Title

Same Wave, Different Memories: Neural mechanisms of improvement in sleep-dependent episodic and working memory

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Publication Date

2023

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA,
IRVINE

Same Wave, Different Memories: Neural mechanisms of improvement in sleep-dependent episodic and working memory

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Cognitive Sciences

by

Jing Zhang

Dissertation Committee:
Dr. Sara C. Mednick, Chair
Dr. Aaron Bornstein
Dr. Emily Grossman

2023

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ACKNOWLEDGEMENTS

I would like to express my deepest gratitude towards my doctoral advisor, Sara Mednick. Without her spending countless hours guiding my professional as well as personal journey, my success would not have been possible. Her friendly and approachable nature cultivated an environment in which I felt comfortable sharing ideas and discussing difficult issues. Her unwavering support and encouragement have been an immense source of motivation, especially during times of uncertainty and self-doubt, which is not a rare occasion for me.

I would also like to thank Dr. Arielle Tambini for her guidance and mentorship throughout the development and analysis of my fMRI project. Her expertise and support were instrumental in the success of my project, and I am grateful for the time and effort she invested in mentoring me.

I would like to thank my committee members, Dr. Aaron Bornstein and Dr. Emily Grossman for their guidance and thoughtful feedback on my advancement and this dissertation. Their insight on fMRI tasks and analyses helped move my project forward.

This dissertation would not have been possible without the help of research assistants in the Mednick Lab at UCI. Thank you to Andres Pena, Nicole Delano, Karla Vinces, Anisha Upadhya, Thomas Shenz, Ashley Chen, Kevin Sam, Shreya Cho, Ash Arumugam, and Spencer Mair.

Lastly, I extend my heartfelt gratitude to the alumni and current members of the Mednick Lab for their unwavering support and thought-provoking discussions. Thanks to Ben Yetton, Pinchun Chen, Lauren Whitehurst, Lizzie McDevitt, Tenzin Tselha, Mohsen Naji, Hamid Niknazar, Kate Simon, Paola Malerba, Negin Sattari, Frida Corona, Alyssa Shuster, Abhishek Dave, and Allison Morehouse.

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ABSTRACT OF THE DISSERTATION

Same Wave, Different Memories: Neural mechanisms of improvement in sleep-dependent episodic and working memory

by

Jing Zhang

Doctor of Philosophy in Cognitive Sciences

University of California, Irvine, 2023

Dr. Sara C. Mednick, Chair

Sleep plays a critical role in the improvement of both episodic memory and working memory, with non-rapid eye movement neural oscillations, including slow oscillations (0.5-1Hz, SO) and sleep spindles (12-15Hz), causally implicated in these processes. However, studies elucidating the precise mechanisms underlying these processes are needed. Specifically, it remains unclear how neural oscillations during sleep coordinate with functional changes in the brain to facilitate the maintenance of information-specific episodic memories, or the increases in information-general working memory.

The present dissertation aims to address these gaps in knowledge by investigating the neural mechanism underlying sleep-dependent episodic memory consolidation and working memory improvement. In study 1, I investigate how sleep protects episodic memory against waking interference. I ask whether sleep protects memory against future interference or if it rescues memory after interference has already occurred. In study 2, I probe the role of sleep spindles underlying sleep-dependent episodic memory consolidation. Specifically, I present a placebo-controlled, double-blind study that

pharmacologically enhances sleep spindles to establish a causal role of sleep spindles and their temporal coupling with SOs in episodic memory consolidation. In study 3, I employ simultaneous EEG-fMRI to examine the neural activities associated with working memory as well as subsequent sleep, with a specific focus on SO as it's a shared resource for both episodic and working memory.

Together, these studies lead to a theoretical model of how the same sleep event may facilitate improvements across multiple cognitive domains. Specifically, SOs and it's temporal coupling with sleep spindles coordinate with functional changes in specific memory networks to facilitate performance.

CHAPTER 1 Overview

The Basics of Sleep

Sleep is a natural and reversible physiological state characterized by reduced muscle activity, inhibited sensory input, and altered consciousness. Studies have shown that sleep supports restoration of energy in cellular, system, and behavioral level, as well as a range of cognitive functions, from long-term memory to executive functions. It consists of two parts, non-rapid eye movement (NREM) sleep and rapid-eye movement (REM) sleep. NREM sleep consists of stage 1, stage 2, and stage 3 (or slow wave sleep (SWS), figure 1A). The early part of the nocturnal sleep is dominated by SWS sleep, and REM sleep becomes more prevalent towards the end of the night. Stage 1 sleep is a transitional state from wake to sleep, making up 3% of adult nocturnal sleep. About 60% of adult sleep is stage 2 sleep, which is marked by distinct electrophysiological events called sleep spindles and K-complexes (figure 1B). SWS makes about 20% of human sleep, and it is marked by slow high-amplitude oscillations (<4Hz). REM sleep also makes about 20% of human sleep, and it is marked by sudden bursts of eye movements and wake-like fast and low-amplitude oscillations (theta waves 4-7Hz).

Here, we focus on specific NREM events including sleep spindles and slow oscillations (SO) as they have been implicated in the memory consolidation process (Rasch & Born, 2013). Sleep spindles, which are hallmarks of stage 2 sleep, are sudden bursts of neural activities in the frequency of 11-16 Hz. Sleep spindles are thought to be generated from the thalamus, a key relay center in the brain that regulates the flow of sensory information to the cortex. Specifically, sleep spindles reflect the synchronous firing of thalamocortical neurons, which promotes the synchronization of cortical activity and facilitate memory consolidation (Fernandez & Lüthi, 2020). SOs are high-amplitude, low-frequency oscillations (<1Hz) mostly occur during SWS. They reflect fluctuations of the membrane potential and orchestrate transitions from neuronal silence (hyperpolarized downstates) to neuronal excitation (depolarized upstates) (Maquet et al., 1997).

One prominent theoretical framework to explain the regulation of sleep and wakefulness is the two-process model of sleep regulation. This model proposes the regulation of the timing and intensity of sleep and wakefulness is governed by the interaction between the circadian process and the homeostatic process. The circadian process (process S) is responsible for regulating the timing of sleep and wakefulness based on the body's internal biological clock. The homeostatic process (process C) regulates the need for sleep based on the duration and intensity of prior wakefulness (Borbély et al., 2016).

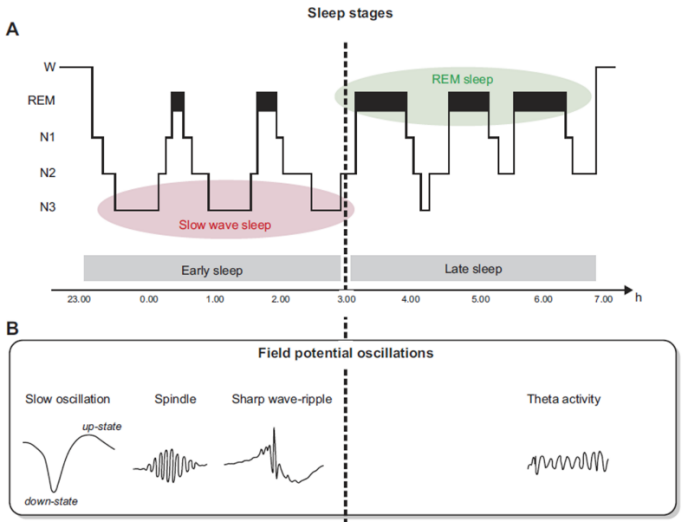

Figure 1-1 A: Typical human sleep profile, B: Sleep related signals (Rasch & Born, 2013)

The Basics of Memory

Working memory (WM), the ability to maintain and manipulate a small quantity of information, is essential to higher order cognition and to performance of daily activities. There are several different models of WM, but one of the most influential is the Baddeley and Hitch model, which proposes that WM consists of a central executive, which controls and coordinates cognitive processes, and two sub-systems: the phonological loop, which is involved in the temporary storage of verbal information, and the visuospatial sketchpad, which is involved in the temporary storage of visual and spatial information (Baddeley, 1992).

Forming a long-term memory involves three steps: encoding, consolidation and retrieval (Melton, 1963). Encoding refers to the initial learning of information through sensory input, consolidation is the process of storing information for later use, and retrieval is the process of calling information from storage to conscious awareness (Melton, 1963). The term *consolidation* is coined by Müller and Pilzecker to describe the process of stabilizing memories while increasing their resistance to interference (Müller & Pilzecker, 1900). In their landmark study, two groups of participants were presented with a list of paired associates and were tested on their ability to recall the second word in each pair after a delay. The experimental group was then presented with a second list of paired associates, while the control group was not. The results showed that participants in the experimental group performed significantly worse on the second recall test compared to the control group, indicating that the learning of the second list interfered with the retention of the first list. They concluded that memories require a maturation process to become long-lasting and stable (Müller & Pilzecker, 1900). Because newly learned information is more vulnerable to forgetting, they proposed a physiological process responsible for the transformation of the vulnerable memory trace into an enduring state.

WM and long-term memory interact with each other intimately. For example, WM is critical in the encoding of information into long-term memory, as some of the information

in WM could be consolidated into long-term memory. Similarly, long-term memory can support WM by providing a store of knowledge and experiences that can be used to guide and inform ongoing cognitive processes (Baddeley, 2010).

One prominent model of memory process is the standard two-stage memory model (Marr, 1971). It states that memories are first encoded into a temporary storage (fast learning) to ensure an efficient, albeit short-lived, learning. Over repeated rehearsal or reactivation of the new memories, the information is integrated in the long-term storage (slow learning) and becomes resistant against interference. This model has received empirical support in declarative memory, which refers to memory that can be consciously retrieved such as factual information and previous experiences (Buzsáki, 1989). Specifically, the temporal storage of declarative memory is associated with hippocampus while the long-term storage is associated with neocortex (Corkin, 2002).

Sleep Promotes Memory

Sleep's role in episodic memory has been widely explored in the last century. The foundational work by Jenkins and Dallenbach in the early 1900 revealed that participants remembered more non-sensical syllables after a period of sleep compared to a period of wake, which the authors interpreted as sleep passively reducing interference to facilitate memory formation (Jenkins & Dallenbach, 1924). This finding has been replicated by later studies using a similar paradigm (Gais et al., 2006; Rasch & Born, 2013; Talamini et al., 2008). Ellenbogen and colleagues investigated whether sleep passively or actively facilitates memory of word-pairs by introducing interference (Ellenbogen, Payne, et al., 2006). Specifically, they trained subjects on a new word-pairs list before testing them on the original list. They found memory became more resistant to the negative effect of interference after sleep compared to wake, leading to the conclusion that sleep is an active processes that stabilizes or protects memories against further interference (Ellenbogen, Hulbert, et al., 2006). However, recent studies using a similar interference paradigm failed to replicate sleep's superiority over wake in stabilizing memories (Cordi & Rasch, 2021). In other words, researchers reported similar memory performance after interference training over a period of sleep compared to wake. Therefore, Chapter 2 will investigate if sleep stabilizes memory against daytime interference over 24 hours and specific features involved.

Over the past couple of decades, numerous studies have investigated neural mechanisms that may contribute to the consolidation process during sleep (Diekelmann & Born, 2010a; Feld & Diekelmann, 2015). Studies have shown that performance improvement on an episodic memory task is associated with SWS duration (Fowler et al., 1973; Plihal & Born, 1997a). In addition, slow oscillations (SO, 0.5-1Hz) and sleep spindles (12-15Hz) emerged as two prominent sleep features that are associated with episodic memory consolidation, possibly due to their role in facilitating the communication between hippocampus and neocortex (Diekelmann & Born, 2010a). The active systems consolidation hypothesis states that during non-rapid eye movement (NREM) sleep, newly encoded memories are strengthened through a dialogue between the neocortex and hippocampus controlled by specific sleep features (Born & Wilhelm, 2012). The neocortical slow oscillations (SOs), with sharp wave-ripples and thalamo-cortical spindles, drive the

repeated reactivation of hippocampal memory representations and turn them into long-term memories (Born & Wilhelm, 2012).

