EÖTVÖS LORÁND UNIVERSITY

FACULTY OF EDUCATION AND PSYCHOLOGY

Theses of the Doctoral Dissertation

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Neurocognitive background of procedural memory: neural oscillations and sleep

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Budapest, 2020

Chapter 1: General Introduction

Memory types

Memory is a fundamental ability that enables adaptive behavior. As such, memory is not a unified construct, it serves multiple different functions. Within long-term memory, we differentiate multiple memory systems, such as explicit and implicit (Graf & Schacter, 1985) or declarative and non-declarative (Squire, 1992) based on the presence or lack of consciousness and medial temporal lobe (MTL) dependence. Non-declarative (or implicit) memory consists of procedural memory, conditioning, priming, and habituation (Squire & Zola, 1996). The aim of the dissertation was to better characterize procedural memory by investigating its subprocesses and neural background, and within that, its association to sleep.

Procedural learning is a crucial ability that facilitates efficient processing of and automatic responses to complex environmental stimuli. It underlies the development of perceptual and motor skills and habits through extensive practice (Fiser & Aslin, 2002; Kaufman et al., 2010; Saffran, Aslin, & Newport, 1996; Turk-Browne, Scholl, Johnson, & Chun, 2010; Ullman, 2004). The acquisition of procedural knowledge is often unintentional and the acquired representations are rigid (Kóbor, Janacsek, Takács, & Nemeth, 2017; Reber, 1967; Szegedi-Hallgató et al., 2017).

At least two processes underlying procedural learning can be further distinguished: sequence and statistical learning (Kóbor et al., 2018; Nemeth, Janacsek, & Fiser, 2013). Sequence learning refers to the acquisition of a series of (usually 5–12) stimuli that repeatedly occur in the same order. In contrast, statistical learning refers to the acquisition of shorter-range relationships among stimuli that are primarily based on frequency information (i.e., differentiating between more frequent and less frequent runs (e.g., pairs, triplets, etc.) of stimuli. Majority of the state-of-the-art studies (and also Study 1 and 2 in the dissertation) however, do not differentiate between these subprocesses and quantify procedural learning with a mixed measure of acquiring both frequency and order information. In Study 3 and 4, we set out to better characterize these subprocesses and explore their differences.

To measure procedural learning, we used the Alternating Serial Reaction Time (ASRT) task in our studies (Howard & Howard, 1997; Nemeth, Janacsek, & Fiser, 2013; Nemeth et al., 2010). In this perceptual-motor four-choice reaction time task, there is a predetermined alternating sequence order. Due to this sequence structure, some runs of three consecutive elements (triplets) occur more frequently than others. In the original version, learning is usually quantified as the performance difference for more and less frequent triplets which incorporates however order and frequency information as well. To measure the acquisition of order and frequency information separately, and differentiate sequence and statistical learning, we used a modified, cued version in Study 3 and 4.

Memory phases

Investigating memory, it is also important to differentiate the memory phases, such as learning, consolidation and retrieval. The initial phase is learning (also referred to as acquisition in procedural memory studies), i.e., encoding of sensory information. Following that, consolidation is the mechanism through which the encoded memory representations get stable, less susceptible to future interferences (McGaugh, 2000). After the successful consolidation, we can retrieve (recall or recollect) the memory when needed. In Study 1, 2 and 4, we focused on learning and in Study 1 and 3, on consolidation.

Neural background

To study the neural background of procedural memory (and sleep), we used electroencephalography (EEG, Study 1 and 3). The advantage of EEG is that it is based directly on neurophysiological events, such as oscillations. Oscillatory synchronization is a key mechanism that integrates anatomically distributed processing and facilitates neuronal communication, thereby supporting synaptic plasticity (Buzsáki & Draguhn, 2004). Revealing

the precise neural mechanisms underlying memory processes could be the foundation of targeted enhancement that can be used to boost everyday memory performance or treat memory-related clinical symptoms (see Study 2).

Procedural memory and sleep

Sleep has been suggested as a crucial phenomenon for memory consolidation (Diekelmann, Wilhelm, & Born, 2009; Walker & Stickgold, 2004). However, it is also important to note that sleep quality in general affects various domains of cognitive performance as well, such as executive functions and attention (Jones & Harrison, 2001) and the learning capacity itself (Walker & Stickgold, 2004). In Study 1 and Study 3, we investigated the sleep-dependent memory consolidation, whereas in Study 1 and 4, we explored the long-term effects of sleep on learning capacity.

Importantly, different methods investigating the relationship between sleep and memory can lead to different results, therefore we included a variety of methods in our studies. Sleep can be studied relying on objective (measured by actigraph or EEG) and subjective (self-reported) measurements. In Study 1 and 3, we investigated the relationship between sleep and procedural memory with objective, whereas in Study 4, with subjective measures. For an outline of the complex relationship we were aiming to explore, see Figure 1.
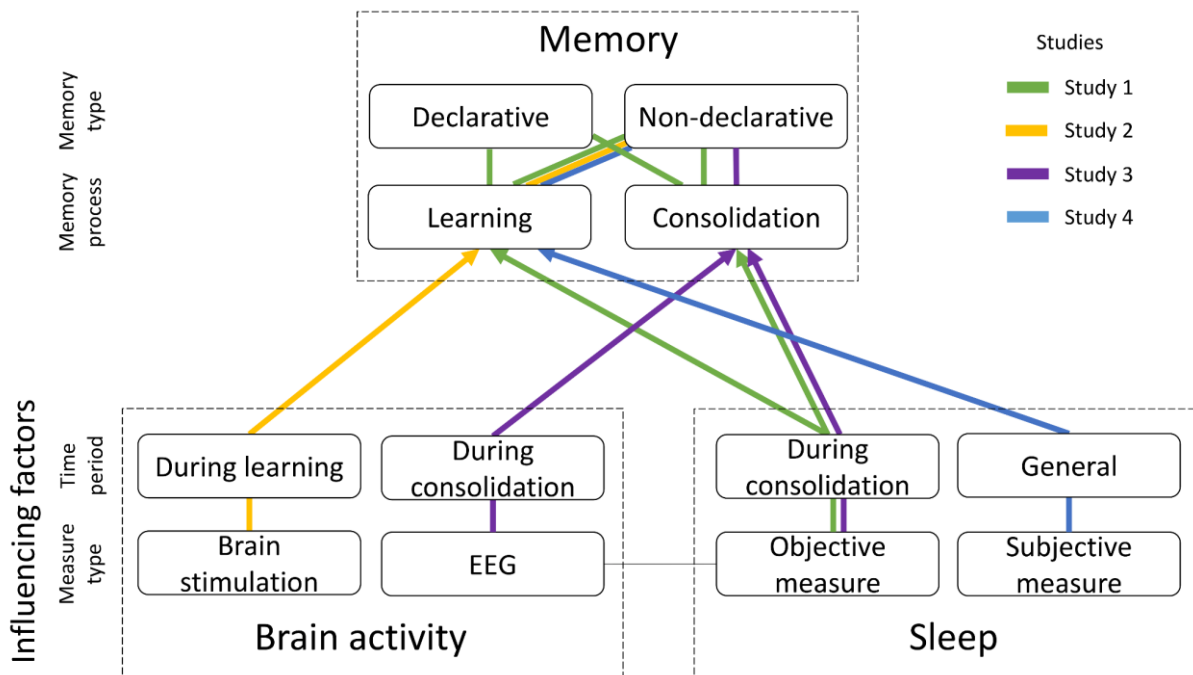

