and the role that music plays in their cognitive and

emotional regulation. Finally, in order to determine the present mood, they used a Likert scale to rate several items (MDBF; Steyer et al., 1997).

In the following morning, we operationalized the subjective sleep quality from the previous night using the SF-A/R questionnaire (Görmelmeier, 2011), and once more, we collected data on the subjects' moods using the MDBF (Steyer et al., 1997).

Moreover, to measure subjects' affective reaction to the stimuli, they rated the musical chords, we assessed the dimensions “Valence” and “Arousal” with the Self-Assessment Manikin (SAM) questionnaire (Bradley & Lang, 1994) which employed a nine-point scale before and after sleep.

Stimuli

We used the programs GarageBand 10.3.2 (Apple Inc., 2019) and Adobe Audition 22.6 (Adobe Inc., 2022) to create the musical stimuli for the study. The grand piano chords were each two seconds long and were triads following major, minor, and western dissonant characteristics. We composed two basic consonant chords: the major chord was constructed with a major third below and a minor third above, and a minor chord with a minor third and a major third above. We also created a dissonant chord which consisted of a triad that included a whole tone (major second) below and half tone (minor second) interval above. These intervals are considered as dissonant (Plomp & Levelt, 1965; Von Helmholtz, 1875). To add more variability, we transposed the pitch of the individual chords by 4 and 6 semitones higher and lower. The notation of the basic chords is presented in Figure 1.

Task before and after sleep

We used the E-Prime software 2.0.10 (Psychology Software Tools Inc., Pittsburgh) to program the randomized musical chords presentation. The task lasted 45 min and consisted of two

20 min parts which were separated by a 5 min break. In both parts, chords are presented acoustically via loudspeaker (range of chord duration: 2–6 seconds) repeatedly and in a randomized order (notation of chords see Figure 1). An interval of 1000-3000 ms between each musical stimuli reduced presentation speed of chords. During the two parts, subjects were instructed move as little as possible to play a simple puzzle game at the computer while the chords were played in the background. After 20 minutes and a presentation of 240 stimuli, a 5 min break followed. Then, the second part followed which was exactly the same as the first part.

Reactivation of musical chords during the night

Again, we used EPrime 2.0.10 (Psychology Software Tools Inc., Pittsburgh), to acoustically play the musical chords at a sound pressure level of 35 dB during sleep via loudspeakers and presented them in a random order. Chords were separated by an interstimulus interval of 5000–7000 ms to avoid a regular rhythm of chord presentation.

As soon as signs of stable sleep appeared (as given by the American Association of Sleep Medicine (AASM; Iber et al., 2007), the experimenter started the presentation of chords manually and paused immediately when signs of arousals or awakenings were detectable. After approximately 3.5 hours, the experimenter terminated the manual reactivation procedure. On average, we presented 363.5 ± 92.6 repetitions of major, minor, and dissonant chords during N2 and SWS.

Polysomnographic recordings

We collected electrophysical data during sleep using different polysomnographic components (PSG): The electroencephalogram (EEG) consisted of twelve single gold-cups

electrodes which we positioned in accordance with the international 10-20 system (C3, C4, Cz, F3, F4, Fpz, P3, P4, M1, M2, O1, O2; Chatrian et al., 1985). Moreover, we attached the electromyogram (EMG), the electrooculogram (EOG) and the electrocardiogram (ECG) according to the international recommendation by the American Academy of Sleep Medicine (AASM, Iber et al. 2007). We derived the EEG referentially, whereas the EMG, EOG and ECG were generated bipolar. However, we maintained all impedances below 5 k Ω and set the sampling rate to 500 Hz, along with the low and high frequency recording filters of each component set to the suggested level of the AASM (EEG: 0.3 Hz / 35 Hz; EOG: 0.3 Hz / 35 Hz; EMG: 10 Hz / 100 Hz; ECG: 0.3 Hz / 70 Hz; Iber et al., 2007).

Sleep scoring

The electrophysiological data was first re-referenced to the contralateral mastoid and filtered as recommended by the AASM (Iber et al., 2007), using the software BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) Then, we segmented the eight hours of bed time (from ‘Lights off’ to ‘Lights on’) into 30-seconds-epochs and two independent scorers visually classified the epochs with the different stages ‘Wake’, ‘REM’, ‘N1’, ‘N2’ or ‘SWS’. In case of disagreements, we consulted a third expert sleep scorer.

Event related analyses

To gain further insights into the oscillatory activity of the manual chord presentation during N2 and SWS, we inspected event-related potentials (ERPs) and performed time–frequency analyses (TFA). We used the BrainVisionAnalyzer 2.2 (Brain-Products Inc, GmbH, Gilching, Germany) to first preprocess the EEG data by removing artifacts from the data. At the beginning

of this process, we imported sleep scorings to serve as segmentation markers. Based on both NREM sleep stages N2 sleep and SWS, chords were separated into equally sized segments with borders set at 3 seconds before and 5 seconds after a musical chord. Then, the following steps were performed following the procedure described by (Ackermann et al., 2015). A high-pass filter was set to 0.1 Hz, a low-pass filter to 40 Hz and a notch filter to 50 Hz. Finally, the data were re-referenced to the averaged value of both mastoids. To ensure that we only analyze artifact-free sections, an automatic artifact rejection excluded segments, if the maximal difference in EMG activity was above 150 μ V and the maximal difference in each EEG channel was above 500 μ V.

For the ERP analyses, the baseline was normalized using a period of -1 to 0 s before stimulus onset. Afterwards, for all subjects and for each musical chord category, data was averaged over both sleep stages. The maximal peak of the event-related response was then exported using automatic peak detection and further analyzed in R Studio software 4.3.1 (RStudio Team, Boston).

For the TFA, artifact-free segments were exported and further analyzed with the Fieldtrip toolbox (Oostenveld et al., 2011). The TFA procedure was adapted from Beck et al. (2021). Similarly, the baseline was normalized with a period of -1 to 0 seconds before stimulus onset. In a next step, we averaged the data per subject and per chord category to compare oscillatory power across different frequencies (1-20 Hz) within a time window of 0 to 4.5 seconds after chord onset. This was done for the averaged power of both frontal channels (F3, F4). Results were compared using cluster-based permutation tests for dependent samples as implemented in the FieldTrip toolbox (Oostenveld et al., 2011). For the cluster-level statistic, we used the maximum sum of t -values within each cluster. The cluster-level statistic was calculated for each of 1000 randomly drawn data partitions, which exceed the actually observed test statistic, resulting in a Monte Carlo

p-value, controlling for multiple comparisons. The alpha level was set to .05 and corrected for two-sided testing.

We compared major, minor, and dissonant chords played during N2 and during SWS. We did this for all chords, separately for each sleep stage.

Statistical analyses

We carried out all analyses using the R Studio software 4.3.1. In order to investigate the differences in ERPs of major, minor and dissonant chords in NREM sleep stages N2 and SWS, as well as within the subjective valence and arousal ratings, we ran several sets of mixed-design analyses of variances (ANOVAs). When Mauchly's tests revealed a violation of sphericity, the correction proposed by Greenhouse-Geisser was used. Effect patterns were further explored by post hoc t-tests. For all analyses, the significance level was set to $p \leq .05$. In the case of multiple post-hoc testing, we used the Bonferroni's correction to minimize potential errors., In addition, we calculated differences between two chord categories (Major-Minor, Major-Dissonant, and Minor-Dissonant) for several parameters of interest and used these differences to explore correlations and modulations.

Results

To test our hypotheses, 47 participants spent one experimental night in the sleep laboratory at the University of Fribourg (see Methods section for more details, see Table 1 for an overview of the sleep architecture). During the nocturnal sleep, single major, minor and dissonant sounding chords in different pitches were presented at a low volume during stable non-rapid eye movement (NREM) sleep stages N2 and slow-wave sleep (SWS). We set a random intertrial interval between 5-7 seconds to avoid a regular rhythm of stimuli presentation, attenuating the response (Bastuji & García-Larrea, 1999). Sleep was recorded using polysomnography involving 12 EEG electrodes.

Table 1. Overview of times spent in the different sleep stages during the experimental night

Sleep parameter	Mean	± SEM
TST (min)	437.54	4.47
WASO (%)	5.09	± 0.50
N1 (%)	3.79	± 0.27
N2 (%)	48.45	± 1.18
SWS (%)	21.51	± 1.09
REM (%)	21.17	± 0.73
SWS latency (min)	25.04	± 3.92
REM latency (min)	101.07	7.50

Table 1. Times in the different sleep stages. SOL: Sleep onset latency; WASO: wake after sleep onset; N1, N2: NonREM sleep stages N1 and N2; SWS: slow wave sleep; REM: rapid-eye movement sleep; TST: Total sleep time. Numbers are means $\pm$ SEM (in minutes or %).

Subjective Rating

Before and after sleep, subjects rated major chords highest in valence (6.56 ± 0.17) and lowest in arousal (3.47 ± 0.26). Minor chords received intermediate ratings in valence (5.28 ± 0.21) and

arousal (4.17 ± 0.24), while dissonant chords were rated lowest in valence (3.44 ± 0.17) and highest in arousal (4.96 ± 0.23). The valence and arousal ratings of all three chord types differed significantly (valence: $F(1.69, 77.59) = 99.65, p < .001, \eta_G^2 = .52$), arousal: $F(1.54, 70.63) = 35.04, p < .001, \eta_G^2 = .12$, see Table 2 for descriptives and ANOVA statistics).