Studies have shown that causally increasing SOs using stimulation interventions significantly improves declarative memory in rodents (Binder et al., 2014) and humans (Marshall et al., 2006; Ngo et al., 2013). In addition, Clements and colleagues (2005) found a positive correlation between overnight verbal memory retention and the number of spindles (Clemens et al., 2005) as well as spindle activity (Lustenberger et al., 2012; Schabus et al., 2004a). Using functional magnetic resonance imaging (fMRI), researchers have linked sleep spindles with functional changes in areas implicated in memory consolidation. In detail, spindle activity memory improvement is associated with increased hippocampal-cortical functional connectivity that co-occurs with spindle activity (Andrade et al., 2011), and that covaries with spindle amplitude (Bergmann et al., 2012). However, interventional studies that show causal relation between sleep spindles and episodic memory consolidation are scarce. Our group previously showed that pharmacologically increasing spindle density is associated with better memory for word-pairs after a daytime nap (Mednick et al., 2013). However, it remains unknown if similar results are present during nocturnal sleep. Based on this previous study from 2013, Chapter 3 examined the effect of Zolpidem, as a pharmacological intervention, on sleep spindles across a whole night of sleep and associated memory change.

Interestingly, SOs have also been linked to improvement in WM. Several studies have found improvement in WM performance is associated with SOs in both young (Ferrarelli et al., 2019; Pugin et al., 2015) and older adults (Sattari et al., 2019). In a recent study, researchers used an acoustic stimulation to enhance SOs during nighttime sleep, and they found that participants with enhanced slow wave activity (<4hz) had better performance on a WM task compared to those without enhanced SWA (Diep et al., 2021). While studies have shown that SWS (including SWA and SOs) facilitates WM and SO-spindle coupling facilitates episodic memory, the mechanism underlying this process remains unclear. Chapter 4 bridges this gap in knowledge by employing simultaneous EEG-fMRI to investigate SO-induced functional changes in the brain and how they might contribute to WM.

CHAPTER 2 The Role of Sleep on Declarative Memory Consolidation: Stabilizing or Rescuing?

Abstract

Prior studies suggest a role for sleep in memory consolidation, with specific contributions from slow oscillations and sleep spindles (Rasch & Born, 2013). However, recent studies failed to replicate sleep's superiority over wake in strengthening memory against interference (Cordi & Rasch, 2021). The goal of the current study is to investigate whether sleep protects newly formed memory from unspecific interference induced by daytime experiences over 24 hours, as well as to elucidate the sleep features that are involved. 56 healthy adults were randomly assigned to either the Sleep First or Wake First group. The Sleep First group encoded word pairs at night before sleep, while the Wake First group encoded word pairs in the morning before a day of wakefulness. Memory was tested 30 minutes, 12 hours, and 24 hours after encoding for both groups. The Sleep First group performed significantly better 12 hours after encoding, replicating prior findings that memory is better after a period of sleep compared to wake. However, after 24 hours, the two groups performed similarly. The Wake First group showed a positive correlation between overnight memory improvement and the theta and delta band power during slow wave sleep, an effect not found in the Sleep First group. These correlations suggest the possibility that after a day of waking interference, the brain recruits extra sleep resources to rescue memories from further forgetting. Our results are not consistent with prior studies showing a significant role for sleep in stabilizing memory from future interference, but they may suggest that sleep rescues memories after interference has occurred.

Introduction

Memory consolidation refers to the process of transforming the vulnerable memory trace into an enduring state by increasing its resistance to interference (Müller & Pilzecker, 1900). Since the 1920s, sleep has been implicated in this process, as Jenkins and Dallenbach reported that experimental subjects remembered more non-sensical syllables after a period of sleep compared to a period of wake, leading the authors to suggest that sleep passively facilitates declarative memory via reduced interference (Jenkins & Dallenbach, 1924). Similarly, other studies have reported that memory was superior following by a period of sleep compared to wake (Gais et al., 2006; Rasch & Born, 2013; Talamini et al., 2008). This enhancement has been reported to last up to 24 hours after initial learning (Benson & Feinberg, 1977).

In the early 2000s, researchers proposed that sleep not only passively shelters memory from interference, but it may also actively stabilize memory against further interference (Ellenbogen, Hulbert, et al., 2006). In other words, memory is more resistant to decay from interference occurring after a period of sleep-dependent consolidation. To explore the question of whether sleep passively or actively contributes to declarative memory consolidation, researchers had subjects learn a word list with a subsequent retrieval test after a night of sleep or a day of wake (Ellenbogen, Hulbert, et al., 2006). Interference was introduced by having half the subjects learn a new word list immediately before retrieval of the old word list. Researchers found that retroactive interference, which is when new learning hinders the memory of previously learned material, was present for both wake and sleep, however, sleep provided more protection from interference than

wake. These results were interpreted to suggest that sleep actively stabilizes memories by making them more resistant to interference (Ellenbogen, Hulbert, et al., 2006).

The active role of sleep in memory consolidation gained further support with the elucidation of neural mechanisms that directly contribute to the consolidation process during sleep (Diekelmann & Born, 2010a; Feld & Diekelmann, 2015). The active systems consolidation hypothesis states that during non-rapid eye movement (NREM) sleep, newly encoded memories are strengthened through a dialogue between the neocortex and hippocampus controlled by specific sleep features(Born & Wilhelm, 2012). The neocortical slow oscillations (SOs), with sharp wave-ripples and thalamo-cortical spindles, drive the repeated reactivation of hippocampal memory representations and turn them into long-term memories (Born & Wilhelm, 2012). Several different interventions have demonstrated the causal role of SOs, sleep spindles and their coupling on hippocampal-dependent memory consolidation, including pharmacological (Mednick et al., 2013), targeted memory reactivation (Antony et al., 2018; Cairney et al., 2018), and transcranial electrical stimulation (Latchoumane et al., 2017a; Lustenberger et al., 2016), which provide empirical support to the active system consolidation hypothesis.

Even still, some studies have failed to demonstrate sleep's superiority over wake in stabilizing memories (Cordi & Rasch, 2021). Specifically, using a similar paradigm by Ellenbogen and colleagues (2006), another group reported no differences between sleep and wake on protecting memories from later interference (Bailes et al., 2020), similar findings have been shown for a daytime nap (Pöhlchen et al., 2021). Moreover, a study reported retroactive interference after sleep but not sleep deprivation, further contradicting sleep's role in stabilizing memories (Deliens et al., 2013). In this study, participants learned a list of word pairs before a night of sleep or sleep deprivation, and they learned an interference wordlist right before retrieval. Researchers found that interference significantly lowered recall after sleep but not after sleep deprivation, suggesting that memories become more labile, and vulnerable to interference with sleep (Deliens et al., 2013). Given that studies typically test sleep's role in resilience to future interference, it is still an open question whether each night of sleep may serve to rescue memories that have occurred the previous day. Specifically, do experiences we have in the morning that are followed by a day of waking interference get selectively recovered during the subsequent night of sleep?

The goal of the current study was to determine if sleep serves to stabilize (strengthen new memory against later interference) or rescue (recover previous memory after interference) memory over a 24-hour period. One group (Wake First) learned a list of word pair-associates in the morning followed by three recall tests: Test 1 (immediate), Test 2 (delayed over a day of wake), and Test 3 (delayed over a night of sleep in the lab). Another group (Sleep First) learned the word-pairs at night followed by three tests: Test 1 (immediate), Test 2 (over a night of sleep in the lab), Test 3 (delayed over a day of wake). We tested the hypothesis that memory performance would be greater at Test 3 in the Sleep First group, compared with the Wake First group, because a night of sleep immediately after learning would stabilize memories against daytime interference between Test 2 and Test 3. We also tested the hypothesis that overnight memory improvement would be correlated with sleep features implicated in memory consolidation for the Wake First

group, but not the Sleep First group, because sleep would rescue memories after a day of interference.

Methods

Subjects and study protocol

A total of 56 subjects (age: 20.67 ± 2.52, 26 females) provided informed consent, which was approved by the University of California, Riverside Human Research Review Board. All subjects were healthy, college-aged adults without any sleep disorders. Participants were randomly assigned to two groups, Wake First and Sleep First. All groups were tested three times, with approximately 12 hours in between each test session. For the Wake First group, memory encoding occurred in the morning followed by 12 hours of wakefulness. For the Sleep First group, memory encoding occurred just before nighttime sleep.

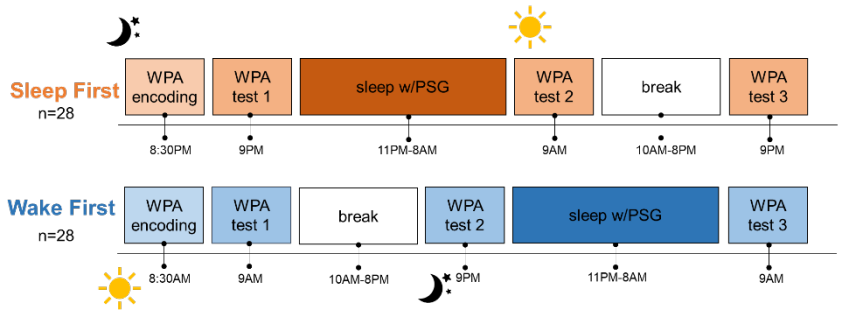

Figure 2-1 The study protocol

The study procedure is outlined in Figure 1. In the Wake First condition (n=28), participants reported to the laboratory in the morning. They completed the word paired associates (WPA) task encoding and immediate testing (Test 1) at around 8:30am in the morning. Then, participants left the lab to continue their day. At around 9pm in the evening, participants returned to the lab for a second memory testing (Test 2). Then, participants went to sleep in a standardized bedroom. Participants were woken up at 9am the next morning and provided breakfast. At 10:30 AM, participants completed the memory task (Test 3) and were permitted to leave the lab. In the Sleep First condition (n=28), participants reported to the laboratory in the evening. They completed the WPA task encoding and immediate testing (Test 1) at around 9pm in the evening before being prepared for nighttime sleep. Participants were woken up at 9am the next morning and provided breakfast. At 10:30 AM, participants completed the memory task (Test 2) and were permitted to leave the lab. At around 9pm in the evening, participants returned to the lab for a third memory test session (Test 3).

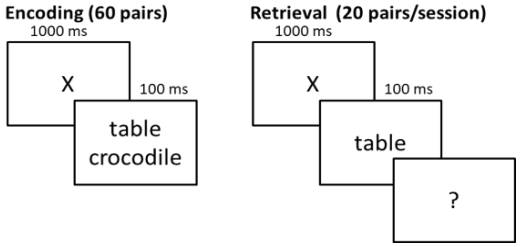

Figure 2-2 The word-paired associates task

Task

The word-paired associates (WPA) task consisted of an encoding session and three testing sessions (Figure 2). During encoding, participants passively viewed 60 pairs of words, each presented vertically stacked and shown twice in random order. Every word pair was presented for 100ms followed by a fixation cross for 100ms. We trained

subjects to criterion using a test in which participants were shown one word of the pair and were required to type in the missing word. Feedback was provided and participants had to achieve 70% accuracy to finish the training. Retrieval was identical to the training to criterion except no feedback was given. The word-pairs were divided into three sets of 20 pairs; one set was tested at each test session and the order was counterbalanced. Three retrieval tests were conducted: 1) immediately after encoding (Test 1), 2) 12 hours after encoding (Test 2) and 3) 24 hours after encoding (Test 3). The accuracy score was calculated for each test.

Sleep Recording and Scoring

EEG data were acquired using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10-20 System (Dang-Vu et al., 2008). Twenty-two electrodes were scalp recordings, and the remaining electrodes were used for electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), ground, an online common reference channel (at FCz location, retained after re-referencing), and mastoid (A1 & A2) recordings. The EEG was recorded with a 1000 Hz sampling rate and was re-referenced to the contralateral mastoid (A1 & A2) and down sampled to 256Hz post-recording. Eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2), the EMG, and EOG were used in the scoring of the nighttime sleep data. High pass filters were set at .3 Hz and low pass filters at 35 Hz for EEG and EOG. Raw data were visually scored in 30-sec epochs into Wake, Stage 1, Stage 2, Slow Wave Sleep (SWS) and rapid eye movement (REM) sleep according to the Rechtschaffen & Kales' manual (Rechtschaffen & Kales, 1968).

Power spectra estimation

To examine which sleep frequency bands might account for memory changes, we analyzed the following sleep frequency bands: sigma (11-15Hz), theta (4-7Hz), delta (1-4Hz), and slow wave activity (SWA) (0-1Hz). Sleep spindles were detected using the same method published before (Zhang et al.,2020). The EEG epochs that were contaminated by muscle and/or other artifacts were rejected using a simple out-of-bounds test (with a ±200 μV threshold) on high-pass filtered (0.5 Hz) version of the EEG signals. The EEG power spectra were computed using the Welch method (4 sec Hanning windows with 50 % overlap) on the artifact-free 30-sec epochs. Then, the estimated power spectra were averaged within each sleep stage/electrode/subject.