Figure 1. Outline of the studied components in the four studies. In all four studies our aim was to provide a deeper understanding of non-declarative (procedural) memory by investigating its neural background, and its relationship to sleep. In the first study (green lines) we investigated the differential association of declarative and non-declarative memory to sleep parameters in a sleep-disordered population. In the second study (yellow lines) we investigated the neural background of non-declarative memory by brain stimulation. In the third study (purple lines) we investigated the effect of sleep vs. wakefulness after learning on non-declarative memory consolidation. In the fourth study (blue lines) we investigated the association of subjective sleep quality and non-declarative memory performance.

Research questions

In order to better characterize procedural memory on the behavioral and the neural level, we aimed to answer the following questions: *How declarative and non-declarative memory are related to sleep in a sleep-disordered population?* (Study 1)*; Is theta oscillation crucial for procedural memory?* (Study 2); *Is sleep essential for the consolidation of different subprocesses of procedural memory?* (Study 3); and *Are subjective measures of sleep associated with different subprocesses of procedural memory?* (Study 4).

Chapter 2: Delta and theta activity during slow-wave sleep are associated with declarative, but not with non-declarative learning in children with sleep-disordered breathing (Study 1)[1]

Sleep-disordered breathing (SDB) is a prevalent sleep disorder among young children (Marcus, 2001). It is associated with daytime impairments, such as behavioral dysregulation, affective symptoms, and reduced cognitive performance (Beebe & Gozal, 2002; Blunden, Lushington, Lorenzen, Martin, & Kennedy, 2005; Csábi, Benedek, Janacsek, Katona, & Nemeth, 2013; Gottlieb et al., 2004; Gottlieb et al., 2003; Halbower et al., 2006; Kohler et al., 2009; O'Brien et al., 2004). However, the precise mechanism that is leading to cognitive impairment and behavioral problems is unknown. A possible candidate for such disrupted but crucial mechanism is slow-wave sleep (SWS). Slow-wave sleep seems to play an important role in memory consolidation (Ferri et al., 2008; Mander et al., 2013; Marshall, Helgadottir, Molle, & Born, 2006; Rasch & Born, 2013) and appears to be altered in case of insufficient sleep (Cajochen, Foy, & Dijk, 1999; Munch et al., 2004). In light of previous studies that reported attenuated SWS-specific slow frequency oscillations in children with SDB (Jussila et al., 2016; Kheirandish-Gozal et al., 2007), our aim was to investigate whether SWS spectral power is associated with learning capacity and overnight memory consolidation within a group of children with SDB in case of declarative and non-declarative memory tasks.

Methods

Participants - Twenty-seven children participated in the experiment who were aged between 5 and 12 years ($M = 8.52 \pm 2.12$). All participants met the International Classification of Sleep Disorders criteria's (Darien, 2014) for sleep-disordered breathing.

Tasks - Declarative memory performance was measured by a story recall test, the classical "The War of the Ghosts" test (Bartlett, 1932; Bergman & Roediger, 1999). Procedural memory performance was measured by the ASRT task (Howard & Howard, 1997; Nemeth et al., 2010).

Procedure - Polysomnography (PSG) recordings were performed in the Sleep Disorders Laboratory of Heim Pál Children's Hospital, Budapest, Hungary. All children accomplished first the declarative and then the procedural memory task in two separate sessions, prior to sleep and after sleep. PSG recordings were performed overnight between the two sessions for diagnostic purposes and to record brain activity via EEG.

Spectral analyses - Sleep stages and conventional parameters of sleep macrostructure were scored according to standardized criteria (Silber et al., 2007) by two experienced sleep researchers. Spectral analyses were performed by a custom-made software tool (FerciosEEGPlus, © Ferenc Gombos 2008-2016) for whole night SWS between 1 - 25 Hz. Since the absolute power values may be biased due to age-dependent differences in the thickness and conductivity of the skull (Carrier, Land, Buysse, Kupfer, & Monk, 2001), we applied the relative spectral power values. In order to reduce the number of parameters, we summed up frequency bins to generate five frequency band windows: delta (1.25-4 Hz), theta (4.25-8), alpha (8.25-11), sigma (11.25-15), and beta (15.25-25 Hz) frequency bands.