Event related responses of musical chord presentation during sleep

Musical chord processing during NREM sleep elicited a very stable event-related response (ERP), which was generally higher in N2 sleep compared with SWS (see Figure 1b). Importantly, the ERP elicited by musical chords during sleep differed significantly between chord types, confirming our hypothesis: In N2 the PTP difference was at $55.64 \pm 4.03 \mu\text{V}$ and lower during SWS at $38.76 \pm 2.76 \mu\text{V}$. Precisely, we observed the largest peak-to-peak (PTP) differences for major chords (N2: $65.58 \pm 4.5 \mu\text{V}$; SWS: $42.3 \pm 3.00 \mu\text{V}$), with lower PTP differences for minor (N2: $53.81 \pm 3.91 \mu\text{V}$; SWS: $37.61 \pm 2.58 \mu\text{V}$) and dissonant chords (N2: $50.54 \pm 3.63 \mu\text{V}$; SWS: $36.36 \pm 2.69 \mu\text{V}$), similarly in both sleep stages N2 and SWS (see Figure 1c and Table 1, for sleep stage specific results). The PTP was calculated between the first positive peak (PP) and the first negative peak (NP) of the ERP. The main effect of chord type was highly significant ($F(2,92) = 26.73, p < .001, \eta_G^2 = .03$). Post-hoc pairwise t-tests remained significant after Bonferroni corrections ($p_{corrected} = 0.00833$) for the PTP comparison for major vs. minor chords as well as major vs. dissonant chords (all $p < .001$, see Table 2). No significant difference in PTP was observed between minor and dissonant chords.

When comparing the type NREM sleep stages N2 and SWS, we observed a highly significant main effect of sleep stage confirming that ERP responses to chords were generally higher in N2 compared with SWS ($F(1,46) = 33.10, p < .001, \eta_G^2 = .11$). Additionally, we detected a significant

interaction between Chord type and Sleep stage ($F(1.61, 74.03) = 5.28, p = .011, \eta_G^2 = .01$). The interaction is driven by generally larger differences in PTP amplitudes between the different chord types in N2 compared with SWS (e.g. the difference in PTP amplitudes between minor and dissonant chords reached a statistical trend in N2 ($p=.091$) but was not significant in SWS ($p=.294$).

The latencies of the positive and negative peak did not differ significantly between the musical chord types (main effect of chord type $p > .171$, see Table 2). Generally for all chord types, the negative peak occurred later in N2 sleep (803.83 ± 18.14 ms) compared with SWS (641.73 ± 12.79 ms), corresponding to the higher amplitude elicited in N2 sleep ($F(1,46) = 156.04, p < .001, \eta_G^2 = .37$). The latency of the positive peak was also descriptively later in N2 sleep vs. SWS (320.68 ± 6.79 ms versus 303.36 ± 9.34 ms), but did not significantly differ between sleep stages ($p > .05$). Additionally, we observed a significant interaction for the latency of the positive peak ($F(1,46) = 5.19, p = .007, \eta_G^2 = .02$): While the latency of the PP was shortest for major chords in N2 sleep, it was shortest for dissonant chords in SWS (see Table 2). However, subsequent post hoc t-tests did not remain significant after Bonferroni correction (all $p > .01$; see Table 2).

In conclusion, the PTP amplitudes elicited by major, minor, and dissonant chords during sleep differed significantly, both during N2 sleep and SWS. These findings suggest that our brain is capable to differentially processes musical chords according to their harmonical properties during NREM sleep.

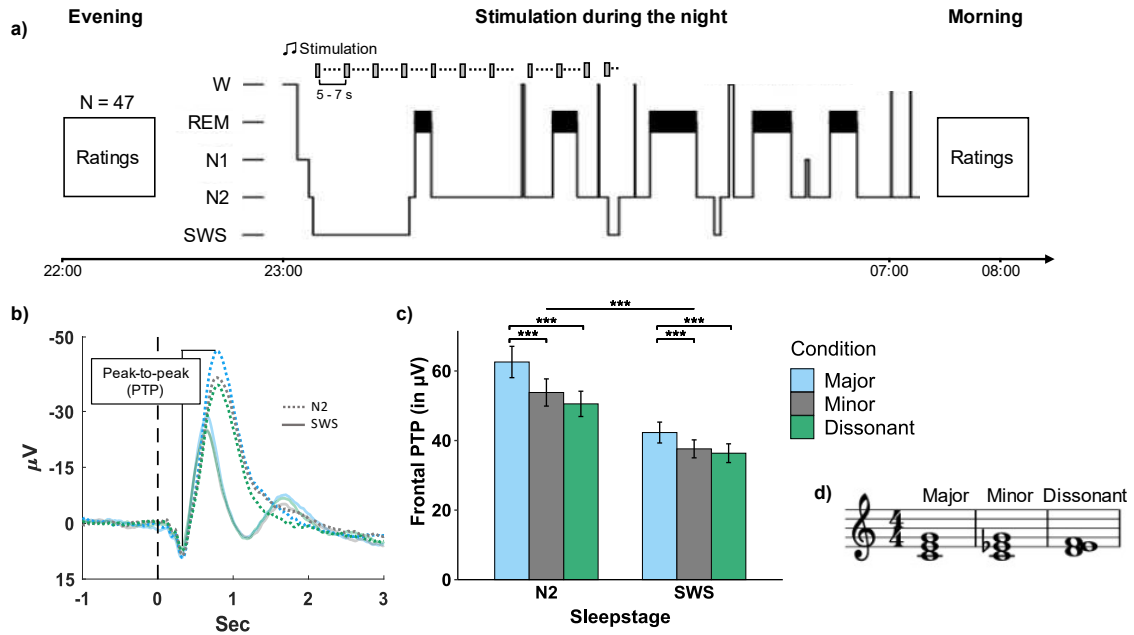
Figure 1

Figure 1. Experimental procedure, behavioral results and notation of chord stimuli. **a)** Experimental procedure. After preparation in the evening, 47 participants rated the different chords according to their valence and arousal. Then, the participants went to bed and slept for 8 hours. During sleep, we presented major, minor, and dissonant chords with an interstimulus interval of 5 to 7 seconds. In the morning, participants listened to the chords and rated them again. **b)** The averaged frontal ERP response (in μV) recorded with F3 and F4 after playing major (blue), minor (gray), and dissonant (green) chords during sleep. Chords were played at time 0. Frontal peak-to-peak (PTP) amplitudes were calculated by subtracting the positive peak from the negative peak **c)** Means $\pm$ SEM as a bar graph of PTP amplitudes (in μV) separated by musical chord condition and sleep stage. Major vs. Minor chords and Major vs. Dissonant chords differed significantly from each other in both sleep stages. In addition, both sleep stages N2 and SWS differed significantly from each other indicated by ***: $p < .001$ **d)** Notation of major (C-E-G), minor (C-E^b-G), and dissonant (D-E-F) chords.

Table 1. Subjective Rating and ERP features of major, minor, and dissonant chords

										ANOVA		
	Major			Minor			Dissonant			Chord type	Sleep stage	Interaction
<u>Subj. Rating</u>	Mean	±	SEM	Mean	±	SEM	Mean	±	SEM	<i>F</i>	<i>F</i>	<i>F</i>
Valence	6.56	±	0.17	5.28	±	0.21	3.44	±	0.17	99.41***	n.e.	n.e.
Arousal	3.47	±	0.26	4.17	±	0.24	4.96	±	0.23	34.25***	n.e.	n.e..
ERP												
PTP (μV)												
N2	62.58^{a,b}	±	4.5	53.81	±	3.91	50.54	±	3.63	26.73***	33.1***	5.28*
SWS	42.3^{a,b}	±	3.00	37.61	±	2.58	36.36	±	2.69			
PP (μV)												
N2	11.09	±	0.87	9.95	±	0.97	8.85	±	0.73	5.66**	0.09	0.01
SWS	10.78	±	0.78	9.8	±	0.8	8.61	±	0.87			
Latency PP (ms)												
N2	312.6	±	5.37	322.38	±	7.21	327.06	±	7.6	0.49	3.23 [#]	5.19
SWS	311.53	±	8.12	307.74	±	10.46	290.81	±	9.31			
NP (μV)												
N2	-51.49^{a,b}	±	4.1	-43.87	±	3.43	-41.7	±	3.5	16.39***	40.43***	5.38**
SWS	-31.52	±	2.85	-27.8	±	2.34	-27.75	±	2.54			
Latency NP (ms)												
N2	818.34	±	16.43	791.79	±	19.9	801.36	±	17.87	1.8	156.04***	0.14
SWS	647.91	±	13.42	634.09	±	13.94	643.19	±	10.81			

Table 1. Data are means ± SEM. Subjectively perceived valence and arousal of major, minor, and dissonant chords are shown, as well as ANOVA test statistics including the factors Condition (Major, Minor, Dissonant), Sleep stage (N2, SWS) as well as a possible interaction of these two factors (*F*; significant *F*-values in bold). Additionally, peaks (in μV) and latencies (in ms) of the ERPs elicited during N2 sleep stage or slow-wave sleep (SWS) are presented. PTP: Peak-to-peak refers to the difference between the positive minus the negative peak; PP: positive peak; Latency PP: latency of the positive peak; NP: negative peak; Latency NP: Latency of the negative peak. Significant differences between conditions are in bold and are indicated by a = significant difference between this category and minor chords and b = significant difference between this

category and dissonant chords. Numbers are means $\pm$ SEM (in ms or μ V). Significant effects are indicated in numbers and by *: $p < .05$; **: $p < .01$; ***: $p < .001$. Non-existent effects are indicated by n.e.

Oscillatory correlates of musical chord presentation during sleep

In addition to our ERP analysis, we conducted time frequency analyses (TFAs). Musical chord presentation during NREM sleep elicited a well-known response pattern consistent with tone-induced K-complexes and spindle oscillations: Increases in frequency power after several hundred milliseconds in the SWA band (1 - 4.5 Hz), theta band (5-7 Hz) and alpha band (8-12 Hz), followed by increases in responses in the spindle band (slow spindles 11-13 Hz; fast spindles 13-15 Hz) and beta activity (15-25 Hz). The increases were generally more pronounced after chord presentations during N2 than in SWS (Figure 2a, Figure 2d).