Statistical analysis

Our primary hypothesis was that the improvement in memory would be higher for the Sleep First condition compared to the Wake First condition. To test this hypothesis, we conducted a mixed ANOVA test with the within-subject factor being time (Test 1 and Test 3) and the between-subjects factor being groups (Wake First and Sleep First).

To examine the hypothesis that sleep rescues memory, we compared the relevant sleep features associated with overnight improvement (Test 2- Test 1 for the Sleep First group; Test 3- Test 2 for the Wake First group) between two groups. If sleep rescues memory, specific sleep features would be correlated with overnight improvement for the Wake First group but not the Sleep First group. To this end, we calculated Pearson's r between each frequency band and the memory difference scores for each group separately. Benjamini-Hochberg correction with false discovery rate set as 5% was used to control for multiple comparisons.

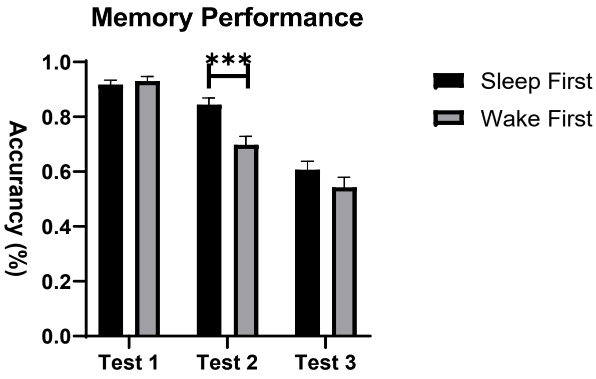

Figure 2-3 Memory performance

Results

Behavioral

As shown in Figure 3, the baseline performance was similar between two groups (t_{54}=-0.55, *p*=0.59), suggesting the differences in encoding and test times between the two groups had minimal impact on immediate recall. At Test 2, the Sleep First group performed significantly better than the Wake First group (t_{54}=3.78, *p*<0.001), showing that memory performance was better after a night of sleep compared to a day of wakefulness. At Test 3, however, the two groups showed similar recall levels (t_{54}=1.33, *p*=0.19), suggesting sleeping immediate after learning did not stabilize memory against further interference. There was a main effect of time, $F_{(1,54)}$=216.17, *p*<0.001), indicating that both groups showed significant forgetting across the three sessions. The main effect of group was not statistically significant ($F_{(1,54)}$=0.78, *p*=0.38), providing additional evidence that sleeping immediately after learning did not protect new memories from waking interference following a night of sleep.

Sleep

Sleep Stage	Wake First	Sleep First	P values
TST (min)	534.90(49.73)	482.32(41.08)	0.00*
N1 (min)	14.96(8.60)	14.38(13.15)	0.85
N1(%)	2.83(1.65)	3.11(3.10)	0.69
N2 (min)	283.06(54.17)	259.57(36.82)	0.07
N2(%)	52.88(8.71)	53.93(7.14)	0.63
N3 (min)	108.75(39.10)	89.34(24.79)	0.03*
[illegible]	[illegible]	[illegible]	[illegible]
REM(min)	[illegible]	[illegible]	[illegible]
REM(%)	[illegible]	[illegible]	[illegible]
WASO	[illegible]	[illegible]	[illegible]

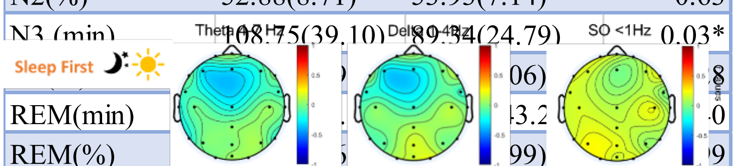

Figure 2-4 The Pearson's r coefficient between overnight memory performance change and power spectra in theta, delta and SO bands for the Sleep First group (top panel) and the Wake First group (bottom panel)

The two groups showed similar sleep architecture except for the Total Sleep Time (TST) and time spent in SWS (Table 1). Specifically, the WASO, and percent time spent in each stage, and time spent in N1, N2 and REM were not statistically different between two groups (p>0.05). The Wake First group had significantly more Total Sleep Time (TST) (p=0.00) and time spent in SWS (p=0.03) than the Sleep First group. When correlating with memory performance, TST has a

positive correlation with overnight memory improvement for the Wake First group (Test 3-Test 2) ($r=0.43$, $p=0.03$), but not for the Sleep First group (Test 2 – Test 1) ($r=0.01$, $p=0.95$). Time spent in SWS was not correlation with any performance measure for either group ($p>0.05$).

Power performance correlation

Overnight memory performance change for the Wake First group (Test 3 – Test 2) was positively correlated with spectra power in theta and delta frequency during SWS (Figure 4, top panel). Specifically, for delta band, 16 electrodes located at parietal, occipital and temporal lobe showed a positive correlation with overnight memory change (Test 3 - Test2) in SWS after Benjamini-Hochberg correction for multiple comparisons. For theta band, 3 electrodes located at prefrontal, left temporal and left occipital area showed a positive correlation with overnight memory change (Test 3 - Test2) in SWS after Benjamini-Hochberg correction for multiple comparisons. The same correlation was not observed in the Sleep First group (Figure 4, bottom panel). In fact, no statistically significant correlation was found between any frequency band and memory performance for the Sleep First group.

Discussion

Prior studies have demonstrated that sleep protects and stabilizes memories against further interference, suggesting an active role of sleep in memory consolidation (Ellenbogen, Payne, et al., 2006). In addition, studies report that sleep must occur shortly after learning to optimize consolidation for declarative memory (Backhaus et al., 2008; Payne et al., 2012), associative memory (Talamini et al., 2008) and motor skills (Van Der Werf et al., 2009). However, whether sleep stabilizes memory is still a debate as other studies show similar memory performance after a period of sleep and wake (Bailes et al., 2020; Deliens et al., 2013; Pöhlchen et al., 2021). Therefore, the goal of the current study was to investigate if sleep plays a stabilizing or rescuing role in memory consolidation and specific features involved.

Consistent with prior studies, we found better memory over a night of sleep compared to a day of wake (Diekelmann & Born, 2010a; Gais et al., 2006; Jenkins & Dallenbach, 1924). However, we also found similar memory performance levels between the two groups at 24-hours, suggesting that sleep before daytime interference did not make memories resistance to this interference. However, we did find participants slept longer when the interference occurred before compared to after sleep, which was associated with overnight memory improvement. In addition, specific sleep features contributed memory improvement after a night of sleep that followed a day of wake, but not with a night of sleep in which interference occurred after sleep, suggesting that sleep may help recover learning after daytime interference. This rescue effect was associated with increased power in theta and delta frequency during SWS. Drosopoulos and colleagues also showed that sleep recovered memory of an older word list when an interference list was learned before sleep (Drosopoulos et al., 2007). Similarly, Backhaus and colleagues reported that both immediate and delayed post-learning sleep enhanced declarative memory (Backhaus et al., 2008). However, they also showed a stabilizing effect of sleep with less forgetting across

wakefulness in the Sleep First group compared to the Wake First group, which was not observed in the current study.

The rescuing effect of sleep on memory has been shown in a non-declarative, perceptual learning task with the amount of REM sleep positively associated with the magnitude of memory recovery (McDevitt et al., 2015). The current study suggests that the rescuing effect of sleep may extend to declarative memory, with TST, theta and delta power during SWS being correlated to the amount of memory recovery. Sleep-dependent declarative memory consolidation has been associated SWS duration (Cairney et al., 2015; Fowler et al., 1973; Plihal & Born, 1997a; Tucker et al., 2006) and specific features during SWS including SOs (Dang-Vu et al., 2008, p.; Farhadian et al., 2021; Marshall et al., 2006; Ruch et al., 2012), The current study shows that theta power is implicated in this process as well. Theta power has been associated with the redistribution of memory from the hippocampus to the neocortex, (Headley & Paré, 2017), and studies have shown that theta power is correlated with successful memory reactivation during NREM sleep (Choi et al., 2021; Schreiner et al., 2018).

There are a few limitations of the current study. The interference was based on subjects' daytime activity instead of a wordlist that is more closely related with the learning stimuli (Ellenbogen, Hulbert, et al., 2006), which might reduce the effect of retroactive interference. Future studies can utilize an interference wordlist before and after sleep to further isolate the effect of sleep on memory against retroactive interference. In addition, the between-subject design decreases the effect size. We cannot rule out the possibility that sleep has a stabilizing effect on memory that is not large enough to be detected in the current study.

In summary, the current study shows that sleep benefits memory on a word list regardless of whether it occurs shortly after learning or after a delay, suggesting that sleep shelters memory from interference. More interestingly, subjects experienced enhanced overnight memory improvement when there was a delay between learning and sleep, and this improvement was associated with theta and delta power. Taken together, our results suggest that sleep rescues memory after interference has occurred instead of stabilizing memory against future interference. Future studies are needed to examine the neural mechanism underlying sleep's rescuing effect on memory after interference has occurred.

CHAPTER 3 The Effect of Zolpidem on Memory Consolidation and Sleep Features Over a Night of Sleep

Abstract

Non-rapid eye movement (NREM) sleep boosts hippocampus-dependent, long-term memory formation more so than a period of wake. Studies have pointed to several electrophysiological events that likely play a role in this process, including thalamo-cortical sleep spindles (12-15Hz). However, interventional studies that directly probe the causal role of spindles in consolidation are scarce. In addition, spindles don't singularly account for changes in post-sleep performance change. Previous studies have examined the role of zolpidem, a GABA-A agonist, for sleep spindles after daytime nap. The current study investigated the effect of zolpidem on nighttime sleep and overnight hippocampal-dependent memories. We used a double-blind, placebo-controlled within-subjects design to test the a priori hypothesis that zolpidem would lead to increased memory performance on a word paired-associates task by boosting spindle activity during the night of sleep. In addition, we explored the impact of zolpidem across a range of other spectral sleep features, including slow oscillations (0.5-1Hz), delta (1-4Hz), theta (4-8Hz), and sigma (12-15Hz) activity, as well as spindle-SO event coupling. We show greater memory improvement after a night of sleep with zolpidem, compared to placebo, replicating a prior nap study. Additionally, zolpidem increased sigma power, decreased theta and delta power, and altered the phase angle of spindle-SO coupling, compared to placebo. These sleep alterations after a night of zolpidem were also associated with next-day memory performance. These results are consistent with the hypothesis that sleep, specifically the timing and amount of sleep spindles, plays a causal role in long-term formation of episodic memories. Furthermore, our results suggest a heretofore unreported role of NREM theta activity in human memory consolidation.

Introduction

Converging evidence from both cellular and behavioral research suggests an essential role of sleep in memory consolidation (Diekelmann, 2014; Mednick et al., 2011; Stickgold, 2005). For hippocampal-dependent episodic memories, studies have shown greater performance improvement following the first half of the night rich in slow wave sleep (SWS), compared to the second half of the night with majority rapid eye movement (REM) sleep (Fowler et al., 1973; Plihal & Born, 1997b). In addition, neocortical slow oscillations (SO, 0.5-1Hz) and thalamo-cortical spindles (12-15Hz) have emerged as two prominent features of non-REM (NREM) sleep associated with episodic memory consolidation (Diekelmann & Born, 2010b). For example, Clemens and colleagues (Clemens, Fabó, & Halász, 2005) found a positive correlation between the number of spindles and overnight verbal memory retention, but not visual skill learning. In another study, spindle density in stage 2 sleep increased after an episodic memory encoding but not after a non-learning task where subjects were instructed to count letters containing curved lines (Gais et al., 2002). More so, performance improvements after an episode of sleep have been associated with increases in spindle activity (Lustenberger et al., 2012; Schabus et al., 2004b). Similar correlations have been shown between SOs and memory improvement in both animals (Binder et al., 2014) and humans (Marshall et al., 2006; Ngo et al., 2013).

Majority of these studies were observational in that they correlated sleep features with memory outcomes. In the current study, we used pharmacology to manipulate spindle activity and investigated the correlation between change in memory performance and multiple sleep features.