Statistical Analysis - In the case of the declarative learning task, we used three measures: evening score, morning score, and memory consolidation score (overnight change). In the case of the procedural memory task, we calculated learning scores as the difference between the reaction times (RTs) and accuracy (ACC) for more and less frequent triplets. Additionally, we calculated a consolidation index both in terms of ACC and RT, by subtracting the learning index

[1] Simor, P., Zavecz, Z., Csábi, E., Benedek, P., Janacsek, K., Gombos, F., & Németh, D. (2017). Delta and theta activity during slow-wave sleep are associated with declarative but not with non-declarative learning in children with sleep-disordered breathing. Sleep Spindles & Cortical Up States, 1(1), 55-66.

at the end of the task of the evening session from the learning index of the morning session. To study the associations between learning performance, memory consolidation and SWS spectral power, we conducted correlational analyses.

Results

SWS spectral power in the delta range showed a positive ($r = .59$, $p = .001$, Fig. 2A), whereas in theta band a negative ($r = -.65$, $p < .001$, Fig. 2B) correlation with the evening story recall score. The correlations with other frequency bands were non-significant (ps $> .68$). Similar correlations were found between the morning story recall score and band-wise spectral power measures (delta: $r = .472$, $p = .02$, theta: $r = -.52$, $p = .006$, all other ps $> .38$). No significant correlations were found between spectral power measures and overnight declarative memory consolidation (all ps $> .59$). Furthermore, SWS spectral power measures did not show associations with the procedural learning and consolidation scores (all ps $> .11$).
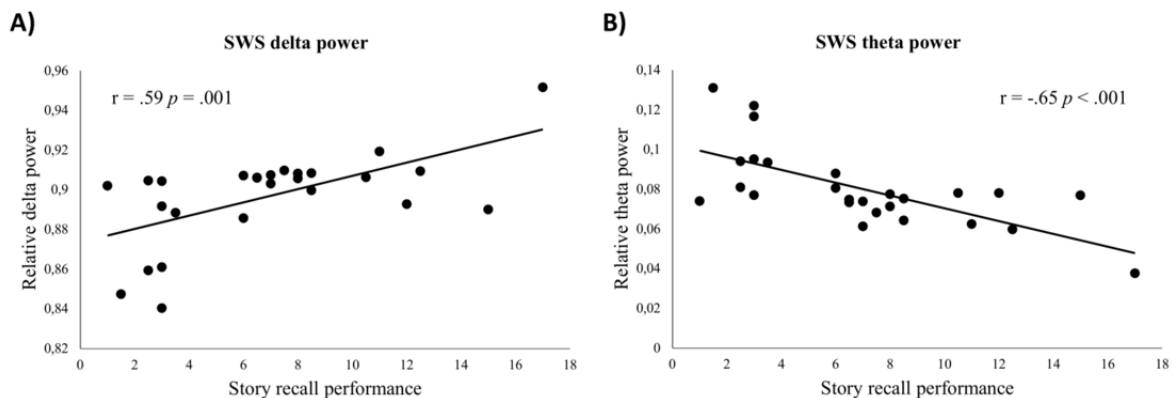

Figure 2. Correlation between slow-wave sleep delta (A) and theta (B) power spectrum and evening story recall performance.

Discussion

Our results indicate that declarative and non-declarative (procedural) memory is differently associated with sleep: we found oscillatory mechanisms during sleep that showed associations with declarative memory performance, but we did not reveal associations between sleep parameters with procedural memory performance. Furthermore, as learning capacity was affected in case of declarative memory, our results might indicate that memory impairments associated with sleep disorders are the result of chronic insufficient sleep quality affecting learning capacity rather than overnight insufficient sleep quality affecting consolidation mechanisms.

Thesis statement 1: Declarative memory is associated with parameters of sleep in a sleep-disordered population, whereas non-declarative is not.
Thesis statement 2: Slow oscillations (delta and theta) of sleep are relevant for declarative memory.

Chapter 3: Frontal-midline theta frequency and probabilistic learning: A transcranial Alternating Current Stimulation study (Study 2)[2]

Previous studies showed competition between neural networks related to executive function/working memory vs. procedural learning (Albouy et al., 2015; Albouy et al., 2008; Ashby & O'Brien, 2005; Daw, Niv, & Dayan, 2005; Poldrack et al., 2001). Theta synchronization has been associated with the former (Gevins, Smith, McEvoy, & Yu, 1997; Hsieh & Ranganath, 2014; Jensen & Tesche, 2002; Meyer, Grigutsch, Schmuck, Gaston, & Friederici, 2015; Onton, Delorme, & Makeig, 2005; Scheeringa et al., 2009; Summerfield & Mangels, 2005; Tóth et al., 2014) while desynchronization with the latter (Tóth et al., 2017) in correlational studies. In this study, our aim was to test the causal relationship between theta synchronization and procedural learning with non-invasive transcranial alternating current stimulation (tACS).

Methods

Participants - Twenty-six young adults (19 females) participated in the study ($M_{Age} = 21.38 \pm 1.52$ years). Participants had no previous history of neurological, psychiatric or cardiovascular disorders, brain injuries and they had no metal implants in the head or neck area and reported not taking any substances that affect the nervous system.

Task - Procedural memory performance was measured by the ASRT task (Howard & Howard, 1997; Nemeth et al., 2010).

Procedure - This study utilized a double-blind, placebo-controlled crossover design. The participants were assessed in two sessions (one week apart) during which they received 1 mA active theta frequency tACS stimulation, or sham stimulation in a counterbalanced order.

Transcranial Alternating Current Stimulation (tACS) - A commercial, battery-driven constant current stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany) delivered a sinusoidal alternating current stimulation to the participant's scalp via two 5 cm × 5 cm electrodes placed over frontal and parietal midline positions. TACS was applied at a peak-to-peak current intensity of 1 mA oscillating at 6 Hz. Active tACS stimulation was administered throughout the task (approximately 20 minutes), while sham stimulation lasted only 30 seconds. In both cases, there were 30 seconds ramp up and ramp down periods.