Importantly, the increases differed according to the different musical chord types: Mean oscillatory response was consistently stronger after major chords than after minor or dissonant chords (see Figure 2). Particularly during N2 sleep, significant clusters occurred in the low frequency range (SWA and theta) as well as later higher frequency ranges (alpha, spindles, beta) when comparing major chords against the two other chord types. The increases in power were smaller and more specific in SWS sleep, encompassing mainly clusters in the higher frequency range (alpha, spindles and beta). We did not observe a significant difference in the comparison of minor vs. dissonant chords. For a better overview, all significant clusters are presented in Table 3 and visualized in Figure 2.

Table 3. Significant TFA clusters of major, minor, and dissonant chords

Frontal Frequency Band	Sleep Stage	Cluster	Significant clusters		
			Maj vs Min Time in s	Maj vs Dis Time in s	Min vs. Dis Time in s
SWA (1 - 4.5 Hz)	N2	Cluster 1	0 - 2.60	0 - 2.60	No cluster
	SWS	No cluster			
Theta (5 - 7 Hz)	N2	Cluster 1	0.24 - 1.06	0.19 - 2.46	No cluster
		Cluster 2	1.18 - 1.70	2.67 - 3.18	
		Cluster 3	1.89 - 2.45		
	SWS	No cluster			
Alpha (8 - 12 Hz)	N2	Cluster 1	0.85 - 1.62	0.27 - 2.39	No cluster
		Cluster 2	2.65 - 3.06	2.70 - 3.36	
	SWS	Cluster 1	1.08 - 1.83	1.08 - 1.83	
		Cluster 2	0.50 - 0.89	0.50 - 0.89	
Slow spindles (11-13 Hz)	N2	Cluster 1	0.85 - 1.25	0.68 - 1.57	No cluster
	SWS	Cluster 1	0.94 - 1.96	0.94 - 1.96	
		Cluster 2	0.45 - 0.74		
Fast spindles (13-15)	N2	Cluster 1		0.79 - 1.27	No cluster
	SWS	Cluster 1	0.92 - 1.94	0.92 - 1.94	
		Cluster 2	2.48 - 3.02	2.48 - 3.02	
Beta (15-25 Hz)	N2	Cluster 1	0.80 - 1.17	0.76 - 1.59	No cluster
	SWS	Cluster 1	0.76 - 1.47	0.76 - 1.47	
		Cluster 2	2.51 - 3.01	2.51 - 3.01	

Table 2. Significant clusters of time-frequency comparison between the different chord types in N2 and slow-wave sleep (SWS). SWA: slow-wave activity (1 - 4.5 Hz); Theta (5 - 7 Hz); Alpha (8 - 12 Hz); Slow spindles (11 - 13 Hz); Fast spindles (13 - 15 Hz); Beta (15- 25 Hz). Clusters are given in seconds (s).

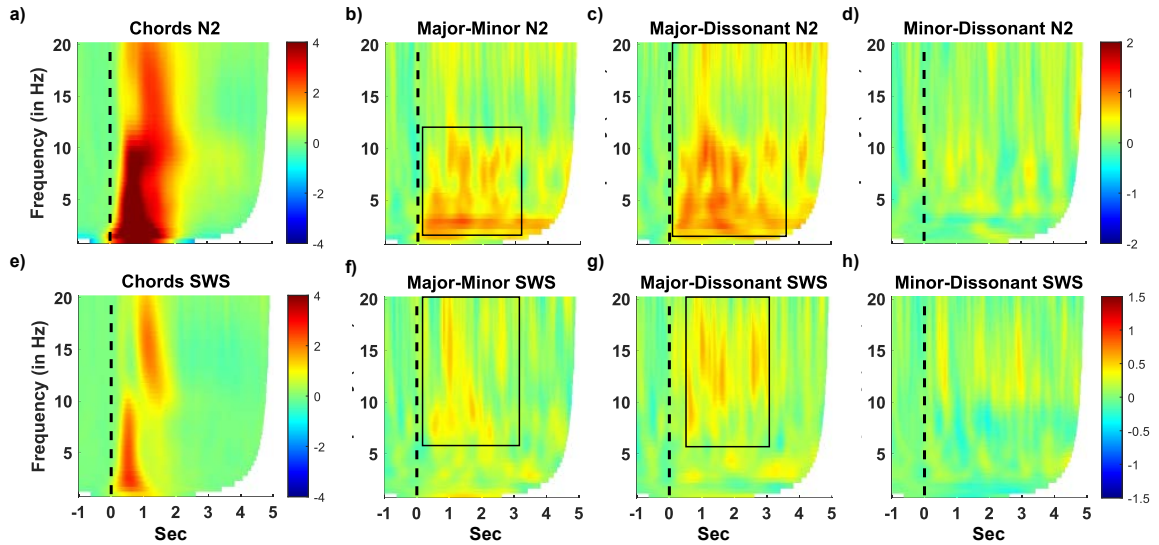
Figure 2

Figure 2. Oscillatory responses to chords presented during N2 and SWS in the time-frequency spectrum recorded at electrodes F3 and F4. **a)** Oscillatory power changes to all chords during N2 and show characteristic increases in the delta, theta, and alpha band, followed by increases in the spindle and beta band **b)** Difference between the neural responses of major and minor chords in N2, **c)** major and dissonant chords in N2, and **d)** minor and dissonant chords in N2 **e)** Oscillatory responses to all chords presented in SWS. **f)** major and minor chords in SWS **g)** major and dissonant chords in SWS, and **h)** minor and dissonant chords in SWS. We observed a general weaker response in SWS in comparison to N2. Moreover, the response to major chords was consistently stronger than the response to the minor and dissonant chords (see text and Table 2 for significant clusters).

Playing an instrument increased differentiation of musical chords during sleep

In subsequent analyses, we explored possible modulations of chord-induced brain responses during sleep by musical experience and subjective ratings, which has been observed during wakefulness (e.g., Minati et al., 2009). In particular, we observed that the differences in PTP amplitudes induced by musical chords presented during sleep depend on the ability of playing a music instrument ($F(2,44) = 3.18, p = .051, \eta_G^2 = .13$, see Figure 3a): Participants who actively played an instrument ($n = 9$) had a PTP difference of $13.49 \pm 4.27 \mu\text{V}$ between major and dissonant chords during sleep. Participants who did play an instrument but stopped ($n = 12$) had a difference of $10.04 \pm 1.96 \mu\text{V}$, while participants who never played any instrument had a PTP difference of $3.34 \pm 1.48 \mu\text{V}$. A Helmert contrast comparing the PTP differences of participants who play an instrument (active and inactive) vs. no instrument confirmed our observation ($t(44) = 2.38, p = .022$). We observed a similar pattern for the difference in PTP between major and minor chords processed during sleep, but no significance ($p = .820$). Actually, playing an instrument enabled the sleeping brain even to significantly differentiate between minor and dissonant chords during sleep, while we observed no such difference between these musical chord types in participants who never played any musical instruments.

As expected, playing an instrument also modulated subjective ratings during wakefulness of the different chord types, with higher differentiation with more musical experience ($F(2,44) = 3.45, p = .041, \eta_G^2 = .14$, see Figure 3b). However, we did not observe any bivariate correlation between valence ratings of chord types during wakefulness and PTP amplitude or PTP amplitude differences during sleep. Similarly, no meaningful correlations occurred for arousal ratings, the emotional regulation score or any other of the music expertise questionnaire (see Figure 3c, for a summary).

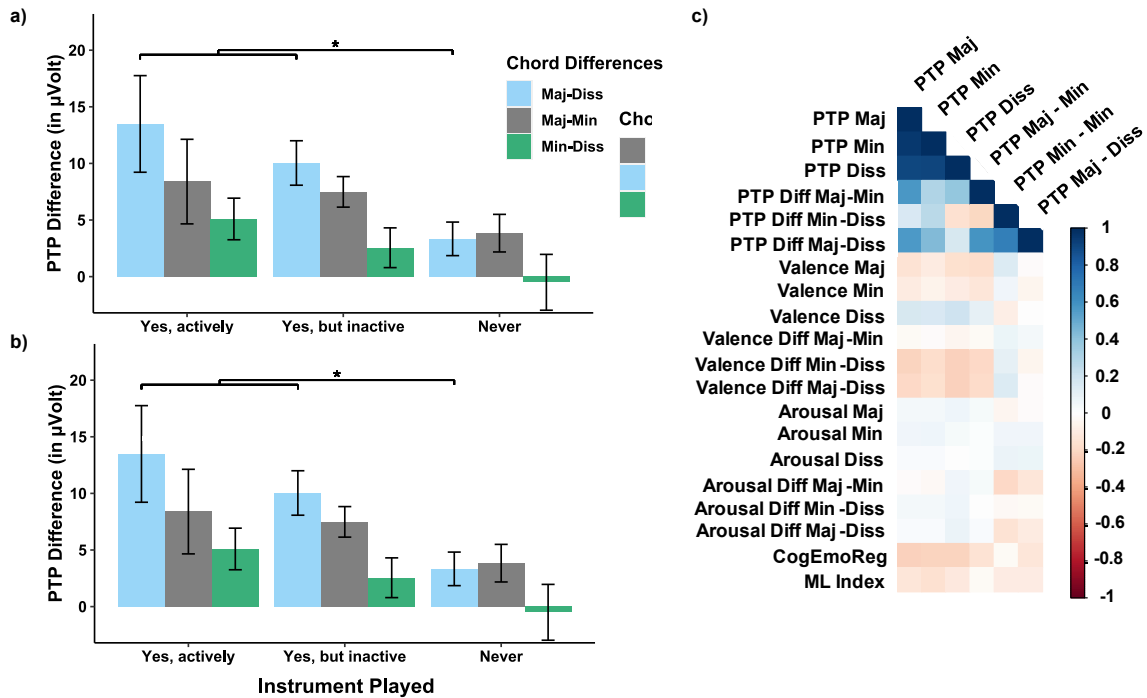
Figure 3

Figure 3. The effect of playing an instrument on Peak-to-peak (PTP) differences and differences in valence rating and correlation matrix. **a)** PTP amplitudes (in μV) and **b)** valence rating separated by chord differences Major – Dissonant, Major – Minor, and Minor- Dissonant for the variable “Instrument played” with the conditions “never”, “yes, actively”, and “yes, but inactive”. Values are Means $\pm$ SEM. Participants who have played or still actively play an instrument showed a more pronounced ERP differentiation between Major and Dissonant chords compared to participants who never played an instrument. Similarly, valence ratings followed the same pattern, with significant differences indicated by *: $p < .05$. **c)** Pearson's Correlation matrix visualizing the individual correlation coefficient between objective and subjective variables by color. The stronger the correlation the stronger the color. PTP Maj: PTP Major; PTP Min: PTP Minor; PTP Diss: PTP Dissonant; PTP Diff Maj-Min: PTP Difference between major and minor chords; Valence Diff Maj-Min: Valence rating difference between major and minor chords; Arousal Diff Maj-Min: Arousal rating

difference between major and minor chord. CogEmoReg: Cognitive Emotional Regulation through music; ML Index: Music listening index.