More recently, the temporal coupling between spindles and SOs have been suggested to reflect hippocampo-thalamo-cortical communication during NREM sleep, and that this coordinated activity pattern may underlie the formation and protection of long-term memories (Mölle et al., 2011; Staresina et al., 2015). Accordingly, several studies suggest that coincident spindle-SO coupling leads to greater memory, optimally when spindle activity occurs during the SO up-state (Gais & Born, 2004; Mölle et al., 2009; M. Niknazar et al., 2015; Sattari et al., 2019). Optogenetically stimulating spindle activity during the up-state of SOs in rodents improved contextual fear-conditioning, compared with random or no stimulation (Latchoumane et al., 2017b). A recent study examining coupling of sigma and SO in relation to fMRI brain activity and memory performance in young and older adults (Helfrich et al., 2018) reported that spindle-SO coupling predicted post-sleep episodic memory improvement in both age groups. However, older adults showed altered timing between spindle-SO coupling and decreased coupling over the frontal pole, which could explain why overnight memory retention is frequently impaired in older compared to young adults. Additionally, optimal spindle-SO timing may compensate for lower total number of spindles and support memory (Demanuele et al., 2017). Specifically, patients with schizophrenia showed reduced spindle number and density but similar spindles-SO coupling compared to healthy individuals, and magnitude of coordination between spindles and SOs was correlated with overnight improvement on a hippocampal-dependent memory task (Demanuele et al., 2017).

Experimental approaches to probe the causal nature of sleep spindles are scarce. Spindles can be pharmacologically increased with zolpidem (Ambien), a GABA-A agonist with a half-life of approximately 1.5-3.2 hours and peak plasma concentration 1.6 hours after ingestion (Drover, 2004). Our group has shown that administering zolpidem during a morning nap increases spindle density compared with placebo and a comparison hypnotic, sodium oxybate (Mednick et al, 2013). Additionally, zolpidem improved episodic memory, but decreased perceptual learning, and had no effect on motor learning, compared with placebo (Mednick et al, 2013). Verbal memory performance was significantly correlated with spindle density in zolpidem and placebo, but not with sodium oxybate (Mednick et al, 2013). Furthermore, zolpidem increased the coincidence of the spindle-SO coupling measured by phase angle, which also correlated with memory improvement (M. Niknazar et al., 2015). Similarly, eszopiclone, a GABA based non-benzodiazepine, increased spindles and the association between spindles and motor learning (Wamsley et al., 2013). Given the small amount of studies that test the impact of directly manipulating spindles on memory, and that zolpidem has only been tested in a morning nap, more research is needed.

The current study investigated the impact of zolpidem on a night of sleep, specifically on spindle activity and spindle-SO coupling, and overnight episodic memory consolidation of word-pair associates. In addition, zolpidem is known to reduce theta oscillation, yet the effect on memory is unknown. Specifically, a study using zolpidem as a treatment for insomnia showed that zolpidem decreased theta power and increased sigma

power with no change in SO in patients (Lundahl, Deacon, Maurice, & Staner, 2012). The reduction of theta activity by zolpidem is consistent between sexes (Dijk et al., 2010). Another study showed that zolpidem decreased band power between 3.75hz to 10hz for sleep-deprived participants, with theta power having the largest reduction (Landolt et al., 2000). Therefore, a secondary goal of the current study was to investigate a range of sleep features, including SO, delta and theta, and their relation to memory performance. Taking into consideration the short half-life of zolpidem (Drover, 2004), we divided the night of sleep into four quartiles in order to assess the effect of zolpidem on sleep physiology during peak plasma periods, as well as across the whole night. We hypothesized that, compared to placebo, zolpidem would show increased performance on an episodic memory task compared with placebo, as well as greater spindle density and spindle-SO coupling during the first two quartiles of sleep.

Methods

Participants

Thirty-six healthy adults (M_{age} = 21.00 ± 2.97 years, 19 Females) with no history of neurological, psychological, or other chronic illnesses were recruited for the study. All participants signed informed consent, which was approved by the Western Institutional Review Board and the University of California, Riverside Human Research Review Board. Exclusion criteria included irregular sleep/wake cycles; sleep disorder; personal or familial history of diagnosed psychopathology; substance abuse/dependence; loss of consciousness greater than 2 minutes or a history of epilepsy; current use of psychotropic medications; and any cardiac or respiratory illness that may affect cerebral metabolism, which was determined during an in-person psychiatric assessment with trained research personnel. Additionally, all participants underwent a medical history and physical appointment with a staff physician to ensure their physical well-being. All subjects were naïve to or had limited contact with (<2 lifetime use and no use in last year) the medication used in the study. Participants received monetary compensation and/or course credit for participating in the study.

Procedure

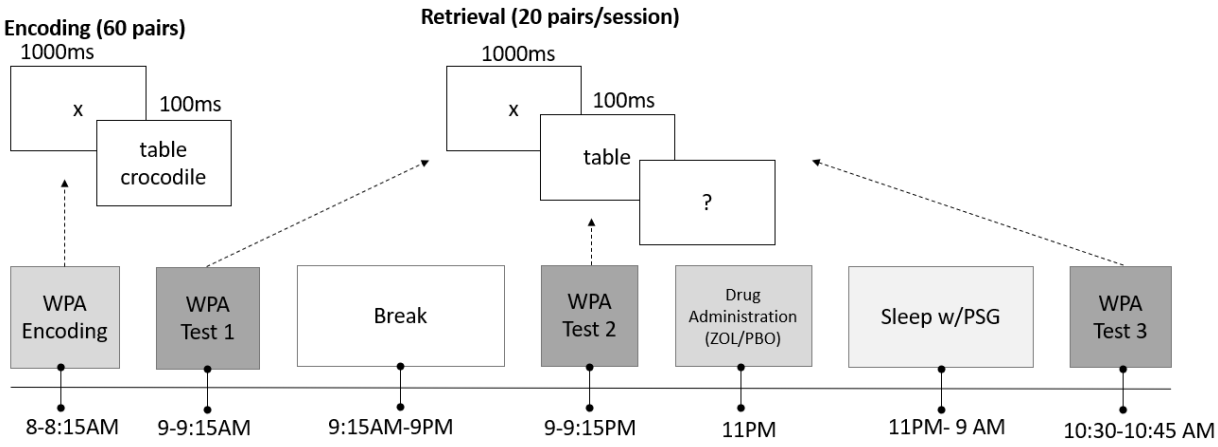

Figure 1, study protocol

This study employed a double-blind, placebo-controlled, within-subject design, in which every subject experienced both zolpidem and placebo. The order of drug conditions was counterbalanced with at least a one-week interval between each experimental visit to allow for drug clearance. Subjects reported to the laboratory at 7:30AM and began encoding for the paired associates verbal memory task at 8:00AM. Participants left the lab after cognitive testing. Participants returned to the laboratory at 9:00 PM at which point a second memory test was given. After testing, participants were prepared for nighttime sleep, which included a 32-channel polysomnography (PSG) recording. Once in bed and directly before lights out, subjects ingested either 10mg of zolpidem or placebo. Participants were woken up at 9:00AM the next morning and provided a standardized breakfast. At 10:30 AM, participants completed the memory task and were permitted to leave the lab after being cleared by study personnel (figure 1).

Task

The word-paired associates (WPA) task consisted of an encoding phase and three retrieval phases. Encoding consisted viewing 60 pairs of words, each presented vertically stacked and shown twice in random order. Every word pair was presented for 100ms followed by a fixation cross for 100ms. We trained subjects to criterion using a test in which participants were shown one word of the pair and were required to type in the missing word. Feedback was provided and participants had to achieve 70% accuracy to finish the training. For testing, the 60 word-pairs were divided into three sets of 20 pairs; one set was tested at each test session and the order was counterbalanced. Three retrieval tests were conducted: 1) immediately after encoding (9AM, Test 1), 2) before sleep (9PM, Test 2) and 3) the morning after sleep (10:30AM, Test 3). No feedback was provided during testing.

Sleep recording

EEG data were acquired using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10-20 System (Jasper, 1958). 22 electrodes were scalp recordings and the remaining electrodes were used for electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), ground, an online common reference channel (at FCz location, retained after re-referencing), and mastoid (A1 & A2) recordings. The EEG was recorded with a 1000 Hz sampling rate and was re-referenced to the contralateral mastoid (A1 & A2) post-recording. Data were pre-processed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany). Eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2), the EMG, and EOG were used in the scoring of the nighttime sleep data. High pass filters were set at .3 Hz and low pass filters at 35 Hz for EEG and EOG. Raw data were visually scored in 30-sec epochs into Wake, Stage 1, Stage 2, Slow Wave Sleep (SWS) and rapid eye movement (REM) sleep according to the Rechtschaffen & Kales' manual (Rechtschaffen & Kales, 1968). After staging, all epochs with artifacts and arousals were identified rejected by visual inspection before spectral analyses. Minutes in each sleep stage and sleep latencies (SL) (the number of minutes from lights out until the initial epoch of sleep, Stage 2, SWS and REM) were calculated. Additionally, wake after sleep onset (WASO) was calculated as total minutes awake after the initial epoch of sleep, and sleep efficiency (SE) was computed as total time spent asleep after lights out (~11:00PM) divided by the total time spent in bed (~11:00PM-9:00AM) * 100.

Spindle detection

For each electrode, we first found the peak frequency f_p of Stage 2 and SWS power spectrum within the 9–15 Hz band. For the electrodes with no power spectrum peak in this range, the average of peak frequencies from other EEG electrodes was considered as f_p. Next, we calculated the time-series of average EEG energy, $E(t)$, after convolving the signals by complex Morlet wavelets $\psi(t) = A\exp(-t^2/2\sigma_t^2)\exp(i2\pi f_0 t)$, where f_0 is in range [f_p -1.5 f_p +1.5] Hz with 0.1 Hz steps, $A = \left(\sigma_t\sqrt{\pi}\right)^{-1/2}$, $\sigma_t = 1/2\pi\sigma_f$, $\sigma_f = f_0/10$, $i = \sqrt{-1}$, and wavelet duration is in range $-5\sigma_t < t < 5\sigma_t$. Spindles were detected at each EEG electrode by applying a thresholding algorithm on $E^2(t)$. The threshold was defined as 4 times the mean amplitude of $E^2(t)$ of all artifact-free 30-sec epochs. A spindle event was identified whenever $E^2(t)$ exceeded the threshold for a minimum of 250 milliseconds. Finally, the detected spindles were refined if the estimated frequency of each spindle fell in range 9–15 Hz. In order to estimate a spindle frequency, the zero-crossings of the high-passed filtered (2 Hz) version of EEG in the candidate spindle intervals were first detected. Then, the spindle frequency was estimated as $f_{est} = (N-1)/2\Delta T$, where ΔT is the time difference between the last and first zero crossings within a candidate spindle interval.

Slow Oscillation detection

SO events were detected based on the algorithm developed by Massimini and colleauges (Massimini et al., 2004) The EEG signals were first filtered (zero-phase bandpass, 0.1–4 Hz). Then, the SO events were detected based on a set of criteria for down to up-state amplitude (>140 μV), down-state amplitude (<-80 μV), and duration of down-state (between 0.3 and 1.5 sec) and up-states (<1 sec) (see Dang-Vu et al., 2008 for more details).

SO–Spindle Modulation Index

Coupling between the phase of SO and amplitude of sigma power (12–15 Hz) during stage 2 and SWS was measured by modulation index (MI) as described by Canolty and colleagues (Canolty et al., 2006), and adapted by (M. Niknazar et al., 2015). First, we based the MI analysis on detected SO events (described in SO detection section above) in order to eliminate spurious EEG coupling from the entire sleep stage. However, in this case, we detected SOs within the frequency range of 0.1-4Hz. In addition, we narrowed our analysis to frontal electrodes (F3 and F4), which have been reported to show the strongest SO activity (Massimini et al., 2004). To calculate the MI, we applied a Hilbert Transformation to SO and sigma power within the SO event windows to construct the composite complex-valued signal of the amplitude of sigma power and the phase of the SO. $Z[n] = a_{sigma}[n] \exp(i\emptyset_{SO}[n])$ The normalized mean of this composite vector across trials is the raw MI. Higher MI values indicate less variability in the timing between spindle amplitude peak and a certain phase of the SO. To account for overestimation of MI due to noise, a normalized MI was calculated. A distribution of surrogate MI values was generated, with mean μ and standard deviation σ and the normalized MI was computed as $MI_{raw} - \mu/\sigma$.