Statistical analysis - For the ASRT, we calculated learning scores as described at Study 1. As the ASRT task is long, we calculated several scores throughout the task, for so-called epochs. To evaluate the learning trajectory, we conducted frequentist and Bayesian repeated-measures analyses of variance (ANOVAs) with STIMULATION (Sham vs. Active) and EPOCH (1-4) as within-subject factors separately for ACC and RT learning scores. In the Bayesian ANOVA, to summarize the importance of the within-subject factors across all models, we calculated the inclusion Bayes Factors, which provide evidence for inclusion of main effects and interactions.

Results

We did not find any significant differences between the active stimulation and sham conditions either in overall learning or in the time course of learning neither for the RT (main effect of STIMULATION: $F(1, 24) = 0.093$, $p = .763$, $\eta^2_P = .004$; STIMULATION * EPOCH interaction: $F(3, 72) = 0.637$, $p = .593$, $\eta^2_P = .026$) nor the ACC learning scores (main effect of

[2] Zavecz, Z., Horváth, K., Solymosi, P., Janacsek, K., & Nemeth, D. (2020). Frontal-midline theta frequency and probabilistic learning: A transcranial Alternating Current Stimulation study. *Behavioural Brain Research*, 112733.

STIMULATION: $F(1, 24) = 0.054$, $p = .819$, $\eta^2_P = .002$; STIMULATION * EPOCH interaction: $F(3, 72) = 1.065$, $p = .359$, $\eta^2_P = .042$, Fig. 3). Furthermore, the Bayesian analyses of effects provided evidence that the stimulation did not influence the RT learning scores ($BF_{Inclusion} = 0.073$) or the ACC learning scores ($BF_{Inclusion} = 0.035$).
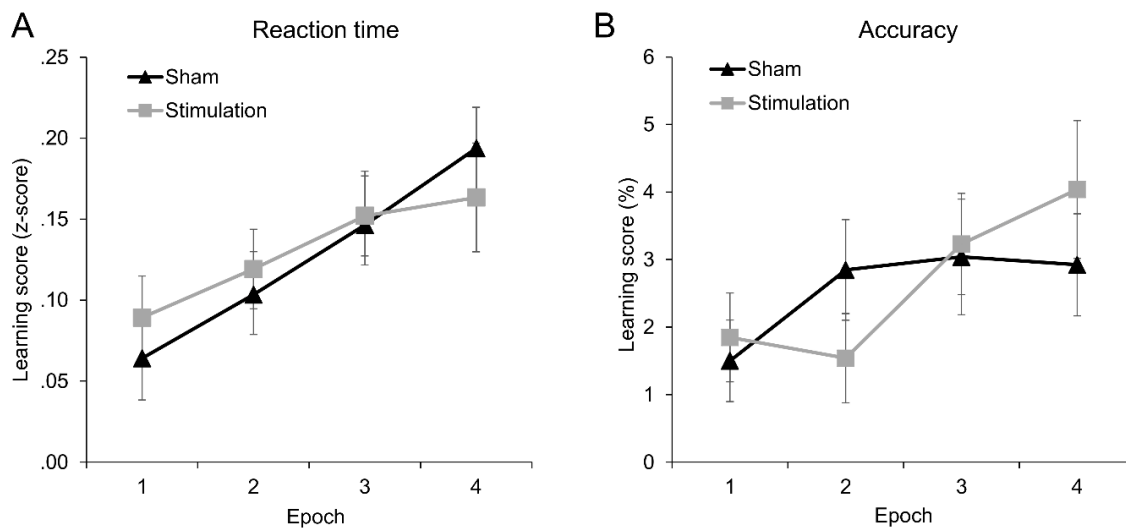

Figure 3. Procedural learning in terms of reaction times (A) and accuracy (B) in the active stimulation vs. sham conditions across the 4 epochs of the ASRT task. There was no significant difference between the active stimulation in theta frequency (grey squares) and sham (black triangles) conditions either in overall learning or in the time course of learning. Error bars indicate the Standard Error of Mean (SEM).

Discussion

We could not find stimulation effects, the overall learning performance and the time course of learning did not differ between the stimulation and the control conditions. This does not mean, however, that theta synchronization is irrelevant for procedural memory measured by the ASRT task. In the lack of an EEG recording simultaneously with or following the stimulation, we could not confirm that the brain stimulation induced the expected changes in brain activity. We chose the stimulation parameters based on studies that could influence brain activity/cognitive performance with a similar setting (Chander et al., 2016; Polanía, Moisa, Opitz, Grueschow, & Ruff, 2015; Violante et al., 2017; Vosskuhl, Huster, & Herrmann, 2015). However, it is likely that the chosen parameters for the tACS stimulation, such as the fronto-parietal midline montage, the relatively weak (1 mA) current intensity, and/or the chosen theta frequency were not appropriate to influence learning in our study. Regarding the current intensity, there have been several recent animal studies suggesting that the usual intensities applied in transcranial electric stimulation studies (including our study) are not sufficient to elicit significant changes in brain activity (Khatoun, Asamoah, & Mc Laughlin, 2019; Krause, Vieira, Csorba, Pilly, & Pack, 2019; Vöröslakos et al., 2018). To be able to confirm if certain brain dynamics are crucial for procedural memory, the changes in brain activity induced by the brain stimulation must be measured and proved. Unfortunately, such devices that can simultaneously measure the electrical activity of the brain and apply electrical stimulation are hardly accessible and were not available for our research group for this study. It would worth replicating this study (possibly with higher current intensity) with methods that enable us to confirm the induced changes in brain activity due to the stimulation.

Thesis statement 3: Non-invasive brain stimulation is a powerful tool to test the causal relationship between brain dynamics and memory performance.

Chapter 4: Deconstructing Procedural Memory: Different Learning Trajectories and Consolidation of Sequence and Statistical Learning (Study 3)[3]

Sleep has been suggested as a crucial phenomenon for memory consolidation (Diekelmann et al., 2009; Walker & Stickgold, 2004). However, based on more recent evidence, sleep and rest without interferences can have similar beneficial effects on memory consolidation (Brokaw et al., 2016; Craig & Dewar, 2018; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). Our primary goal in this study was to test whether sleep has a beneficial effect on procedural memory consolidation compared to wakefulness. Therefore, we compared the consolidation performance of groups of participants who, after learning, either slept, rested quietly or watched a movie. As several studies indicate that not sleep per se, but specific oscillations during sleep facilitate post-sleep improvements in behavioral performance (Rasch and Born, 2013), we also recorded EEG during the consolidation period. We explored associations between the spectral composition of brain activity and the consolidation performance within each off-line activity group. Furthermore, we wanted to test whether different subprocesses of procedural memory, sequence and statistical learning differ in their benefit from sleep.