Discussion

In the current study, we presented isolated major, minor, and dissonant chords during NREM sleep stage N2 and slow-wave sleep (SWS) in a single night and investigated whether the sleeping brain is capable to process musical harmony by examining the neural correlates of musical chord perception.

The present analyses clearly show that the sleeping brain processes chords of varying harmonic degree differently. During both N2 and SWS, major chords consistently exhibited the most pronounced peak-to-peak (PTP) distances compared to minor and dissonant chords. The differential response to musical chord types of the sleeping brain was largest for participants who played an instrument. For these participants, we observed significant ERP amplitude differences for all chord type comparisons during sleep. For participants who never played any musical instrument, amplitude differences between chord types during sleep were smaller or even non-existent. Furthermore, the individual positive and negative peaks for major chords always produced the largest negative and positive amplitudes compared to minor and dissonant chords.

From the perspective of musical harmony, the only difference between the major and minor chord structure is one semitone, specifically a minor and major third (Virtala et al., 2012). Strikingly, our results provide strong evidence that even the sleeping brain is capable to process this tiny structural difference which results in a different harmony of the chord. This finding is consistent with previous waking EEG-studies (Maslennikova et al., 2013; Quiroga-Martinez et al., 2022; Virtala et al., 2011), as well as with imaging studies which confirm that the brain reacts differently to the different harmonious categories even in differing states of conscious listening (Nemoto et al., 2010; Pallesen et al., 2005).

The finding of the biggest differences between major and dissonant chords within all measures (ERP, valence, and arousal), may be due to the greatest difference in chord structure and the degree of harmonicity between these two. In contrast minor and dissonant chords did not differ significantly from each other in the elicited brain response during sleep. This objective result supports Parncutt's (2014) finding that minor triads are perceived as more dissonant due to their roughness and harmonicity compared to major chords. This may be attributed to the greater tonal complexity of minor structures as the structure of a minor chord is closer to a dissonant chord than the major chord (Heinlein, 1928). When examining the subjective perceived valence and arousal again, we found a significant difference between minor and dissonant chords. Still, we were unable to replicate findings that report different brain responses to minor and dissonant chords during wakefulness (Suzuki et al., 2008). This leads to the question of whether the sleeping brain is incapable of distinguishing between these two harmonic categories in contrast to the waking brain. Alternatively, personal experience and learning may mask the subjective ratings, which are attenuated during sleep, and that there is actually no substantial difference between the two chord structures that could lead to a difference in neural responses.

Turning to the oscillatory response, we first saw a consistently stronger response in N2 than in SWS. This higher perception threshold was unsurprising as it is consistent with previous sleep studies using word stimuli (Beck et al., 2021; Schreiner & Rasch, 2017; Wick & Rasch, 2023). This suggests that the perception of different chord structures is possible even during N2 sleep and during SWS albeit with a weaker response power. In addition, even in the frequency domain, the power elicited by the major chords consistently dominated the power elicited by the minor and dissonant chords. It confirms that musical harmony is processed differently in the brain as already done by studies by e.g., Pallesen and colleagues (2005). However, our results provide the first empirical evidence that musical harmony is processed differently in the sleeping brain.

An additional striking finding was that subjective ratings, and most importantly, the perception of major and dissonant chords during sleep, were modulated by musical expertise. This supports the conclusion that differences in ERP amplitudes are not due to inherent physical properties of the musical chords, but rather influenced by the individual musical training, adding a deeper musical meaning to our findings. Moreover, these findings are consistent with waking ERP findings (Maslennikova et al., 2015; Minati et al., 2009), on the basis of which researchers concluded that non-musicians have less effective perceptual strategies for processing musical harmony and a different emotionally driven perception of chords compared to musicians.

In general, ERPs evoked during sleep differ in morphology and topography from those observed during wakefulness (Colrain & Campbell, 2007; Ibáñez et al., 2009). The discrepancies between wake and sleep ERPs are attributed to the greater synchronous firing and inhibition of neurons during sleep, which result in higher ERP amplitudes compared to wakefulness (Coenen, 1995). Furthermore, sounds presented during NREM sleep can evoke K-complexes, which are characterized by very high negative amplitudes ($< 75 \mu\text{V}$). Increasing slow-waves by tones presented during NREM sleep is used to increase slow-wave sleep (SWS) in auditory closed-loop paradigms (Cordi, 2021; Fabbri et al., 2024; Gao et al., 2020; Hu et al., 2020; Tononi et al., 2010). On average, sound presentation during NREM sleep typically elicits a positive peak (at ca. 200 ms) followed by a negative peak around 550 to 800 ms (Bastuji & García-Larrea, 1999; Brualla et al., 1998). The negative amplitude can vary in response to different stimuli (Brualla et al., 1998), indicating a certain extent of stimulus processing during sleep (Colrain & Campbell, 2007). For example, the negative amplitudes are generally elevated for deviant stimuli that differ in intensity and pitch when presented during NREM sleep (Bastuji & García-Larrea, 1999).

Our findings on the varying ERPs moreover support the theory that they also reflect a form of different cognitive processing during sleep. However, the increased negative amplitude induced

by major chords may also suggest a stronger K-complex/slow-wave response, followed by greater power in the slow-wave range. Since K-complexes are believed to help maintain sleep (Halász, 2016), and these findings resemble those observed with relaxing words during sleep, future research should explore whether major chords enhance sleep depth and quality. These effects may possibly arise from their ability to evoke positive emotions, thereby influencing mental activity toward a more restful and positive sleep state. Still, extrapolations from this study should be made with caution, as a study designed to investigate this particular issue is still pending.

Our study has certain limitations and drawbacks that should be taken into account. One potential issue is that the dissonant chord (D-E-F) we used might also be interpreted as a modified minor chord. However, our subjective ratings confirm that the minor and dissonant chords were rated distinctly, aligning with the theory of minor and dissonant interpretation. We used only a minimal set of electrodes, which makes it difficult to pinpoint the location of differences in brain activity given the poor spatial resolution of the EEG. Although we found a difference in activity, we cannot rule out that there are other differences in other brain areas. Therefore, a next study should be conducted with MEG or fMRI to see if we could replicate previous findings during wakefulness (Maslennikova et al., 2013; Maslennikova et al., 2015; Minati et al., 2009; Quiroga-Martinez et al., 2022; Virtala et al., 2012) and build on our current findings during sleep.

Moreover, although it is a matter of debate, literature suggests that differences in consonant and dissonant perception are based on a cultural background (Morrison & Demorest, 2009). Therefore, the generalizability to other cultural contexts than the Western culture should be done with caution. Additionally, the gender ratio in our samples was unbalanced, which casts doubt on how broadly applicable the findings are to both sexes.

Next studies should consider the weaknesses of our current study and further focus for example on the presentation of inverted major and minor chords as they may induce other emotions (Lahdelma & Eerola, 2016; Roberts, 1986). Additionally, more complex chord sequences could be used to investigate the extent to which the sleeping brain processes musical harmony. Comparing musicians with non-musicians in such studies would also provide valuable insights.

All in all, this is the first study showing that the sleeping brain is capable to differentiate musical harmony during sleep, with musical expertise providing an advantage in distinguishing major and dissonant chords. Moreover, this study paves the way for further research on music and harmony perception during sleep. Future research should provide mechanistic insights on the contribution of subcortical brain areas and the potential of using musical stimuli and sounds as a tool to improve sleep.

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Disclosure Statement

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3 Discussion

The main aim of this dissertation was to investigate the phenomenon of reactivations during sleep in greater depth, particularly in the context of memory consolidation as well as cognitions, and emotions. This was achieved by addressing three specific research gaps in three empirical studies. The following discussion begins with a brief summary of these research gaps and the corresponding findings. Subsequently, the discussion examines two important aspects of reactivations during sleep in more detail: firstly, the process of memory consolidation in light of the results of Study 1 and secondly, the MemoSleep-Hypothesis and the reactivation of cognitions and emotions considering the results of Studies 2 and 3. On this foundation, aspects of the MemoSleep-Hypothesis are further evaluated and refined in greater detail. Furthermore, the findings from all three studies are further elaborated and new research questions and avenues are discussed. In the end, limitations are summarized, followed by a conclusion.

3.1 Brief summary of major findings

The first study (Study 1) on reactivations originated in the context of memory consolidation and the questioned isolated involvement of sleep stages N2 and SWS in this process. The results show no significant differences between the recall performances of N2- and SWS-words. Noteworthy, there was a missing overall benefit of TMR-words compared to non-reactivated control words.

The second study (Study 2) was conducted following the introduction of the MemoSleep-Hypothesis (Rasch, 2015). Again, this hypothesis posits that activated cognitions are embodied and reactivated during sleep, thereby affecting sleep quality. This may also be assumed in the context of the FNE by evaluating an unfamiliar sleeping environment and situation. Specifically, the question was whether a single night in an unfamiliar environment is sufficient to reduce stressful

pre-sleep appraisals and to adapt to the environment before returning to the same environment one week later. The contributions of situational and environmental factors causing an FNE were examined by comparing sleep architectures of the first nights in an unfamiliar environment with either a prior home adaptation or no prior home adaptation. Additionally, the occurrence of frontal asymmetric activity during SWS were analyzed. The results reveal that one adaptation night is sufficient since an FNE was only present during the first night. Furthermore, the FNE was present in both familiar and unfamiliar environments, although sleep was generally better in the familiar environment compared to the unfamiliar environment. Sleeping in the familiar environment before sleeping in the unfamiliar environment also attenuated the FNE in the following nights spent in the unfamiliar environment. Additionally, IAAs were present on all nights and their existence was not correlated with the FNE.