We also measured the phase angle of the composite signal Z[n], which is the SO phase at which the amplitude tends to peak. In other words, for each SO event, the SO phase at the peak spindle amplitude envelope was calculated. A value of zero for SO phase ($\emptyset_{SO}$ = 0) represents the negative peak of the oscillation (SO trough), and a positive value suggests the up-state of the SO. Modulation index and phase angle were computed for zolpidem and placebo separately to determine the consistency and preference of the temporal relationship between the phase of SO to the amplitude of spindles. If MI or phase angle variables were significantly different between drug conditions, we computed Pearson's r between memory performance and the variable to determine if such a difference plays a role in behavioral change.

- **Power spectrum estimation**

To examine whether other sleep frequency bands might account for memory changes, we analyzed the following sleep frequency bands: sigma (11-15Hz), theta (4-7Hz), delta (1-4Hz), and slow wave activity (SWA) (0-1Hz). The EEG epochs that were contaminated by muscle and/or other artifacts were rejected using a simple out-of-bounds test (with a ±200 μV threshold) on high-pass filtered (0.5 Hz) version of the EEG signals. The EEG power spectra were computed using the Welch method (4 sec Hanning windows with 50 % overlap) on the artifact-free 30-sec epochs. Then, the estimated power spectra were averaged within each sleep condition/stage/quartile/electrode/subject.

Statistical analysis

- **Data reduction**

8 Participants (6F) did not complete both visits due to scheduling conflicts, which resulted in 28 subjects being included in the analyses.

- **Behavioral data**

To assess the impact of zolpidem on memory, we examined memory performance using 2 difference scores (24-hour retention: Test 3 - Test 1, and Overnight retention: Test 3 - Test 2). We conducted a two-sample paired t-test for each difference score comparing placebo and zolpidem conditions. Our primary hypothesis was that the improvement in memory in the zolpidem condition compared to placebo is correlated with a corresponding increase in spindle-related activity. To test this hypothesis, we calculated a change score for spindles density from zolpidem to placebo for each electrode, within each sleep stage, averaged within each quartile. We then calculated Pearson's r between the spindle difference scores and the memory difference scores. Benjamini-Hochberg correction with false discovery rate set as 5%was used to control for multiple comparisons. We computed similar differences scores for the sleep frequency bands and Pearson's r were calculated between difference scores for sleep frequency bands and memory performance.

- **Power spectrum estimation**

To examine the effect of zolpidem on the sleep frequency bands, we performed paired t-tests on the estimated power spectra averaged among all the electrodes for zolpidem and placebo from 0 to 30 Hz in 0.5 frequency bins, corrected by Benjamini-Hochberg correction test (Benjamini & Hochberg, 1995). To investigate the spatial distribution of sleep frequency bands, we then performed paired t-tests for each sleep frequency band at each electrode. To control for multiple comparison, we performed Benjamini-Hochberg correction test (Benjamini & Hochberg, 1995) and cluster-based permutation (Maris & Oostenveld, 2007).

- **Cluster-based permutation**

Cluster-based permutation tests have been widely used in the field of fMRI studies to control for multiple comparison problems (Woo et al., 2014). Maris and Oostenveld developed a method to incorporate cluster-based permutation tests in EEG data, which is used in the current analysis (Maris & Oostenveld, 2007). This technique increases the statistical power to find a drug effect, while sacrificing temporal and spatial specificity (i.e. we cannot say which electrode or which quartile had the significant effect). To test a significant drug effect within each sleep stage and each quartile, we performed a paired-t tests on each electrode site "sample" pair. Clusters were identified if one or more than one adjacent electrode reached significance level ($p<0.05$) in the same direction. Within each cluster, t-statistics were summed, and the max of the summed t-stats across all samples was calculated thereby creating the "real" cluster level statistic. Then, the assigned drug condition to each electrode data point was randomly shuffled, and a "permuted" cluster level statistic was calculated using the same above procedure. We repeatedly shuffled and calculated the "permuted" cluster level statistic 2000 times to get the expected distribution of the cluster level statistic if there was no drug effect (permutation distribution). The real cluster level statistic was then compared with permutation distribution and drug was considered to have a significant effect when it was larger than 98.75% of the shuffled t-values after correcting for multiple comparisons (i.e. 100 – 5/number of quartiles). The

reported statistic is the number of times the real cluster level statistic happens in the 2000 permutations.

Results

- **Behavioral data**

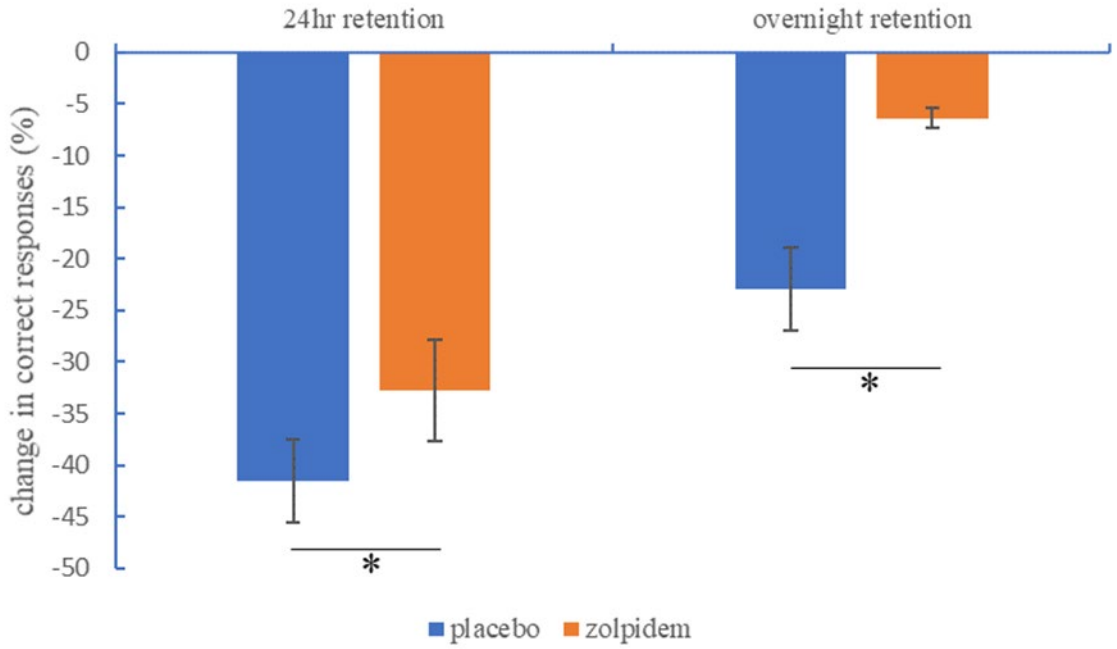

Figure 3-1 Behavioral results

Similar to prior reports (Mednick et al., 2013), memory recollection was improved in the zolpidem group compared to the placebo group. Specifically, participants in zolpidem condition had better verbal memory retention both at the 24-hour retention (t_{27}=2.40, p=0.02) and overnight retention (t_{27}=2.64, p=0.01) tests (Figure 2).

Sleep Stage	PBO	ZOL	P values
TST (min)	536.18(47.92)	537.71(39.15)	0.42
N1 (min)	14.46(8.44)	13.32(11.73)	0.57
N1(%)	2.74(1.62)	2.55(2.28)	0.54
N2 (min)	283.66(53.44)	288.61(46.66)	0.67
N2(%)	52.87(8.61)	53.75(8.19)	0.71
N3 (min)	110.09(37.99)	121.66(41.68)	0.99
N3(%)	20.64(7.32)	22.58(7.46)	0.98
REM(min)	127.95(32.07)	113.66(29.06)	0.99
REM(%)	23.76(5.26)	21.01(4.58)	0.99
WASO	31.30(27.60)	25.73(26.00)	0.93
SE	92.39(5.64)	93.26(4.89)	0.87

Table 2 Sleep architecture

-Sleep data

The two groups showed similar sleep architecture (table 1). Specifically, total sleep time, WASO, SE, and time spent in each stage and quartile were not significantly different between two groups (p>0.05).

As shown in Figure 3, when averaged across all electrodes, zolpidem showed 1) decreases in power in theta frequencies in stage 2 (quartiles 1 & 2) and SWS (quartile 1), and 2) increases in sigma frequencies in stage 2 (quartiles 2), after correcting for multiple comparisons. Importantly, expected peak plasma concentrations occur during quartile 1 & 2.

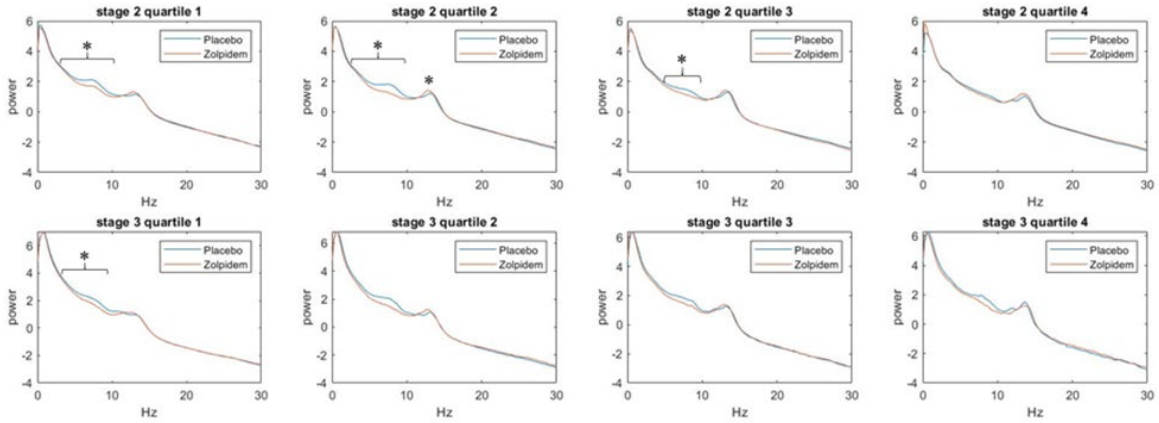

Figure 3-2 power spectrum for zolpidem (zol) and placebo (pbo) in stage 2 and stage 3 divided into 4 quartiles, averaged across electrodes.

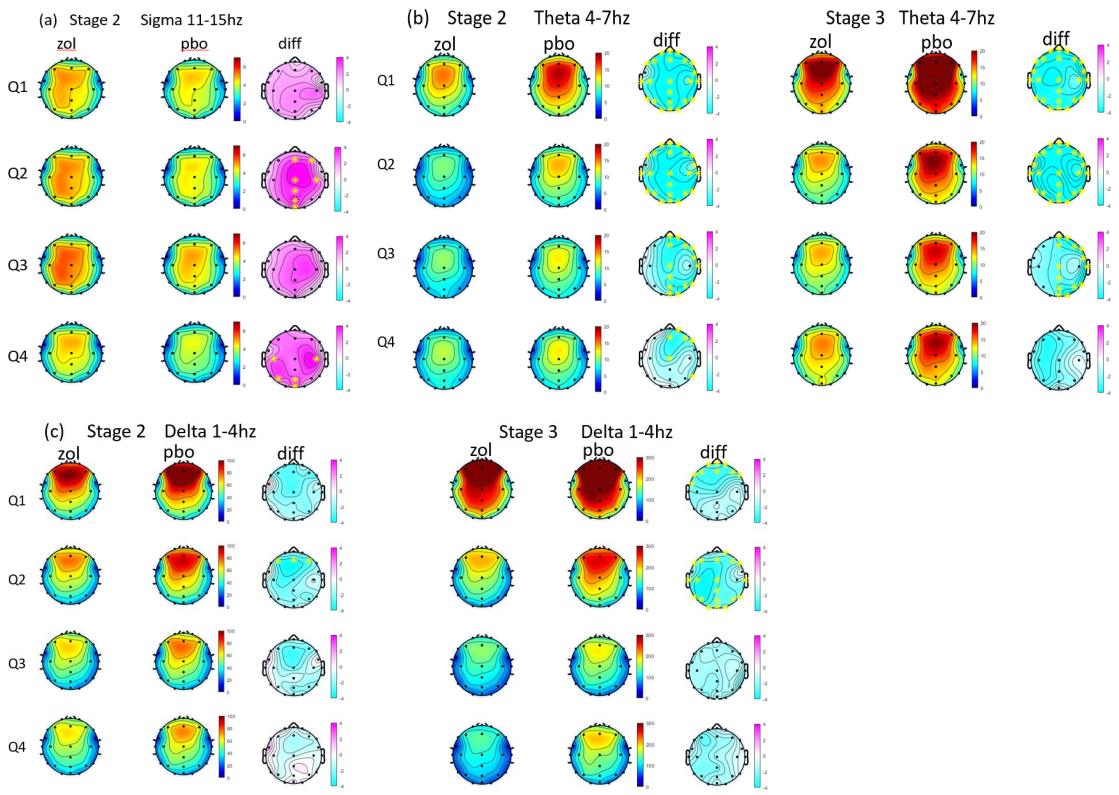

Figure 3-3 Topographic plots of the estimated marginal mean difference in spectral power between zol and pbo

Sigma

- *Electrode-based power spectrum estimation*

Zolpidem show significantly greater sigma activity in Stage 2 (33% of electrodes) and SWS (10% of electrodes), compared to placebo. After correction for multiple comparisons across electrodes using the Benjamini-Hochberg correction, 7 electrodes remained significant in quartile 2 and 5 electrodes in quartile 4 in stage 2, as shown in Figure 4(a). The range of increase is between 14% to 16%.