Methods

Participants - Seventy-eight young adults (58 females, $M_{age} = 21.71 \pm 1.97$) were included in the final sample of the study. Participants had no previous history of neurological, psychiatric or cardiovascular disorders, brain injuries and reported good to moderate general sleep quality and no regular consumption of pills other than contraceptives.

Task - Procedural memory performance was measured by the cued version of the ASRT task (Nemeth, Janacsek, & Fiser, 2013), which enables us to differentiate sequence and statistical learning.

Procedure - At the beginning of the session, EEG caps were fitted by two assistants. This was followed by the cued ASRT task composed of the training phase, testing phase, off-line period, and retesting phase. Participants were assigned to one of three groups for the off-line period: Active Wake, Quiet Rest, Nap. The Active Wake group was instructed to watch an approximately one-hour long documentary. The Quiet Rest group was asked to sit quietly with eyes closed and opened in turns of 5 minutes. Participants in the Nap group had the opportunity to spend a daytime nap in the laboratory.

EEG recording and analysis - EEG activity was measured using a 64-channel recording system (BrainAmp amplifier and BrainVision Recorder software, BrainProducts GmbH, Gilching, Germany). In order to remove muscle and eye movement related artifact from the awake EEG data, EEG preprocessing was performed using the Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) toolbox (Nolan, Whelan, & Reilly, 2010). Spectral power analyses were performed by a custom-made software tool for EEG analysis (FerciosEEGPlus, © Ferenc Gombos 2008-2017). We summed up frequency bins to generate five frequency bands for the wake groups: delta (1.5-4 Hz), theta (4.25-8), alpha (8.25-13), sigma (13.25-16), and beta (16.25-25 Hz), and the sleep group: delta (0.75-4 Hz), theta (4.25-8), alpha (8.25-13), sigma (13.25-16), and beta (16.25-31 Hz).

Statistical analyses - For the ASRT, we calculated learning scores for sequence and statistical learning. Sequence learning was quantified as the difference between the RTs for

[3] Simor, P., Zavecz, Z., Horváth, K., Éltető, N., Török, C., Pesthy, O., Gombos, F., Janacsek, K., & Nemeth, D. (2019). Deconstructing procedural memory: Different learning trajectories and consolidation of sequence and statistical learning. *Frontiers in Psychology*, *9*, 2708.

sequence and random elements that were the last elements of equally frequent triplets. Statistical learning was quantified as the difference between the RTs for random elements that were the last element of more or less frequent triplets. Again, as the ASRT task is long, we calculated several scores throughout the task, for so-called epochs. To evaluate the learning trajectory and consolidation, we conducted mixed-design analyses of variance (ANOVAs) with EPOCH and LEARNING TYPE (Statistical Learning, Sequence Learning) as within-subject factors, and GROUP (Active Wake, Quiet Rest and Nap) as a between-subject factor. Finally, we aimed to examine the associations between EEG spectral power measured during the off-line period and sequence and statistical memory consolidation in each group separately with correlation analyses. For the memory consolidation scores, we subtracted the learning scores of the testing session from the first epoch of the retesting session both for sequence and statistical learning.

Results

Sequence and Statistical Learning trajectories - Sequence and statistical learning showed different learning trajectories (EPOCH x LEARNING TYPE interaction: $F(4,300) = 5.52$, $p = .002$, $\eta_p^2 = .07$). As illustrated in Figure 4, participants exhibited a steady increase in Sequence Learning, whereas Statistical learning occurred at the beginning of the task and remained unchanged throughout practice. Learning scores were unchanged during the off-line period regardless of the learning type ($p = .86$).
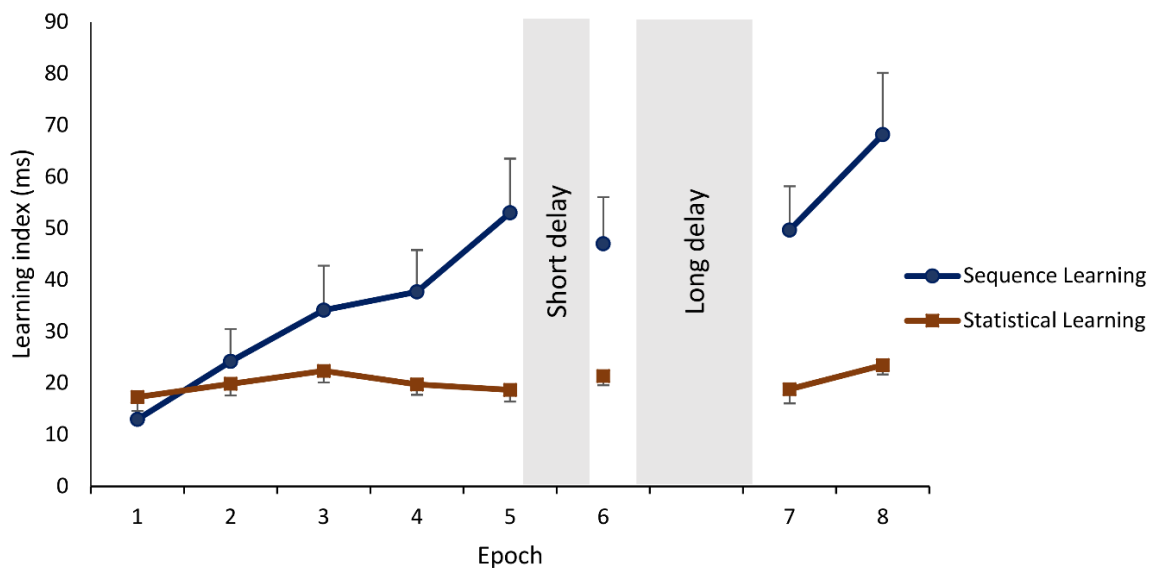

Figure 4. Learning and off-line changes in Sequence and Statistical Learning. Means and standard errors of Sequence Learning and Statistical Learning during each epoch. Sequence Learning (blue) exhibited a steep increase during training (epochs 1-5) and additional practice after the off-line periods (epochs 7-8), whereas Statistical Learning (red) remained unchanged throughout the sessions.