The third study (Study 3) was designed to test whether the fundamental assumptions of the MemoSleep-Hypothesis could be extended to include not only cognitions and thoughts but also emotions. In particular, the objective was to determine whether the targeted activation of an emotion in the evening could be externally reactivated and reinforced during subsequent sleep by using the TMR-technique, following the aim to influence sleep quality. Isolated musical major, minor, and dissonant chords were utilized, which vary in their harmonic degree. This proof-of-concept study showed that different musical chords evoked distinct emotion ratings prior to sleep and elicited different ERPs during sleep. Additionally, the ERP responses and ratings were modulated by the musical expertise. These results show that the sleeping brain is able to perceive differences in musical harmony, a topic that has received very little attention to date.

3.2 New insights into the memory consolidation process

Study 1, which investigated memory reactivations more closely found no significant difference between the recall performance of reactivated N2 and SWS words, as well as any overall memory benefits associated with TMR-words. The absence of an overall effect precludes the formulation of a definitive conclusion regarding the exact contribution of N2 and SWS but casts further doubt on the Dutch vocabulary paradigm used in this and previous studies (e.g., Wilhelm et al., 2020), questions the robustness of existing TMR-findings, and empowers voices already suggesting a publication bias that overestimates the effect size of this technique (Cordi & Rasch, 2021; Hu et al., 2020).

It is worthy to note that a few months later in 2024, Carbone et al. published a comparable study on N2- and SWS-TMR employing a distinct memory paradigm that has been successfully applied in their laboratory. Similarly to Study 1, no significant difference in memory performance was observed between cues presented in the two different sleep stages. Hence, the authors reached the conclusion that TMR can be used in both sleep stages.

However, caution is advised as Carbone et al. (2024) did not include a control condition which leads to the inability to control for the overall efficacy of their TMR-benefit compared to the normal retrieval rate. Furthermore, the test comprised only 30 items, 15 cues were presented in N2 and 15 cues in SWS. All of them were reactivated only once within the first hour of sleep.

In light of both studies, the isolated sleep stage view within memory consolidation should be subjected to even greater skepticism. Moreover, since both sleep stages may provide a suitable window for TMR, the focus should be further shifted to the overall neural oscillations and processes during N2 and SWS together rather than the isolated view of sleep stages. Especially since, in contrast to animal sleep, only human NREM sleep is further divided into sleep stages N2 and SWS (Ackermann & Rasch, 2014). Furthermore, since both studies tried to keep the number of

exogenous reactivations on the same level within both sleep stages, it is astonishing that the word retrieval rate was nearly identical for both sleep stages. This contradicts the existing body of literature, which assumes that SWS should provide better conditions for the application of TMR (see Rasch & Born, 2013).

It may also be the case that memory consolidation mechanisms of N2 may be different from those in SWS and for now underestimated and in need to be further investigated. Following the idea of different mechanisms in both sleep stages N2 and SWS, a second possibility is that these processes are interdependent, and that the optimal memory consolidation promotion is achieved by reactivating the same memory cues within both sleep stages. Similarly, isolated reactivations within the two separate sleep stages might also lead to competing or interfering memory consolidation effects. This could also explain the lack of a general effect of TMR in comparison to the control condition in Study 1. To provide answers to all these points mentioned above and in Study 1, future investigations should imperatively consider replications but also within-subject comparisons between words only played in N2, only played in SWS, not reactivated control cues, and another category of cues presented in N2 *and* SWS together, to precisely test the interdependency of both sleep stages.

From the comparison of Study 1 and Carbone et al. (2024), further clear basic recommendations can be derived for research in the area of TMR. The two existing studies differ in the number of reactivations during the night. To date, no optimal repetition rate for TMR-cues has been recommended. As already suggested by Carbone et al. (2024), this should be investigated experimentally. However, it should also be analyzed as a moderator in meta-analyses regarding the effects of TMR. A nearly identical argument can be made for the number of items to learn within a memory task. Study 1 included 120 word-pairs whereas the study of Carbone et al. (2024) included only 30 sound-syllable-word associations. This is only one example for the great discrepancies

between the utilized tests within TMR research (see also Cairney et al., 2016; Oudiette et al., 2013; Rudoy et al., 2009). Hence, future studies should give more consideration to the specifics of the utilized TMR-tests, particularly since the Dutch-vocabulary test employed in Study 1 may not have worked properly.

When considering the TMR-literature and a particular study based on the MemoSleep-Hypothesis, a further recommendation can be proposed. Combertaldi et al. (2022) demonstrated that the pre-sleep instruction to react to tones during nocturnal sleep led to a modification in the ERP-response to these particular tones. This finding may also be of great interest for the TMR-research. To date, no official, common rule has been defined as to whether or not subjects should be informed about the presentation of TMR-cues during the night. In several experimental procedures, this point is not defined or even varies across studies (e.g., Rudoy et al., 2009; Schreiner & Rasch, 2015). Although TMR-cues should not wake up and require participants to behaviorally respond as instructed within the study by Combertaldi et al. (2022), it still suggests that knowledge about the TMR-presentation may alter brain responses to respective cues. In a next study, this should also be systematically investigated. Moreover, in future studies it should be clearly stated whether participants were aware or unaware of the stimulation during the night.

All of the aforementioned suggestions should be considered additionally to previous recommendations (as listed in Cordi & Rasch, 2021) regarding the planning of the optimal sample size, preregistering all projects, replicating findings and a general call for the publication of all results. Additionally, TMR-research needs to address Hu et al.'s (2020) list of all unresolved questions e.g., whether there is a clear difference between externally administered TMRs and naturally occurring endogenous spontaneous reactivations. All these points would help to gain deeper insights into the reactivation process during memory consolidation and possibly help to

resolve the question of the contribution of both sleep stages N2 and SWS within the consolidation process in the future.

3.3 Insights into the reactivations of cognitions and emotions during sleep

Deeper insights into the reactivation process during memory consolidation would also help to understand other potential reactivation processes, including the reactivation of cognitive concepts postulated by the MemoSleep-Hypothesis. These potential reactivations were also assumed in the two other studies of this dissertation. Therefore, in the following sections, the results of Study 2 on the FNE and the results of Study 3 on music perception during sleep will be discussed in relation to this hypothesis. Thereby, a special focus will be laid on the reactivation premise of the MemoSleep-Hypothesis. In the beginning, the FNE is explained in terms of the premises of the MemoSleep-Hypothesis and its integration is critically reviewed. Next, it will be examined whether the postulated reactivations of cognitions can also be extended to include emotions and music as a specific emotion generator will be examined more precisely.

3.3.1 The FNE and the MemoSleep-Hypothesis

As proposed in the introduction, sleeping in a new environment is associated with unfamiliarity or even insecurity and might evoke corresponding cognitions. According to the MemoSleep-Hypothesis, these cognitions are subsequently embodied and lead to a cognitive and physiological arousal. Then, during the following sleep these embodied concepts of unfamiliarity and insecurity are repetitively reactivated, leading to a negative change in sleep architecture and poor sleep quality, typical characteristics of an FNE. Because in Study 2 sleep was generally better in the familiar environment and in the unfamiliar environment after a familiarization with the equipment, it appears that the concepts of novelty and unsafety were less activated and less

reactivated during sleep. These patterns of results show that pre-sleep appraisals of the sleeping environment and situation seem to decrease after a non-consecutive adaptation night.

Still, different attempts to explain these findings can be made. It is well established that stressful cognitions lead to a complex cognitive and physiological stress response, which, in turn, has a negative impact on sleep (Akerstedt, 2006; Buckley & Schatzberg, 2005; Tang et al., 2023). The psychological and physiological mechanisms responsible for the FNE are also connected to acute stress induced by anxiety and environmental factors (Zhang et al., 2024). Therefore, it may also be assumed that the FNE is only caused by the acute stress situation and the cognitive hyperarousal before sleep and that the reactivation premise of the MemoSleep-Hypothesis does not apply.

Still, existing studies on the effects of acute stress on sleep are not able to fully explain the observed effects of FNEs on sleep. These studies show that acute stress tends to have a small effect on subsequent sleep, limited to the first part of sleep, while anticipation of stress tends to affect later sleep time (see Beck et al., 2023). Beck et al. (2023) summarize these findings by suggesting that cognitive concepts related to stress anticipation are reactivated during the night. Likewise, Brosschot et al. (2007, 2010) examined the impact of stressors on sleep and inferred that stressors and worries remain active and are unconsciously reactivated during sleep, thereby negatively influencing physiological parameters in this process.

Moreover, sleeping in a novel environment and situation may not be an acute stressor that ends before sleep, but continues throughout the night, due to the fact of being observed or being limited in the freedom of movement (Le Bon et al., 2001), which is unusual and novel and therefore possibly dangerous (Ellsworth & Scherer, 2002). Taking the sleep parameters affected by the FNE into consideration, it becomes apparent that these changes in sleep architecture occur not only at the beginning of sleep, such as a prolonged SOL, but continue to influence various sleep parameters

throughout the night, as a prolonged REM latency, increased WASO and N1 and decrease in REM, TST and SE (Ding et al., 2022). The affected sleep parameters in Study 2 provide further evidence in that regard. When interpreting the affected sleep parameters by the FNE in the context of Beck et al.'s (2023) explanation, sleeping in a new environment seems to take the role of an acute and an anticipated stressor. Because of its at least partial anticipatory character, the process can not only be limited to pre-sleep stress. Hence, the unknown and potential anticipated danger within this new environment may lead to the reactivation of the embodied stressful appraisals and cognitions during sleep in the first night leading to a diminished sleep quality, an interpretation in line with the MemoSleep-Hypothesis.