- *Cluster-based permutation for power spectrum estimation*

Cluster based permutation tests confirmed the individual electrode analysis, where the zolpidem group exhibited significantly greater sigma in stage 2 quartile 1(p =13/2000), quartile 2 (p<1/2000), quartile 3 (p<1/2000), and quartile 4 (p<1/2000). Significance was also detected in SWS quartile 2 (p=2/2000) and quartile 3 (p=42/2000).

- *Correlation between EEG activity and performance*

No significant correlations emerged between sigma activity and performance change in either the cluster-based permutation or individual electrode site after Benjamini–Hochberg correction.

Spindle density

- *Electrode-based estimation*

Spindle density was correlated with sigma power (r=0.36, p<0.001), and zolpidem showed increases in spindle density in stage 2 (4% electrodes were significant) and SWS (5% electrodes were significant), compared with placebo. However, no comparisons survived Benjamini-Hochberg correction.

- *Cluster-based permutation for power spectrum estimation*

No drug effect was detected for spindle density.

- *Correlation between EEG activity and performance*

For spindle density, 3 electrodes located at central occipital and left temporal areas displayed a positive correlation with overnight retention at quartile 2 in stage 2 after Benjamini-Hochberg correction (figure 5). Similarly, overnight retention and cluster-based permutation on spindle density was significantly correlated during stage 2 quartile 2 (p=33/2000).

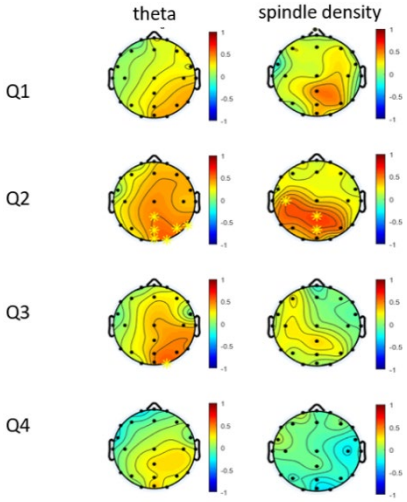

Figure 3-4 Topographic plots of Pearson's r in spectral power change (zol-pbo) and performance change (zol-pbo) for overnight retention

Theta

- *Electrode-based power spectrum estimation*

When each electrode was considered separately, there was a general decrease in theta power in the zolpidem condition compared to placebo in stage 2 (68% electrodes were significant) and SWS (40% electrodes were significant). As shown in Figure 4(b), after correction for multiple comparisons using Benjamini-Hochberg correction, 23 electrodes remained significant in quartile 1 and 2, 14 electrodes located in the left hemisphere in quartile 3 and 6 electrodes located in central frontal in quartile 4 for stage 2 remained significant. For SWS, 23 electrodes remained significant in quartile 1 and 2, and 14 electrodes located in the left hemisphere in quartile 3.

Cluster-based permutation for power spectrum estimation

The zolpidem group exhibited significantly lower theta in stage 2 (p=98/2000). All 4 quartiles showed a significant decreased theta for zolpidem compared to placebo in stage 2 (p<1/2000 for quartiles 1-4), and quartile 1 (p<1/2000) and 2 (p<1/2000) in SWS.

- *Correlations between EEG activity and memory performance*

The correlation between differences in overnight memory performance and theta power was significant during stage 2 quartile 2 (p=37/2000) from cluster-based permutation. As shown in Figure 5, after Benjamini-Hochberg correction for multiple comparisons, 6 electrodes located at left occipital lobe displayed a positive correlation with overnight retention at quartile 2 in stage 2, 1 electrode remained significant at quartile 3 stage 2, suggesting increased theta power has a positive association with better memory retention.

Delta

- *Electrode-based power spectrum estimation*

When each electrode was considered separately, there was a general decrease in delta power in the zolpidem condition compared to placebo in stage 2 (23% electrodes were significant) and SWS (18% electrodes were significant). After correction for multiple comparisons using Benjamini-Hochberg correction, 3 frontal electrodes remained significant in stage 2 quartile 2. 9 frontal electrodes were significant in quartile 1 SWS and 19 electrodes for quartile 2 SWS, as shown in Figure 4 (c).

- *Cluster-based permutation for power spectrum estimation*

The zolpidem group exhibited significantly lower delta in stage 2 quartile 1 (p=4/2000), quartile 2 (p<1/2000), and quartile 3 (p=7/2000) , as well as quartile 1 (p<1/2000) and 2 (p<1/2000) in SWS.

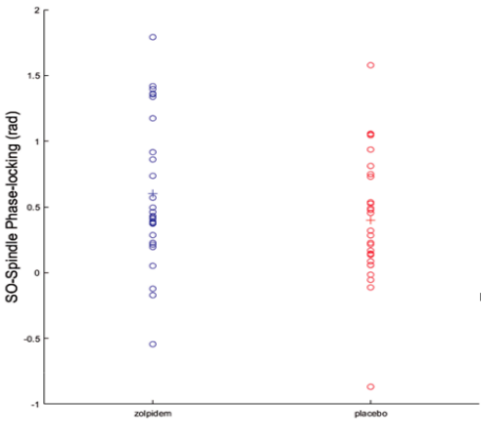

Figure 3-5 The phase angle of SO–spindle coupling for placebo and zolpidem. Individual phase angle is marked in circles while the average value for each condition is marked by a plus sign.

- *Correlations between EEG activity and memory performance*

The correlation between overnight retention and delta power change was significant in stage 2 quartile 2 using the cluster-based permutation analysis (p<42/2000). However, there was no significant correlation between delta power and performance at individual electrodes after Benjamini–Hochberg correction.

Slow wave activity

- *Electrode-based power spectrum estimation*

When each electrode was considered separately, changes in SWA did not survive Benjamini-Hochberg correction.

- *Cluster-based permutation for power spectrum estimation*

No drug effect was detected for SWA.

- *Correlations between EEG activity and memory performance*

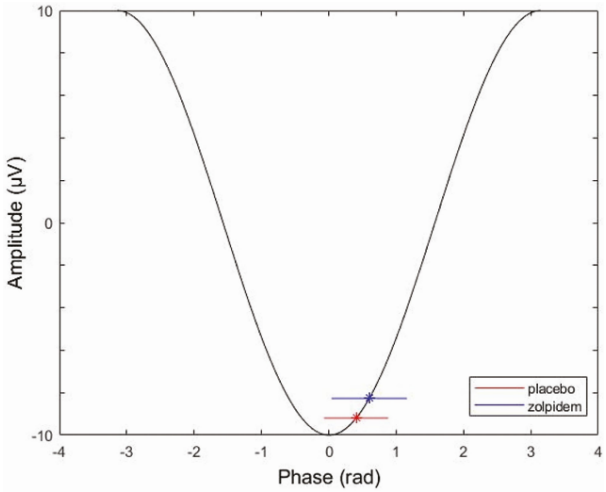

Figure 3-6 Mean and standard deviation of SO–spindle coupling phase angle for zolpidem and placebo on a schematic SO.

No correlation was detected between SWA and performance by cluster-based permutation or individual electrode analysis after Benjamini–Hochberg correction.

Spindle-SO coupling

Similar to Niknazar et al. (2015), we found significantly higher phase angle measures for zolpidem (0.60 ± 0.56) compared to placebo (0.40 ± 0.48) at F4 ($t27 = -2.18$, $p = 0.04$), but not at F3 ($p > 0.05$) (Figure 6). Higher phase angle measures indicate the spindles were clustered in the up-state of the SO phase closer to the positive peak (Figure 7). Furthermore, a positive relationship was observed between phase angle and memory performance in zolpidem ($r = 0.46$, $p = 0.01$) but not placebo ($r = 0.11$, $p > 0.50$) at F4, as shown in Figure 8. These findings are similar to Niknazar et al., which showed spindles clustered in the up-state closer to the positive peak of the SO in the zolpidem condition com-pared to placebo, as well as the significant correlation between phase angle and memory in the zolpidem condition and only marginal correlation in placebo. A higher positive phase angle and the positive correlation between phase values and memory performance in zolpidem suggest that spindles occurring during the up-state of the SO and closer to the positive peak may be optimal as this phase-locking was associated with better memory enhancement. There was no difference in MI between zolpidem and placebo for F3 or F4 ($p > 0.05$), nor was there a correlation between MI and memory improvement.

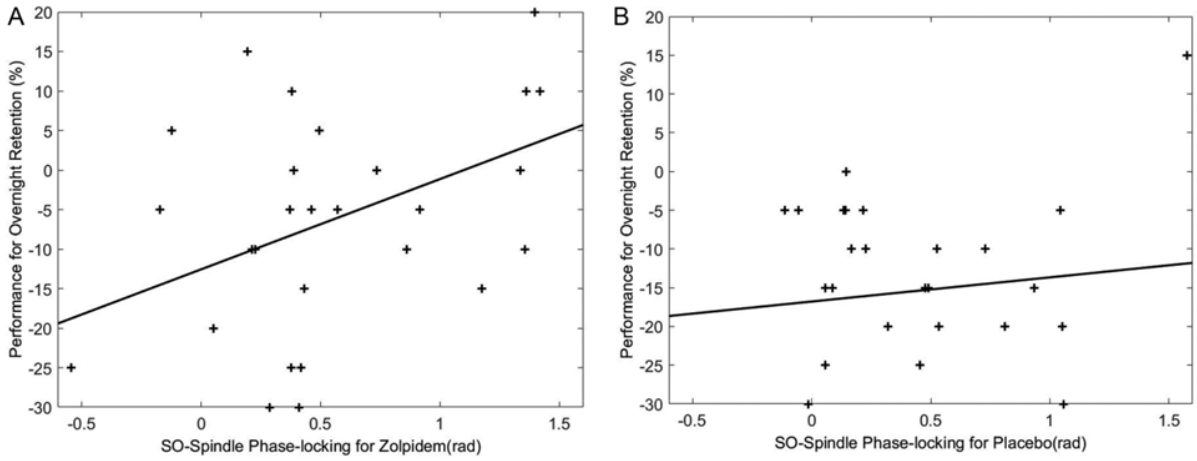

Figure 3-7 Memory performance improvement and SO–spindle coupling: phase angle and memory performance are positively associated in zolpidem (r = 0.46, p = 0.01) but not placebo (r = 0.11, p > 0.50) at F4.

Discussion

The current study showed that zolpidem led to higher memory retention after a night of sleep compared to placebo, which adds valuable information regarding the effect of zolpidem on memory. Zolpidem also led to increased sigma power and decreased theta and delta power. Overnight retention in the zolpidem condition was associated with increased spindle density, replicating prior work (Mednick et al., 2013), and theta power, a novel finding. Studies investigating the effect of hypnotics on sleep-dependent memory consolidation have shown mixed results. While our group report a positive effect of zolpidem on declarative memory consolidation here and in a prior study (Mednick et al., 2013), others have observed no effect (Meléndez et al., 2005) or even a negative effect (Hall-Porter et al., 2014). Conflicting findings may be due to methodological differences between studies. Specifically, Hall-Porter et al. (2014) used the extended-release version of zolpidem with 6–8 h of action and found decreased memory performance after drug administration, while zolpidem used in our study has a half-life of approximately 1.5–3.2 h. Meléndez et al. (2005) used the same version and dosage of zolpidem as our study and found no memory differences between zolpidem and the control condition. However, they investigated item-memory while we probed associative memory, which has been shown to engage the hippocampus to a greater extent (Davachi & Wagner, 2002). The current study builds on this literature by showing that zolpidem administered over a full night of sleep enhances associative memory, replicating a prior result using 90-min daytime naps (Mednick et al., 2013).