Are Sequence and Statistical memory consolidation different across the groups? - The Active Wake, Quiet Rest and Nap groups did not show different consolidation of Sequence or Statistical Learning (non-significant main effect of GROUP: $F(2,75) = 0.65$, $p = .53$, $\eta_p^2 = .02$), GROUP x EPOCH interaction: $F(4,150) = 0.52$, $p = .67$, $\eta_p^2 = .01$, GROUP x LEARNING TYPE interaction: $F(2,75) = 0.65$, $p = .53$, $\eta_p^2 = .02$, and GROUP x EPOCH x LEARNING TYPE interaction: $F(4,150) = 0.73$, $p = .55$, $\eta_p^2 = .02$, Fig. 5)
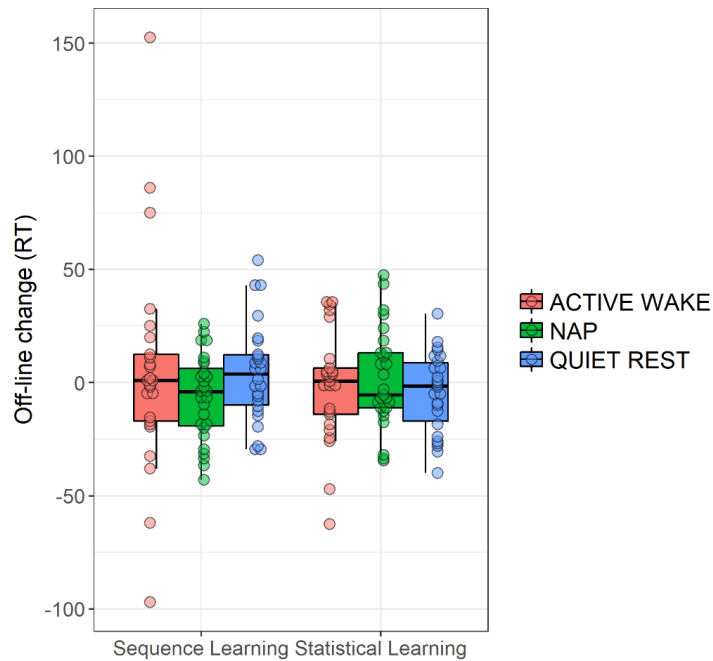
Figure 5. Consolidation of Sequence and Statistical Learning within the three groups. Dots show individual data points, the vertical line within the boxes show the medians, boxes represent the first and third quartiles, whiskers indicate the interquartile range of 1.5. The Active Wake, Quiet Rest and Nap groups did not show different consolidation of Sequence or Statistical Learning

Associations between EEG spectral powers and memory consolidation - Within the Nap group, the consolidation of Sequence Learning was positively associated with frontal theta power ($r = .44$, $p = .028$, Fig. 6), whereas the consolidation of Statistical Learning did not show associations with any spectral power measures. In the awake groups, neither the consolidation of Sequence nor that of Statistical Learning was associated with any spectral power measures.
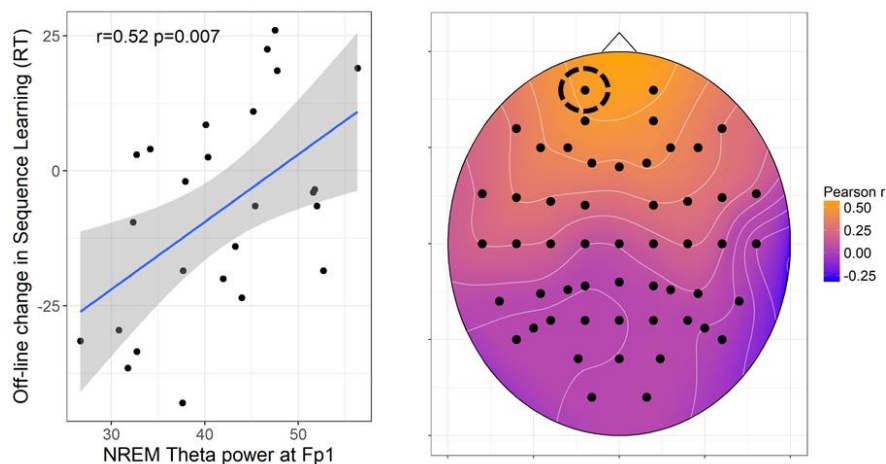

Figure 1. Associations between theta power during sleep and consolidation of Sequence Learning. The heat plot on the right indicates the magnitude of correlation coefficients for different electrodes, while the scatterplot on the left shows the association in a prominent (left frontal) electrode site.

Discussion

Consolidation of sequence and statistical knowledge did not seem to differ in case of the off-line period spent sleeping or awake. This result is in line with previous studies that did not find beneficial effects of sleep on procedural memory tasks involving regularities (Peigneux et al., 2003, 2006; Song et al., 2007; Nemeth et al., 2010; Hallgató et al., 2013). However, EEG spectral power assessed during the off-line period showed associations with memory

consolidation during sleep, but not during awake states. This association was selective for sequence learning, namely frontal theta band power during sleep showed a positive association with the consolidation of sequence knowledge. This finding suggests that not sleep per se, but sleep-specific slow oscillations (2-8 Hz) are associated with memory consolidation.