It is also possible that the reactivation premise is not captured entirely accurately and activated concepts do not undergo repeated reactivations but instead remain active during sleep. An active system during an FNE is also assumed by Tamaki et al. (2016). The researchers refer to a “night watch system” (Tamaki et al. 2016, p. 1192) which is associated with interhemispheric asymmetric SWA in the default mode network and remains active during sleep in order to scan the unfamiliar surroundings, thereby protecting the organism from potential danger. If an active system during the night is more accurate, the reactivation process described in the MemoSleep-Hypothesis would not be required to explain the FNE and should be rather replaced by mental concepts which remain active during sleep.

The assumption of an active system during sleep also finds support when turning to the existing body of sleep research, assuming that cognitive systems seem to remain further active during sleep (Bastuji & García-Larrea, 1999). Several studies show that the sleeping brain is still capable of perceiving external stimuli (Andrillon & Kouider, 2020). Brain responses to these stimuli vary, depending on their particular salience, which can even be manipulated through specific instructions before sleep (Colrain & Campbell, 2007; Combertaldi et al., 2022; Legendre

et al., 2019). Another interesting phenomenon is the ability of individuals to plan their wake-up time intrinsically without external time feedback (Hayashi et al., 2010). All these findings suggest that cognitive systems are somehow active during sleep and even able to prioritize different stimuli. They appear to influence processes and sleep architecture during sleep through previous situations, intentions, and instructions.

In consideration of all the aspects above, it could be appropriate to interpret the FNE and the corresponding results of Study 2 as indicative for the MemoSleep-Hypothesis. However, the different aforementioned perspective also highlights that further studies are required to investigate the underlying reactivation premise of the MemoSleep-Hypothesis more precisely. Otherwise, it remains difficult to distinguish whether the concept of reactivation is needed or not.

Still, finding scientific evidence to support the second reactivation premise of the MemoSleep-Hypothesis is particularly challenging, since analyzing unconscious thought processes during sleep is a major scientific difficulty (Brosschot et al., 2010). A future FNE-study could inquire participants immediately following an endogenous awakening, what thoughts were present in their minds right before and immediately after awakening.

3.3.2 The dichotomous view on emotions and cognitions

A question postulated within this dissertation addresses whether the MemoSleep-Hypothesis can be extended to include emotions, as the current version of the hypothesis neither mentions nor takes emotions into account. Given the existing body of literature on emotions and thoughts, this neglect is controversial, as cognitions and emotions are both complex, closely interdependent and bi-directionally influenceable (Krizan et al., 2024; Storbeck & Clore, 2007). Thoughts activate emotions, and emotions entail and arise from cognitive processes such as appraisals and thoughts (Lazarus, 1991, 1999; Russell, 2003). Following this line, a neglect and dichotomous view of

emotions and cognitions is highly problematic. An activated mental concept such as “unfamiliar” and “unsafe” and the cognitive evaluation of the environment during the first night in Study 2 should also lead to the activation of corresponding emotions such as fear and a corresponding physiological stress response which, in turn, influences brain structures controlling cognitions and emotions (Ellsworth & Scherer, 2002; Rodrigues et al., 2009). This co-dependency would also mean that the emotion “fear” would activate stressful thoughts. Both scenarios would result in an embodiment of stressful mental concepts, which would increase the likelihood of their reactivation during subsequent sleep. Although this is clear from the existing literature, it seems necessary to extend the MemoSleep-Hypothesis to explicitly account for this co-dependency between cognitions and emotions.

Again, it is highly difficult to separate thoughts and emotions (Lazarus, 1991; Pessoa, 2008; Storbeck & Clore, 2007). However, one potential advantage of this given co-dependency is the possibility to activate not only specific thoughts but also emotions through a specific stimulus prior to sleep. In addition, it offers the possibility of reinforcing a cognitive concept by additionally activating corresponding emotions through a specific stimulus. In turn, the activation, embodiment, and following reactivations of thoughts during sleep may also be diminished or prevented through the strategic induction of non-corresponding, contradicting emotions. For instance, a positive low-arousing emotion may be induced after the activation of stressful cognitions such as the arousing evaluation of the unfamiliar environment during a first night. As Tice et al. (2007) demonstrated, the induction of positive affect has a beneficial effect on experienced stress.

Until now, the main focus of the behavioral studies on the MemoSleep-Hypothesis laid specific focus on the activation of cognitive concepts and not emotions, because of the current version of the MemoSleep-Hypothesis (e.g., Beck et al., 2023; Combertaldi & Rasch, 2020). However, since the direct activation of cognitions rather supported the assumption that especially

stressful cognitions are reactivated deteriorating sleep quality, a next idea would be to shift the focus from cognitions to emotions and to activate a specific emotion through particular stimuli. Studies with this broader focus could investigate whether the targeted activation of emotions, especially positive emotions, leads to a strong enough or stronger effect on a positive embodiment. Moreover, it may also increase the following probability of repetitive positive reactivations than the power of cognitive concepts, capable to influence sleep quality even in a more positive way.

Based on all aspects mentioned above, the MemoSleep-Hypothesis needs to be extended to include also emotions in order to fully capture pre-sleep activated mental concepts with all its aspects to fully understand the exact embodiment, reactivation, and influence on sleep quality. However, for an extension of the MemoSleep-Hypothesis to include emotions it is important to be precise: According to Russell's affective circumplex model (1980), emotions are located on two continuous dimensions - valence and arousal. Positive emotions which are rated high on the arousal dimension are also associated with physiological arousals such as a change in heart rate variability or blood pressure (Dockray & Steptoe, 2010). Following the core assumptions of the MemoSleep-Hypothesis, it is therefore important to activate especially positive, deactivating emotions which are scored high in valence but low on the arousal dimension to not interfere with sleep quality since hyperarousal is a core complaint of insomnia (Tang et al., 2023).

Nevertheless, it should be noted that the emotional process is not static but rather dynamic. Therefore, it is challenging to observe an isolated activation of a single categoric emotion, as such occurrences are highly infrequent in contrast to the activation of a mixture of several emotions (Scherer & Meuleman, 2013; Scherer & Moors, 2019). Moreover, it should be also emphasized, that a recent meta-analysis of Krizan et al. (2024) including 31 studies examining the causal effects of emotions on sleep demonstrated that negative emotions were exclusively linked to a delayed SOL, with no discernible influence on other sleep parameters and no observable impact of positive

emotions on sleep. However, the authors did not consider the different appraisals of the emotions and also highlight several limitations in their discussion, including a potential publication bias, varying study designs, and the activation of global stress, which in turn triggered a range of different appraisals and emotions. Additionally, numerous studies did not consider the impact of varying emotional arousal levels or failed to directly manipulate the emotions prior to sleep. Furthermore, the effect of positive emotions on sleep was not sufficiently investigated. Consequently, the authors advise that their conclusions are provisional and advocate for more targeted research, including investigations of emotional arousal levels and cognitive appraisals.

3.3.2.1 Emotion (re)activation through music

The limitations addressed in this meta-analysis of Krizan et al. (2024) may be resolved by establishing the MemoSleep-Hypothesis and using music and the new proof-of-concept findings of Study 3. Again, the results of this study show that isolated musical chords of different harmonic degrees have been rated differently in arousal and valence prior to sleep and were differently perceived during the night. The different perception was reflected in specific ERP differences. Musical chords may therefore serve as appropriate generators of certain emotions and may create the possibility to employ them as cues for the standardized induction of emotions prior and during sleep.

Following these ideas, the reactivation of isolated major, happy chords during sleep, might help to attenuate the endogenous reactivations of stressful cognitions, for example during a first night, and might help to improve sleep quality by reducing the symptoms of an FNE. Diametrically opposed, the reactivation of minor or dissonant chords could decrease sleep quality. Therefore, musical major, minor, and dissonant chords might potentially be used as a standardized manipulation tool for the activation of e.g., happy or sad emotions. This may serve as a starting

point to address the limitation which has been listed in the meta-analysis of Krizan et al. (2024). The presentation of musical chords could be done similarly to the study by Beck et al. (2021), who presented relaxing words during sleep to reactivate the concept of relaxation thereby improving sleep. Another orientation may give the study by Xia et al. (2023), although they did not focus on sleep quality. Still, the researchers successfully updated the emotional tone of aversive memories by presenting positive words paired with the aversive memories during sleep.

However, reflecting on the emotional power of music and the existing literature on this topic, an interesting, ambiguous debate emerges, which may be of practical importance for using musical chords for emotion induction before sleep. In particular, it concerns the question of which musical elements are universally perceived emotionally, and which elements only evoke an emotional reaction after a particular musical culture exposure (Fritz et al., 2009; McDermott et al., 2016).

For example, major and minor chords dominate Western music (Bakker & Martin, 2014). Studies in which Western musical chords and Western music have been presented to non-exposed listeners of Western music have found that Western musical modes do not convey emotions in those individuals as they do in Western music listeners (Athanasopoulos et al., 2021; Lahdelma et al., 2021). However, another study showed that happy and sad Western musical pieces were distinguishable also in non-exposed Western music listeners (Fritz et al., 2009).

To solve this debate is beyond the scope of this dissertation. Still, it is important to underline the importance of further research into this topic because it would have further implications for the universality of using musical chords to convey specific emotions to improve sleep quality.

The aforementioned sleep improving strategies based on the presentation of musical major chords may only be suitable for subjects who have been exposed to Western music and may not be suitable for non-Western music cultures. It would therefore be necessary to adapt the used stimuli for other cultures to provide a universal sleep aid with exchangeable musical stimuli, always

targeting to activate positive emotions before sleep. These emotions should become embodied before sleep and reactivated during sleep to beneficially influence sleep quality. A possible pathway is to not use isolated musical features such as chords, but musical pieces.