The positive correlation between theta power and memory performance suggests that even though zolpidem leads to a decrease in theta power globally, participants who had the least reduction in theta tended to have a better memory retention. Even though we did not find significant increases in spindle density in the zolpidem condition compared to placebo, this relationship has been consistently shown in previous studies (Dijk et al., 2010; Mednick et al., 2013; M. Niknazar et al., 2015). Discrepancies between prior results and the current data may be due in part to algorithm-based spindle detection used here while prior studies used visual inspection to hand count spindles (Lacourse et al., n.d.; Warby et al., 2014). A positive association between spindle density and memory improvement is consistent with previous findings, adding more support to the theory that sleep spindles are critical for memory consolidation (Latchoumane et al., 2017b). Even though we did not find a correlation between SO and memory improvement, the coupling of SO and spindles was associated with memory, which is consistent with prior literature (Clemens et al., 2011; M. Niknazar et al., 2015).

Current models of sleep-dependent memory consolidation may help clarify the role of spindles and spindle–SO coupling in this process. One of predominate views of long-term memory consolidation is the active system consolidation theory, which indicates that memories are consolidated during sleep by reactivating memory traces associated with learning and re-distributing them in the neocortex (Rasch & Born, 2008). The three oscillations that are hallmarks of memory reactivation include sharp wave ripples, spindles, and SOs (Mölle et al., 2009; Paller & Voss, 2004). Sharp wave ripples have been found to be nested into the troughs of faster spindle oscillations (Clemens et al., 2011; Staresina et al.,

2015)), and spindles occur to a great extent in the upstate of the SO (Latchoumane et al., 2017b; Mölle et al., 2011; Ngo et al., 2013), emphasizing the interdependent role of these three oscillations in relaying information from hippocampus to neocortex (Latchoumane et al., 2017b). Indeed, the simultaneous occurrence of all three oscillations naturally or by experimental intervention leads to great memory consolidation, compared with the features occurring out of phase with one another (Latchoumane et al., 2017b). In addition to facilitating the thalamo-cortical communication (Rasch & Born, 2008), spindles have been shown to induce long-term potentiation (LTP), which a key process in long-term memory consolidation (Rosanova & Ulrich, 2005; Ulrich, 2016). Interestingly, LTP could only be in induced by synchronous pre- and postsynaptic spindles but not asynchronous spindles (Rosanova & Ulrich, 2005), suggesting the timing between spindles and occurrence of pre- and postsynaptic events is crucial for memory consolidation (Ulrich, 2016). Similar results have been shown in humans where memory improvement was observed when auditory stimuli were applied in phase but not out phase with SO and spindles (Ngo et al., 2013), and both Niknazar et al. (2015) and the current study showed hippocampus-dependent memory improvement is associated with the coupling of SO and spindles during the up-state of the SO. It has been proposed that the up-state of neocortical SOs leads to depolarization and provides an opportunity for reactivation (Diekelmann & Born, 2010b). In short, the positive association between spindle density, spindle-SO coupling, and declarative memory improvement supports the notion that sleep benefits hippocampus-dependent memory by transferring the information from hippocampus to neocortex as well as inducing synaptic plasticity.

The inhibitory effect of zolpidem on theta power has been previously reported (Dijk et al., 2010; Landolt et al., 2000; Lundahl et al., 2012), and such an effect has been suggested to result from binding to GABA receptors (Kopp et al., 2004). Specifically, mice with insensitive alpha1GABAA receptors and controls both had decreased sleep-latency after taking zolpidem, but only the wild type and not the mutants showed significant power reduction encompassing a broad power band >5Hz, which suggests that alpha1GABAA receptor is responsible for decreased EEG power while the other two are responsible for promoting sleep (Kopp et al., 2004). The current study showed that theta power was positively associated with memory improvement, suggesting that engineering zolpidem to preserve theta could potentially create an optimal environment for memory consolidation. Prior studies indicate candidate mechanisms by which theta preservation might be achieved. For example, histaminergic neurons in the hypothalamus are known to promote wakefulness, and increased GABA activity in these areas promotes sleep (Sherin et al., 1998). Increasing GABA activity only on histamine neurons using zolpidem promoted sleep in mice without reducing EEG power (Uygun et al., 2016). Specifically, zolpidem-insensitive mice were genetically manipulated to be selectively sensitive to zolpidem in histaminergic neurons in the tuberomammillary nucleus of the hypothalamus, and they experienced the sleep promoting effect of zolpidem without having reduced EEG power (Uygun et al., 2016). Further pharmacological research may be useful in optimizing the memory-enhancing effects of sleep.

Theta oscillation during wakefulness is essential for episodic memory consolidation (Klimesch et al., 1994; Nyhus & Curran, 2010) and has been proposed to integrate

information between hippocampus and neocortex (Lega et al., 2012). Specifically, theta oscillation tend to occur in close temporal proximity to synaptic and neuronal changes after memory encoding (Buzsáki, 2002), signaling its role in memory consolidation. Specifically, animal studies show that theta peaks signal the depolarization phase of the cell membrane, which leads to increased neuron reactivity to inputs (Buzsáki, 2002; Fox et al., 1986) and facilitates the induction of LTP during wakefulness (Klimesch, 1999). Such a neural firing pattern is replayed during REM sleep (Poe, Nitz, McNaughton, & Barnes, 2000), supporting theta's role in memory consolidation during sleep. Specifically, Poe and colleagues (2000) found that hippocampal cells that were active when animals were in novel places tended to fire during theta peaks in REM sleep, whereas cells that were associated with familiar places tended to fire during the trough of the theta oscillation. Therefore, theta oscillation is implicated in memory consolidation through neural replay during REM sleep (Poe, 2017). Although the theta that can be measured via scalp EEG in humans is unlikely the same as the hippocampal theta measured in rodents, human memory studies have shown a relation between theta EEG and emotional memory consolidation during REM sleep (Hutchison & Rathore, 2015; Nishida et al., 2009). Our study suggests that theta oscillation during NREM might also play a role in hippocampal-dependent memory consolidation by showing a positive correlation between theta power and memory improvement.

The current study has limitations. Even though our discussion on GABA receptor subtypes provides a plausible mechanism and intervention to increase spindles while preserving theta pharmacologically, alternative explanations about how decreased theta contribute to memory retention are possible. For example, it might be the case that as the number of spindles increased, theta power decreased as a simple side effect of the fact that a greater portion of each 30s epoch was taken up by sigma frequency activity. In this scenario, participants with "preserved" theta might be those for whom sigma power increased as a result of an increase in the amplitude of spindles, rather than the number or duration of spindles. Here, we showed that spindle density, but not sigma power, is positively correlated with memory, suggesting that the number of spindles contribute to memory, which weakens the possibility that spindle amplitude contributes to memory. However, a specific investigation of how theta and sigma independently and collectively contribute to memory is warranted. Other limitations include small sample size and that the dosage is not based on mg/kg. Factors like sex and BMI could influence the metabolism of zolpidem, which would increase the individual variability of the drug effect (Greenblatt et al., 2014). In addition, we were not able to tease apart the specific and potentially independent roles that theta and spindles may play in memory consolidation. Recent findings by Kim et al. (Kim et al., 2019) have demonstrated that SO and delta activity may support different and even opposing aspects of the memory process. It would be interesting to investigate how theta and spindles may contribute to different aspects of the memory process using a more complex memory task. For example, a memory task that distinguishes sensory rich content from non-sensory content to investigate the possibility that theta during NREM preferentially enhances sensory rich information (Fuentemilla et al., 2014; Karakaş et al., 2007).

Taken together, this study demonstrates a positive role of zolpidem on overnight memory performance and highlights a role for spindle density and theta frequency power in these performance improvements. Furthermore, it provides additional support for the

critical role of sleep spindles as well as the coupling between SO and spindles in memory consolidation. Future studies are needed to tease apart mechanisms behind the role of NREM theta power and spindle–SO coupling on memory consolidation.

CHAPTER 4 Slow Oscillations Modulate Neural Correlates of Working Memory Efficiency

Abstract

Working memory (WM) is a cognitive process that temporarily stores and manipulates information to achieve a goal. Sleep, specifically slow oscillations (<1Hz) during slow wave sleep, has been shown to benefit overnight WM improvement. However, the neural mechanisms underlying sleep's benefit on WM function remain unknown, which is the goal of the current study.

Participants performed a WM task in the fMRI scanner before and after sleep, and the first part of their sleep was monitored by simultaneous EEG-fMRI. We examined WM-related activation during the task and how it changed over sleep. To explore how SOs influence WM-related activation, we looked at correlations between activations in WM-related regions overnight change and during SO compared to non-SO NREM sleep.

We found that overnight sleep is linked to an increase in neural efficiency related to WM, as evidenced by a decrease in the recruitment of the precuneus during the WM task. Furthermore, SOs modulated the WM-related areas. There was increased connectivity between the precuneus and frontal as well as occipital areas, and decreased connectivity with other parts of the precuneus and lateral occipital area during OSPAN versus math overnight. During SO versus non-SO NREM sleep, there was decreased connectivity between the precuneus and frontal area. We also discovered a negative correlation between SO-induced WM activation and overnight WM activation changes in task-related areas that are specific to our dataset and the Ventral Attention Network.

Overall, our findings provide important insights into the neural mechanism of WM over a night of sleep. Our study is the first to demonstrate the direct role of SOs in functional changes in the brain associated with WM.

Introduction

Working memory (WM) is a critical aspect of cognition that allows individuals to temporarily store and manipulate information to achieve a goal. Baddeley and Hitch proposed the modular WM model, which suggest that there are three components involved in the WM process: the phonological loop (or the verbal working memory), visuospatial sketchpad (the visual-spatial working memory), and the central executive which involves the attentional control system (Baddeley and Hitch, 1974; Baddeley, 2000b). Within these subcomponents, WM supports a wide range of cognitive functions that are fundamental to many everyday tasks, such as decision-making, problem-solving, and language comprehension (Baddeley, 1992; Conway et al., 2002; Engle et al., 1999). Due to its importance, understanding the neural processes that support WM has been a focus for decades of work in the field. Previous research has shown that WM engages a distributed network of brain regions, including the prefrontal cortex and parietal cortex (Chai et al., 2018; Cohen et al., 1994; D'Esposito et al., 2000; Diwadkar et al., 2000; Levy & Goldman-

Rakic, 2000). Moreover, WM function depends on the successful allocation of attention both to the external environment as well as to internally maintained information, and studies have shown the involvement of two distinct attention networks when performing WM tasks: the dorsal attention network, comprised of the intraparietal sulcus (IPS) and the superior frontal gyrus (SFG), and the ventral attention network, involving the temporoparietal junction (TPJ), inferior frontal gyrus, the anterior insula, and the dorsal cingulate cortex (Corbetta et al., 2008; Majerus et al., 2006, 2012). The dorsal attention network is associated with top-down task-focused attention and WM load (Majerus et al., 2018). The ventral attention network is thought to govern the bottom-up attention, typically engaged by stimuli that are novel, salient, or unexpected, and are not the primary focus of the current task (Asplund et al., 2010; Cabeza et al., 2012; Zhao et al., 2022).

Despite the significance of WM in our everyday functioning, it is prone to age-related decline. This decline is evident in the normal aging process and is particularly pronounced in adults older than 75 years old (Hale et al., 2011). Therefore, cognitive training to improve WM function has become a focus in this field. The hope is that by improving working memory, other cognitive functions will also improve, which could mitigate cognitive aging. Studies on WM training have challenged the traditional notion that WM capacity is a fixed trait, by demonstrating that working memory capacity can be enhanced through training and is subject to plastic changes (Au et al., 2015; Jaeggi et al., 2008; Karbach & Verhaeghen, 2014). Specifically, Jaeggi and colleagues trained participants on a WM task for multiple days, and they found the extent of WM improvement is positively correlated with the number of train sessions. They also reported improved fluid intelligence as a result of WM training (Jaeggi et al., 2008). WM-training induced changes in brain activity include increased activation in the prefrontal (Miller et al., 2022) and parietal regions (Olesen et al., 2004), and decreased functional connectivity within the striatum-prefrontal network (Lin et al., 2017), which might suggest increased neural efficiency after WM training.