Albeit the primary focus of the study was to explore the effects of sleep and the neural background of procedural memory, this was also one of the first studies characterizing the subprocesses of procedural memory, namely sequence and statistical learning separately. Our findings indicate that sequence and statistical learning have different learning trajectories. Sequence learning exhibited a steady increase with practice, even after returning to the task following the off-line period. In contrast, statistical learning was acquired rapidly and remained stable throughout practice. Our fine-grained analyses showed that statistical learning occurs already after very little exposure to regularities, although additional training is required to strengthen the acquired statistical knowledge. Regarding consolidation, both forms of learning were preserved, as no significant off-line changes emerged in either sequence or statistical learning. This latter could indicate, that the consolidation of these two subprocesses might rely on more similar mechanisms than their acquisition. However, the dissociation of the relevant oscillations during the off-line period indicates otherwise. In a follow-up study, we are aiming to reveal in greater detail whether the studied subprocesses rely on distinct neural oscillations.

Thesis statement 4: Sequence and statistical learning show different learning trajectories.
Thesis statement 5: Sleep does not seem to benefit the consolidation of procedural memory more than wakefulness.
Thesis statement 6: Sleep-specific slow oscillations however are associated with the consolidation of sequence knowledge.

Chapter 5: The relationship between subjective sleep quality and cognitive performance in healthy young adults: Evidence from three empirical studies (Study 4)[4]

Previous studies have shown that subjective and objective sleep parameters, such as sleep duration or sleep efficiency differ (Armitage, Trivedi, Hoffmann, & Rush, 1997; Guedes et al., 2016; Landry, Best, & Liu-Ambrose, 2015). Extreme deviations can occur between subjective and objective measures in sleep disorders, such as insomnia or sleep-state misperception. According to Zhang and Zhao (2007) and Stepanski et al. (1989), subjective sleep quality of insomniac patients determines both seeking medication and type of effective treatment. Furthermore, one's belief about their own sleep quality induce placebo and nocebo effects both in insomniac patients and healthy individuals (Draganich & Erdal, 2014; Gavriloff et al., 2018). Thus, subjective sleep quality has therapeutic importance, as well as further explanatory value for cognitive performance compared to objective measures. However, scientific evidence on the relationship between subjective sleep quality and cognition is still inconclusive, and memory, in particular, procedural memory has been scarcely investigated in relation to subjective sleep quality. In this study, we aimed to fill this gap by providing an extensive investigation on the relationship between subjective sleep quality and cognitive performance including procedural memory in healthy young adults.

Methods

Participants - The data was obtained from three different projects. Forty-seven participants took part in Project 1 (Török, Janacsek, & Nemeth, 2016), 103 participants took part in Project 2 (Simor et al., 2019), and 85 participants took part in Project 3 (Á. Takács et al., 2016). Participants had no previous history of neurological, psychiatric or cardiovascular disorders, brain injuries and reported no regular consumption of pills other than contraceptives.

Questionnaires and tasks - *Subjective sleep quality questionnaires –* To capture the general sleep quality of the last month, we administered the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989; J. Takács et al., 2016) and the Athens Insomnia Scale (AIS) (Novak, Mucsi, Shapiro, Rethelyi, & Kopp, 2004; Soldatos, Dikeos, & Paparrigopoulos, 2000). Additionally, in Study 2, we administered a Sleep diary (Gilson et al., 2015) to assess the sleep quality of the last one-two weeks, and the Groningen Sleep Quality Scale (GSQS) (Meijman, de Vries-Griever, De Vries, & Kampman, 1988; Simor, Köteles, Bódizs, & Bárdos, 2009) to capture the sleep quality of the night prior testing. *Cognitive performance tasks –* Working memory was measured by the Counting Span task (Case, Kurland, & Goldberg, 1982; Conway et al., 2005; Engle, Tuholski, Laughlin, & Conway, 1999; Virag et al., 2015). Executive functions were assessed by the Wisconsin Card Sorting Test (WCST) (Berg, 1948; Nemeth, Janacsek, Polner, & Kovacs, 2013; Piper et al., 2015). Procedural learning was measured by the cued version of the ASRT task (Nemeth, Janacsek, & Fiser, 2013), which enables us to study sequence and statistical learning. In this study, we included several learning indices besides sequence and statistical learning to characterize procedural learning. We measured the average RTs and ACC, which reflect the average general performance of the participants across the task, and the changes in RT and ACC from the beginning to the end of the task, which indicate general skill learning that occurs due to more efficient visuomotor and motor-motor coordination as the task progresses (Hallgato, Győri-Dani, Pekár, Janacsek, & Nemeth, 2013).

Procedure - Subjective sleep quality and procedural learning, working memory, and executive functions were investigated in three separate projects. We assessed subjective sleep quality questionnaires online, and cognitive performance tasks in a single session in the lab.

Statistical analysis - Subjective sleep quality scales (PSQI and AIS) were combined into a single metric, using principal component analysis hereinafter referred to as sleep disturbance. Then separate linear mixed-effect models were created for each cognitive outcome measure (i.e., performance metric), where the sleep disturbance metric was used as a predictor, and 'Project' (1, 2 or 3) was added as a random intercept. To control for possible confounding effects, we included age, gender and morningness score as covariates in our analyses. Furthermore, we used Bayes Factors (BF_{01}) to provide evidence for no associations. We report BF_{01} values, where values greater than 1 indicate evidence for the lack of associations between two measures, whereas values below 1 indicate evidence for existing associations (Wagenmakers, Wetzels, Borsboom, & van der Maas, 2011). To test the association between the additional subjective sleep quality measures and cognitive performance in Project 2, we used robust linear regression, this time without random effects. We included the same potential confounders (age, gender, morningness score), and calculated Bayes factors as well.

Results

Sleep disturbance did not show an association with any of the cognitive performance metrics (Table 1). Bayes Factors ranged from 5.01 to 14.35, indicating substantial evidence for no association between subjective sleep quality and the measured cognitive processes.