Such a strategy is supported by the existing body of literature establishing that listening to music prior to sleep has a positive effect on sleep quality (Dickson & Schubert, 2022; Trahan et al., 2018) and could prevent the activation of cognitive hyperarousal (Dickson & Schubert, 2019). Moreover, it could be useful for individuals who do not respond to other sleep improving interventions such as hypnosis (Cordi et al., 2014, 2019).

This sleep improving strategy would also offer the opportunity to personalize and adapt musical stimuli based on the preferred genre of an individual or even more precisely, the favorite song. This is particularly important in light of the finding that people listen to different music genres before going to sleep (Dickson & Schubert, 2022; Scarratt et al., 2023).

Along this path, future studies should present more complex musical stimuli, such as multiple chords, to create harmonic sequences which are known to induce emotions (Daikoku et al., 2024). For musical perception and sleep improving strategies during sleep, it would be important to know how complex musical stimuli may be and to what extent the sleeping brain is able to distinguish them and perceive musical harmony. Additionally, it would also be necessary to investigate how long the music stimuli need to be to induce emotions during sleep without deteriorating its architecture and its quality. An orientation might give the TMR study by Gao and colleagues (2020) who played a complete classical song during SWS and only interrupted when EEG-signs of arousal were detectable. Moreover, it would be also important to investigate whether the perception of musical stimuli and their complexity is dependent on musical expertise which would have further consequences for the applicability of this sleep-improving intervention.

For now, caution should still be advised, because even if the musical chords are differently perceived in terms of valence and arousal during wakefulness (Pallesen et al., 2005), it is not yet clear whether the presentation of single musical chords and the presentation of music induce actual emotions (see Scherer & Zentner, 2001). Moreover, it is not clear whether the induced emotions are actually reactivated during sleep. The differences in ERPs may also be due to the perception of physical characteristics of the musical chord. In addition, it is not clear whether the mere perception of different emotions during sleep is sufficient to improve sleep, or whether an actual induction of emotions is necessary.

Therefore, future studies on this topic are imperatively required and should include objective measures of emotions as heart rate, skin conductance, and respiration and neuroimaging techniques (Gomez & Danuser, 2007; Koelsch et al., 2006).

3.3.3 Neural aspects of the reactivations of cognition and emotions

After examining the FNE within the context of the MemoSleep-Hypothesis and extending it conceptually to include emotions that may be elicited and reactivated by music, it is important to consider the second reactivation premise of the MemoSleep-Hypothesis from a neural perspective. This is especially important because the underlying neural aspects of the reactivation of mental concepts are not entirely clear. Additionally, deeper insights might help to develop strategies to activate and reactivate more positive concepts and improve sleep. Moreover, Study 1 in this dissertation offers the opportunity to consider this premise against the memory reactivation background. Therefore, the following chapter will elaborate the neural mechanisms underlying possible reactivations of activated and embodied cognitions and emotions, highlighting key aspects that should be the focus of future investigations. In particular, the following chapter aims to draw

attention to the area of interest for the assumed reactivations, followed by the questions of what exactly is being reactivated and when these reactivations may take place.

3.3.3.1 Areas of interest

A key issue which has been discovered within the introduction (see Chapter 1.3.1 Memories of Sleep Hypothesis) is that it is unclear whether the reactivations of cognitions and emotions are analogous to memory reactivations, following the same neuronal mechanisms of the active system consolidation hypothesis (see e.g., Diekelmann & Born, 2010) during sleep. The exact mechanisms of these reactivations are not defined in the original form of the MemoSleep-Hypothesis (Rasch, 2015) but the explanation was based upon the reactivation process of memories. Therefore, some analogies may be assumed, as, for example, the crucial involvement of the hippocampus. Nevertheless, the exact process and location of the reactivation of cognitions and emotions are still unclear since neuroimaging studies are pending.

Turning to Study 2 and the FNE: Sleeping in a new environment may automatically and subconsciously activate a schema. A schema is an abstract, adaptable representation built upon several similar experiences (Ghosh & Gilboa, 2014; Robin & Moscovitch, 2017). When sleeping the first night in an unknown surrounding it may activate the schema “sleeping in a new environment”. Existing research suggests that the activation of a schema does not primarily involve the activation of the hippocampus (Ghosh & Gilboa, 2014; Robin & Moscovitch, 2017). Therefore, possible reactivations of the hippocampus seem to be challenged. However, in animal studies memory reactivations were observed not only in the hippocampus but in different brain networks and brain regions, such as the prefrontal cortex, putamen, thalamus, and striatum (Buhry et al., 2011; Ribeiro et al., 2004). Moreover, existing theories also assume the involvement of the hippocampus during the retrieval of declarative memories (Heckers et al., 2002; Ritchey et al.,

2013; Tanaka et al., 2014). Besides, the cognitive evaluation of environmental conditions and its embodiment is much more complex than the mere activation of a schema. In accordance with the multimodal storage assumption of embodiment, it may activate several other brain areas and even emotions (Barsalou, 2008; Ellsworth & Scherer, 2002; Niedenthal, 2007) before sleep.

In context of Study 3, the perception of music activates several brain structures, e.g., among many other areas the auditory cortex, neocortical areas, limbic, and paralimbic structures which interact with several other systems e.g., the visual systems (Koelsch, 2011, 2014). Moreover, music also activates the hippocampus whose activity has been found to correlate positively with music retrieval (Mueller et al., 2011). Additionally, there is accumulating evidence that music does not only trigger emotions but also evokes autobiographical memories (Belfi et al., 2016; Janata et al., 2007), a process which is also linked to hippocampal and prefrontal cortex activity (Cabeza & St Jacques, 2007). Moreover, the underlying mechanisms of the emotion induction by music have been proposed to include next to episodic memories also evaluative processes, brain stem reflexes, visual imagery processes, and the individual musical expectancy which are associated with activity in many different brain areas (Juslin & Västfjäll, 2008; Koelsch, 2011).

Given that several brain areas are involved and activated during the generation of cognitions and emotions (Pessoa, 2008), the extent to which these reactivations rely on single or different brain areas during sleep, thereby influencing sleep quality, needs to be investigated. A critical area of interest for potential reactivations is still the hippocampus, but should also include regions of the prefrontal cortex, the paralimbic and limbic system, including the amygdala. The amygdala is a particular area of interest because it plays a central role in emotional regulation, including fear, attention distribution, and vigilance (Anders et al., 2004; Davis & Whalen, 2001; Levenson, 2011).

One potential method would be to investigate the activity of brain areas listed above with functional magnet resonance imaging and perform correlational analyses. Such analyses would

compare neural activity pattern during wakefulness with the activity during sleep (Helfrich et al., 2021). This method may also be applicable during the pre-sleep activation of a mental concept e.g., through a specific stimulus and the subsequent reactivation during sleep. In special regard to Study 2, it would also be interesting to investigate the activity of the default mode network, as this network has been shown to exhibit interhemispheric asymmetry during the FNE (Tamaki et al., 2016), which may also be associated with potential reactivations of mental concepts.

3.3.3.2 Content and timing of reactivations

Another challenge which needs to be addressed is the question of what aspect of activated and embodied thoughts or emotions is exactly reactivated during sleep. This is also a question which has not been clarified for memory reactivations (Picard-Deland et al., 2023; Robertson & Genzel, 2020). Since various concepts and components, such as autobiographical memories or emotions, are triggered during the activation of mental concepts and music listening, an important question to ask is, what exactly is embodied but also reactivated during sleep thereby influencing sleep: the embodied cognitions or emotions, a memory to a past experience, or a combination of all these variables?

Another question which emerges especially in context of Study 1 is when exactly the endogenous reactivations of cognitive concepts occur. This was also not defined in the current version of the MemoSleep-Hypothesis. A large body of studies observed memory reactivations during NREM sleep but also during REM sleep, albeit to a weaker amount (see Picard-Deland et al., 2023). Still, in which sleep stage exactly the reactivations of mental concepts occur endogenously, and which sleep stage is optimal for external cuing of cognitive concepts or emotions, is not entirely clear yet. A first study by Beck et al. (2021) provided evidence that relaxing words can successfully be externally reactivated during NREM sleep stages N2 and SWS

to improve sleep. Moreover, in the study by Xia et al. (2023), positive words which were paired with aversive memories were presented exclusively during SWS. However, this study did not include a comparison to N2 sleep and did not focus on sleep quality. Therefore, as similarly addressed in Study 1, it is not yet clear which NREM sleep stage provides a better window to externally reactivate mental concepts. Additionally, it is not yet clear whether reactivations of cognitive concepts happen during REM sleep, and whether the external reactivation of especially emotion triggering stimuli such as music, are even more beneficial to improve sleep quality. This is a question for future research.

All these neural issues need to be addressed in future neuroimaging studies to further understand the neural mechanisms underlying the MemoSleep-Hypothesis. Based on these neural insights, strategic interventions to activate especially positive mental concepts including emotions before sleep to improve sleep quality may be adjusted and lay the foundation for the successful use of externally administered reactivations of these concepts.

3.3.4 Further characteristics of memory and reactivations of cognitions and emotions

Despite the lack of detailed knowledge concerning the exact areas, the content, and timing of these reactivations, further analogies between the memory reactivation process and the reactivations of cognitive concepts mentioned within the MemoSleep-Hypothesis can nevertheless be proposed. The following chapter, therefore, focuses on two specific characteristics which have emerged in consideration of the studies included in this dissertation.

3.3.4.1 *Relevance*

As indicated in the introduction, evidence suggests that memory reactivation is a selective process, particularly favoring the consolidation of salient and relevant memory traces (Diekelmann

& Born, 2010; Klinzing et al., 2019). This selective process might also be detected in the activation of mental concepts assumed by the MemoSleep-Hypothesis.

The findings regarding the FNE in Study 2 have shown again, that especially stressful cognitions, negative emotions, and the embodiment of these concepts lead to a disrupted sleep, especially in the unfamiliar environment. This is in alignment with previous literature on stress and sleep, and the especially adaptive function of negative emotions (Akerstedt, 2006; Folkman, 2008; Roseman & Smith, 2001; Seligman, 2009; Tang et al., 2023) and further shifts the applicability of the MemoSleep-Hypothesis in a rather negative direction. The activation and the corresponding embodiment of stress-associated negative concepts seem to be easier and stronger (Seligman, 2009). Therefore, these concepts become probably reactivated to a greater amount during sleep, thereby influencing sleep in a negative way. The reason for this may lie in the relevance of these concepts to the organism.

Sleep is a vulnerable state (Lima et al., 2005; Rasch & Born, 2013), and stress and anxiety have a survival function that puts the organism in a state of alarm during a threatening situation (Izard, 2013; Marks & Nesse, 1994). This state subsequently affects cognitive and emotional processes (Rodrigues et al., 2009) as well as sleep (Akerstedt, 2006; Buckley & Schatzberg, 2005). In order to ensure the survival in this vulnerable state of sleep, for example during a first night in a new environment, the organism may be more susceptible to stressful cognitions and negative emotions. Potentially, the activated cognitive concepts of “unsafe”, “unfamiliar”, and “novel” before sleep result in the relevant psychophysiological alarm state, increasing the levels of reactivations of the particular mental concepts during sleep and thereby disrupting sleep in order to scan the environment, situational factors and as such secure the survival (Ellsworth & Scherer, 2002). Thus, this selective process of the reactivation of rather negative mental concepts on sleep

is due to the link to the survival instinct and the accompanied consequences of the biological stress responses (see Han et al., 2012).

An interesting question that emerges from this background is how positive mental concepts can gain in relevance in order to have an influence on sleep. The mere intention to sleep better seemed to be not strong or relevant enough to improve sleep (Combertaldi & Rasch, 2020). However, an unconscious activation via hypnosis has already been shown to deepen sleep (Cordi et al., 2014). This could serve as a basis for future studies to increase the relevance by subconsciously activating the specific positive concept.

Moreover, the relevance of a specific mental concept, and thereby the reactivation of it during sleep, might also be increased by using the TMR technique. A first study using this technique has already found supporting evidence for the MemoSleep-Hypothesis by the repetitive presentation of relaxing words (Beck et al., 2021) and the study by Xia et al. (2023) who found that TMR was even able to update the emotionality of a specific memory.

Future studies therefore need to investigate the subconscious activation of specific relaxing or security-associated concepts to attenuate the concept of “insecurity” during the FNE. In consequence, this concept may become less reactivated which increases sleep quality. Additionally, sleep quality may potentially be externally increased by TMR cues of relaxing words or positive, preferred music.

3.3.4.2 Pre-existing memories

There is another reasonable assumption when considering analogies from the memory consolidation process compared to the assumption of the reactivation process as assumed by the MemoSleep-Hypothesis. The process of memory reactivation also activates and integrates memories into pre-existing long-term memory networks (Diekelmann & Born, 2010; Rasch &

Born, 2013). Moreover, prior knowledge as well as the congruence between the learning material and an existing schema seems to be beneficial for the use of TMR and memory consolidation during sleep (Cordi et al., 2023; Durrant et al., 2015; Groch et al., 2017).

If these findings are applied to the MemoSleep-Hypothesis, the significance of pre-existing memories may become evident here as well. For instance, in individuals who have already experienced significant sleep disturbances due to the FNE, the mental concept of “unsafe” and “unfamiliar” may manifest differently compared to those who have had a good night’s sleep in this unfamiliar environment. Moreover, this may also be applied to music, since it has the power to trigger vivid autobiographical memories (Belfi et al., 2016).

This supports the assumption that next to the factor of relevance, pre-existing memories or knowledge may shape activated mental concepts, as well as the level of embodied arousal or relaxation. This further reinforces the recommendation to individualize specific stimuli or situations for participants to either relax or arouse before sleep in order to influence sleep quality in the most beneficial way.

3.3.5 Implications and extensions of the MemoSleep-Hypothesis

The Memosleep-Hypothesis has already been established in important aspects. However, this dissertation provides an important opportunity to improve the accuracy of the core assumptions of the MemoSleep-Hypothesis and gives indications of possible extensions. In the following, all points mentioned above will be summarized and concretized.

Based on the existing body of literature cognitions and emotions are closely related and mutually dependent (e.g., Lazarus, 1991), therefore, the MemoSleep-Hypothesis needs to be extended to include not only cognitions but explicitly emotions to fully capture the activated concept. The core assumptions should be adapted to activate not only sleep/wake memories, but

also positive low-arousing and negative high-arousing emotions. These mental concepts are then embodied and reactivated with a higher probability during sleep which affect sleep architecture and its quality.

Further precision concerning the nature of the reactivated cognitions and emotions should also be added. In context of the process of memory consolidation and the assumptions of the generation of emotions, it seems that the strength of an activated mental concept and its subsequent reactivation are contingent upon the individual relevance. The personal relevance of a specific situation or stimulus as well as previous experience saved in long-term memory networks, may form and weight the activation of the specific mental concept and emotions (Lazarus, 1991, 1999). All these points lead to the general recommendation, that specific situations and stimuli have to be individualized for subjects to especially improve sleep.

How the activation of mental concepts can be specifically manipulated to facilitate restorative sleep should be further considered in future studies. A potential tool to externally modulate the reactivation process may be the TMR technique, which may enhance the reactivation of positive mental concepts during the night through a particular stimulus, such as hypnotic suggestions or music. The presentation of hypnosis and music prior to sleep and hypnotic words during sleep have already been found to work beneficially (Beck et al., 2021; Cordi et al., 2014, 2019). Still, the fundamental problem which cannot be ignored is that it remains unclear whether the second reactivation premise of the MemoSleep-Hypothesis is adequately described or not.

3.4 Emerging pathways interhemispheric asymmetric activity

After considering the MemoSleep-Hypothesis in greater detail, the topic of frontal IAAs during SWS, should not go unmentioned because especially the synthesis of the included studies may point further research into a particular direction. Again, Study 2 identified IAAs on all nights,

with no correlation between IAAs and the FNE. Therefore, further research is required to ascertain the factors that influence or are causally responsible for IAA, as called for in the discussion of Study 2.

Interestingly, when the results of the asymmetric brain activity during SWS in Study 2 and the main object of music in Study 3 are taken together, another phenomenon becomes apparent. As previously laid out, a large body of literature confirms that music activates different brain areas but also emotions (e.g., Koelsch, 2014). It has already been shown that listening to music prior to sleep influences brain activity during sleep. Participants who listened to music as a control condition prior to sleep exhibited a greater left-lateralization of SWA during subsequent SWS than those who conducted a progressive muscle relaxation (Simon et al., 2022). Additionally, emotions are also known to activate state-like interhemispheric asymmetric brain activity during wakefulness, especially dominantly in the alpha band (Davidson, 2004; Wheeler et al., 1993). Moreover, acute stress has also been shown to modulate hemispheric brain activity (Berretz et al., 2022).

Considering these findings together with the existing IAAs in Study 2, there is a valuable opportunity to further investigate the asymmetric activity observed during sleep in different but complementary avenues: firstly, the asymmetric brain activity during music perception during sleep, and secondly, the emotions that music evokes, the associated activated brain areas, and potential asymmetric activities. These directions would represent further investigations of state factors, as called for in Study 2.

3.5 General limitations across the studies

While this dissertation has provided new insights, it has also general limitations, and several questions remain to be answered in future investigations. For example, all investigations regarding the memory consolidation and the MemoSleep-Hypothesis, were exclusively done on healthy

young subjects who reported a healthy wake-sleep cycle. Moreover, the majority of participants were students. It was shown that the symptoms of the FNE increase with age (Ding et al., 2022). Moreover, research on the MemoSleep-Hypothesis in older participants with age-typical changes in sleep architecture (Feinberg, 1974) or clinical patients suffering from mild or clinically relevant sleep disorders are very little in number (e.g., Cordi, et al. 2015) and still pending. This is of great importance since it might have limited the room for improvements (Combertaldi & Rasch, 2020), which is especially essential to generate sleep improving strategies for subjects who are more susceptible for bad sleep quality or already suffering from bad sleep quality.

Moreover, the investigation of personality traits of subjects was not included in the studies of this dissertation which could have an impact on the stress generation (Ebstrup et al., 2011) and have an impact on the perception of the emotion in music (Vuoskoski & Eerola, 2011).

In addition, all studies included in this dissertation are based on EEG-methods only and not on neuroimaging techniques. Therefore, this dissertation can only highlight what still needs to be investigated regarding the underlying neural mechanisms but cannot provide empirical neuroimaging data. This should be done in future studies using e.g., functional magnetic resonance imaging.

3.6 Conclusion

The main aim of this dissertation was to present three studies addressing existing research gaps regarding reactivation processes of memories, pre-sleep appraisals, and emotions evoked by musical chords, as well as their influence on sleep quality

The included Study 1 challenges the unique role of SWS during the memory consolidation process and provides concrete recommendations for future studies to improve the TMR strategy in order to gain deeper insights and find clearer evidence in the future.

Moreover, this dissertation established the patterns of an FNE across non-consecutive nights in familiar and unfamiliar environments. The results lead to the recommendation to implement an adaptation night also in non-consecutive experimental nights. Additionally, they show a beneficial effect of the prior familiarization with the recording equipment in a familiar environment to attenuate the FNE when sleeping in an unfamiliar setting.

Study 3 of this dissertation provided the first evidence that the sleeping brain is capable of processing musical harmony. This finding could serve as a foundation for improving sleep quality by activating and reactivating positive emotions before and during sleep.

Within the context of the MemoSleep-Hypothesis, this dissertation offers possible explanations for the existence of an FNE and advocates for extending the hypothesis to explicitly include emotions. The synthesis of all three studies has also highlighted several aspects that remain underexplored or insufficiently researched, including the underlying neural mechanisms, the characteristics of cognitive concepts, and the accuracy of the reactivation premise within the MemoSleep-Hypothesis.

All these aspects demand further investigation in order to improve practical recommendations and to develop effective interventions to optimize sleep in all its components so that all people can benefit from a good and restorative sleep, laying a solid foundation for a good quality of life.

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