Table 1. The association of sleep disturbance with cognitive performance metrics

Outcome	β	95% CI	df	p	BF_{01}
ACC learning indices					
ACC Higher-order sequence learning	-.041	[-0.18, 0.11]	205	.58	12.28
ACC Statistical learning	-.038	[-0.17, 0.09]	205	.56	12.42
ACC Triplet learning	-.067	[-0.19, 0.06]	205	.30	8.50
RT learning indices					
RT Higher-order sequence learning	.014	[-0.15, 0.16]	205	.85	14.29
RT Statistical learning	-.062	[-0.21, 0.07]	205	.39	10.48
RT Triplet learning	-.028	[-0.17, 0.12]	205	.71	13.60
General skill indices					
ACC general skill learning	.037	[-0.06, 0.13]	205	.45	11.06
Average ACC	.065	[-0.04, 0.17]	205	.23	6.79
RT average	-.019	[-0.17, 0.12]	205	.80	14.05
RT general skill learning	-.075	[-0.23, 0.07]	205	.33	8.83
WM and EF indices					
Counting Span	-.013	[-0.17, 0.14]	205	.87	14.35

WCST – perseverative error	.107	[-0.03, 0.24]	199	.13	5.01

Note: The table shows standardized regression coefficients for sleep disturbance, where the 'Project' random intercept was included in separate linear mixed-effect models for each cognitive performance metrics. Age, gender, and morningness score were added as covariates. ACC = accuracy. RT = reaction time. WM = working memory. EF = executive function. WCST = Wisconsin Card Sorting Test.

In Project 2, Sleep diary scores did not show association with any of the cognitive performance metrics (all ps > .05). Bayes Factors ranged from 2.51 to 12.58, indicating evidence for no association between subjective sleep quality and measures of cognitive performance. Similarly, GSQS scores did not show association with any of the cognitive performance metrics (all ps > .11). Bayes Factors ranged from 3.46 to 16.46, indicating substantial evidence for no association between subjective sleep quality and the measured cognitive processes.

Discussion

We did not find associations between subjective sleep quality and cognitive performance measures using the robust frequentist statistical analyses. Moreover, the Bayes factors provided evidence for no association between subjective sleep quality and measures of working memory, executive functions, and procedural learning. This pattern held when subjective sleep quality was reported retrospectively for a longer period (i.e., a month; with PSQI and AIS), as well as when monitored daily (for one to two weeks; with the sleep diary) or reported for the night prior to testing (with GSQS). These results suggest that neither moderately persistent nor transient subjective sleep quality is associated with cognitive performance in healthy young adults. Importantly, however, our findings do not imply that sleep per se has no relationship with these cognitive functions. There is a great dissociation between subjective and objective sleep quality (Armitage et al., 1997; Guedes et al., 2016; Landry et al., 2015), therefore generalization from one aspect of sleep to the other should be avoided. Instead, this is another aspect of sleep that does not seem to affect procedural memory.

Thesis statement 7: Subjective sleep quality is not associated with procedural memory, as in sequence, statistical or general skill learning and motor abilities.

Chapter 6: General discussion

Conclusions of the studies on the behavioral level

On the behavioral level, we provided evidence for the differentiation of the investigated two subprocesses of procedural memory: sequence and statistical learning have different learning trajectories (Study 3 and 4). Furthermore, on the behavioral level, we did not find a beneficial effect of sleep on learning capacity or consolidation of procedural memory, nor for sequence or statistical learning (Study 3 and 4). Importantly, we did not find associations between sleep and procedural memory with neither objective nor subjective sleep parameters. This is in line with previous studies that also did not show associations between sleep and procedural memory (Csabi et al., 2015; Nemeth, Csábi, Janacsek, Varszegi, & Mari, 2012; Wilhelm, Diekelmann, & Born, 2008).

Conclusions of the studies on the neural level

In contrast to the behavioral level, it is not clear if sleep, or more specifically sleep-related oscillations on the neural level could affect procedural memory. In Study 1, the spectral composition of SWS did not correlate with procedural memory. In Study 3, however, where we dissected sequence and statistical learning, the findings were mixed. Statistical memory performance did not show associations with neural activity during sleep, whereas, we found associations between the spectral composition of sleep and the consolidation of sequence knowledge. Interestingly, this association emerged between slow oscillations of sleep and memory performance, similar to the association between declarative memory and sleep in Study 1.

This similarity in the neural correlates of declarative memory and explicit sequence learning could occur for two reasons: 1) Declarative memory and explicit sequence learning share some characteristics, such as consciousness or MTL dependence and/or 2) slow oscillations during sleep support different types of memory as well. There is some evidence for both of these possibilities. However, the precise associations between slow oscillations of sleep and declarative vs. sequence learning differed: the associated frequency bins, direction of the association and the associated memory phase all varied. Thus, it is not clear, if these similar associations rely on similar mechanisms.

While our findings regarding the neural correlates of procedural memory independent of sleep are inconclusive, there is still some enlightenment to be found in our studies. We introduced transcranial electric stimulation as a potential way to test causal relationship between brain activity and behavior. Furthermore, it also became clear that more sophisticated measures of EEG are necessary to reveal the neural correlates of procedural memory consolidation in awake states. A more sophisticated analysis could be functional connectivity analysis, which we are currently using successfully in several ongoing EEG studies that are not presented here.

Summary

The aim of the dissertation was to provide a deeper understanding of procedural memory processes by investigating their behavioral characteristics, neural background, and their relationship to sleep. We provided evidence that procedural memory is not unitary, and at least two subprocesses, sequence and statistical learning should be differentiated. These subprocesses have different learning trajectories and neural correlates. Moreover, procedural memory seems to be independent of sleep, however, sleep-specific oscillations might have a role in the consolidation of sequential information. We used a wide variety of methods to explore associations between memory, sleep and their underlying brain activity: brain stimulation, electrophysiology, objective and subjective sleep measures. A deeper understanding of memory and its neural background could help improving everyday memory performance, as well as treating memory-related clinical disorders (amnesia, post-traumatic stress disorder or dementia).

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Note: Each co-author has granted permission for the given publication to be included in the current dissertation.

List of publications directly not used in the dissertation

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