The WM training literature typically employs a multi-day training paradigm, which highlights the importance of offline processing as it allows time for sleep. Indeed, several studies have demonstrated that a period of sleep, compared to wake, between WM sessions can enhance subsequent WM performance(Zinke et. al., 2018; Kuriyama et al. 2008; Lau et al. 2015; Chen et al., 2020). In these studies, training adult participants on a WM task over several sessions improved accuracy of performance, but only if the interval between training sessions contained nocturnal sleep (Zinke et al., 2018; Kuriyama et al., 2008) or nap (Lau et al., 2015), compared to daytime wakefulness. It is also evident that sufficient sleep duration and quality play a functional role in WM performance. For example, sleep deprivation or restriction leads to a profound impairment in sustained attention and deficits in executive function (Goel et al., 2009; Lo et al., 2012). Sleep deprivation has been shown to negatively impact performance on WM-related tasks, such as digit span (Quigley et al., 2000) and N-back tasks (Choo et al., 2005). These effects are likely driven, in part, by altered functioning of frontal and parietal networks (Chee & Choo, 2004). Although studies have repeatedly demonstrated that a sleep-deprived brain, compared with a well-rested one, performs worse on WM tasks (Lo et al., 2012), the neural mechanisms underlying sleep's benefit on WM function still remains unknown.

Several studies have reported a specific role of slow wave sleep (SWS) in cognitive processing during task, partly because it has been linked to synaptic plasticity and cortical reorganization (Tononi and Cirelli, 2003; Takashima et al., 2006; Dang-Vu et al., 2010). For example, researchers demonstrated that digit span backward performance improvement following nocturnal sleep was positively correlated with SWS duration between training sessions (Scullin et al., 2012). Interestingly, SWS is markedly reduced with increasing age as well as in younger adults with dementia relative to the healthy population (Mander et al., 2013). As Scullin et al (2012) linked WM improvements to relatively preserved SWS in neurodegenerative conditions, this suggests that age-related SWS reductions might explain why WM training is usually less effective in older compared to younger adults.

Slow wave activity (SWA) has been shown to play a role in memory benefits of SWS. SWA refers to the slow, high-amplitude waves (<4Hz) that are observed in the electroencephalogram (EEG) during SWS. These waves reflect the synchronized firing of large populations of neurons in the brain (Cirelli, 2017; Maquet et al., 1997). Increases in SWA in prefrontal areas after three weeks of WM training correlated with WM performance improvement (Pugin et al., 2015). Furthermore, SWA predicted WM gains across a period of sleep in both young (Ferrarelli et al., 2019a) and older adults (Sattari et al., 2019). Importantly, a potential causal role of SWA in WM improvement has been shown in one recent study. Participants with greater SWA induced by an acoustic slow-wave stimulation during nighttime sleep showed better WM improvement, compared to individuals who did not show enhanced SWA (Diep et al., 2020).

A recent study has further pinpointed the WM benefit of sleep to slow oscillations (SO, <1Hz), which reflect fluctuations of the membrane potential and orchestrate transitions from neuronal silence (hyperpolarized downstates) to neuronal excitation (depolarized upstates) (Mölle & Born, 2011; Niethard et al., 2018). Slow oscillations refer to the oscillations that are less than 1Hz, while SWA includes delta frequency (1-4Hz). Specifically, this study showed SOs coupled with autonomic events positively correlate with WM improvement overnight (Chen et al., 2021a). The increased long-range causal communications across brain areas during SOs in the midst of broadly reduced communication during the rest of SWS might provide neural basis for SOs-related memory benefits (H. Niknazar et al., 2022). Furthermore, ventromedial prefrontal cortex, which is implicated in WM (Mukahirwa et al., 2021; Yin et al., 2021), has been shown to regulate SOs (Dang-Vu et al., 2010).

Taken together, these studies support the role of sleep, specifically SOs during SWS, in WM performance. The next logical question is to explore how SOs modulate functional changes in the brain to facilitate memory processing. One potential hypothesis is that sleep, specifically SO, increases neural efficiency during WM. In other words, we hypothesize that during SOs, WM-related regions show increased activation and increased connectivity compared to NREM periods without SOs, leading to fewer resources needed during subsequent WM task after sleep and improved performance.

This study aims to investigate the role of SOs in WM improvement by measuring how WM-related brain activity changes over a night of sleep (as a proxy for neural efficiency) and relating them to neural processing during SOs. We examine WM using the

operational span task (OSPAN), which measures the individual's ability to maintain a set of items in their WM while performing a secondary task, such as doing simple math equations. In the evening, participants performed the OSPAN task in the fMRI scanner and then fell asleep while their brain activity was recorded using simultaneous EEG-fMRI. In the morning, participants were retested on the OSPAN task in the scanner. To increase the robustness of our data, each participant performed two sessions, with a 2-week washout period between sessions. Our analysis took two approaches, a data-driven analysis that examined how the brain activity associated with task performance changed across the night; and *a priori* network-targeted approach that focused on the Ventral Attention Network, to see how activity in this network was associated with SO brain activity. Specifically, we examine the correlation between overnight change in WM activity to activity during SOs. To our knowledge, this is the first study to examine how functional changes time-locked to SOs contribute to neural processing during WM (e.g. overnight changes in WM activity) using simultaneous EEG-fMRI. By addressing these questions, we hope to gain a deeper understanding of the neural mechanisms underlying WM and the role of sleep in shaping WM function.

Methods

Participants

The study complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and was approved by the University of California, Irvine, IRB committee (HS# 2020-5912). Sixty healthy females (18-40y) signed informed consents. Sixteen participants dropped out before the first experimental visit. Ten participants were excluded during or after the first experimental visit due to inability to sleep in the scanner. In total, 34 participants completed the entire study protocol consisting of two overnight visits. All participants gave written informed consent prior to participation. Participants had no current or past history of major psychological or medical conditions or sleep disorders, and additionally were not taking any medications (e.g., hypnotics) that would affect cognitive function or sleep. All participants included in the study reported consistent sleep habits in advance of the study, and reported sleep times before 1 am and wake times before 10 am. Participants completed the Morningness-Eveningness Questionnaire (Horne & Östberg, 1976) and Epworth Sleepiness Scale (ESS) as screening assessments. with an acceptable range between 6-21 for Morningness-Eveningness Questionnaire and <15 for ESS.

Procedure

All participants completed an orientation session to give consent and practice the OSPAN task, which occurred on a day prior to the experimental visits. During the practice session, participants practiced the OSPAN task by viewing it on a computer monitor and responding as they would with the response keypads in the MRI unit. After task practice, participants spent 15 minutes in a mock scanner to get familiarized with sleeping in the

scanner. On each experimental visit, the participant arrived at 8 PM to undergo the T1 structural scan. Participants then performed the OSPAN task, followed by a paired associate learning task (unrelated to the OSPAN task and beyond the scope of the current paper), while fMRI scanning was performed. Following the behavioral tasks and bedtime preparation, participants had the EEG cap placed on their heads. At around 11 pm, participants had a 2.5h sleep opportunity with continuous EEG-fMRI recording. Participants were provided with earplugs (~33 dB sound attenuation), comfortably bedded on a viscoelastic mattress, and covered with a light blanket. The lights were turned off and subjects were equipped with an alarm bell to alert the experimenter and terminate the scan at any time. After awakening, subjects spent the remaining night in the adjacent sleep laboratory, during which their sleep was monitored using OURA ring. Participants were woken up around 7:30 AM the next morning and returned to the scanner around 8 AM to perform the OSPAN task.

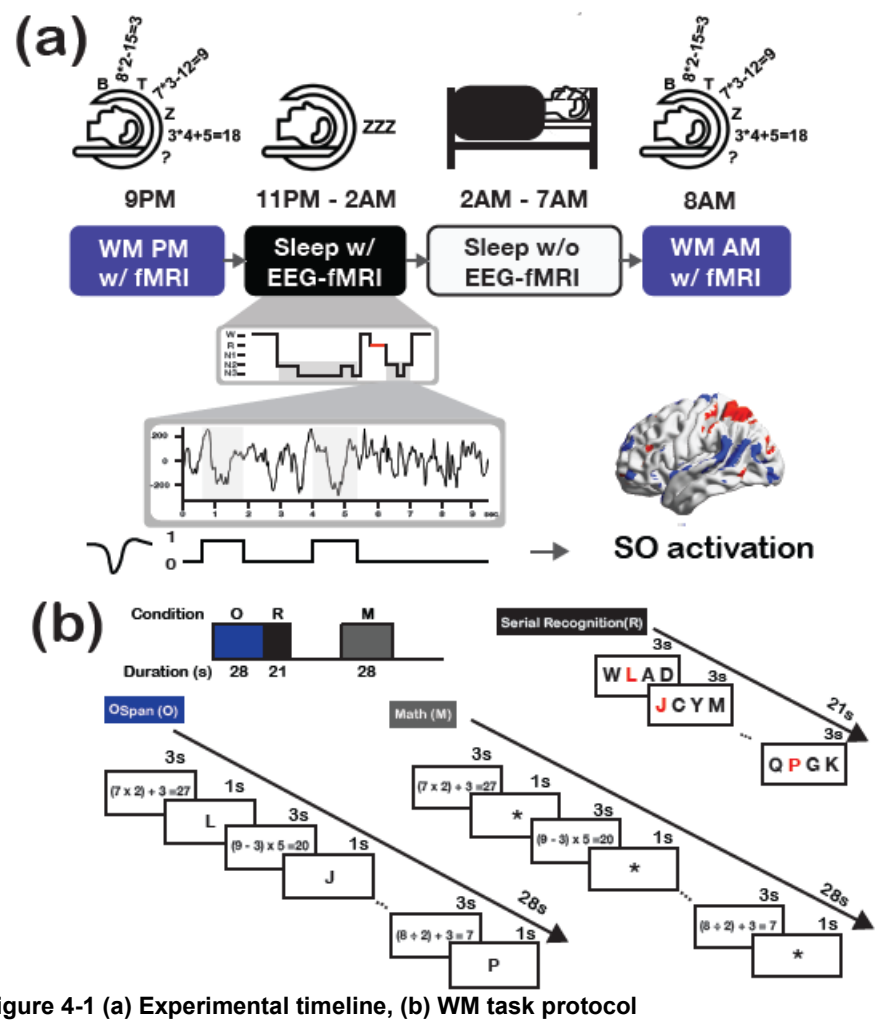

Figure 4-1 (a) Experimental timeline, (b) WM task protocol

Task and stimuli

The task was programmed using MATLAB UI Figure; stimuli were displayed using a BOLDScreen32 LCD monitor (1920×1080 pixels with a 120Hz framerate). Responses and reaction times (RT) were recorded using MR compatible response keypads. Participants performed the OSPAN task in a similar fashion to Faraco et al. (2011). Each run consists of fixed alternating conditions of OSPAN (O), Math (M), and Baseline, each lasting 28s. The OSPAN epochs were always followed by 21 s Serial Recognition (R) epochs, in which participants identified the letter and the serial order in which it was presented from seven arrays of 4 letters in a multiple-choice

response manner. Each run contained a total of 17 epochs: 4 OSPAN + 4 Serial Recognition + 3 Math + 6 Baseline. Within each epoch, this sequence of stimuli repeated 7 times. Participants performed 2 runs back-to-back during each session. During the Math condition, participants judged if a math equation was correct. An asterisk was shown in between the equations. During the OSPAN condition, participants also judged if equations were correct, but instead of showing an asterisk between equations, they were presented with a letter to remember in serial order. The Baseline condition requires participants to indicate if an arrow was pointing to left or right. Presentation of arrows alternated with the presentation of asterisks to make sure participants were paying attention. The Baseline condition was not included in further analyses.

WM Task Behavioral Analysis

We calculated performance as: number of correct letters recognized in the correct order divided by total number of letters in the string, which is 7; therefore, the maximum score is one. WM performance was evaluated by averaging all the trials across both runs for each session and each participant. Performance change between AM and PM tests (overnight change) was calculated for each visit to examine the overnight sleep effect. A paired t-test was conducted between the 2 visits for overnight change to measure a visit effect. Then, performance between 2 visits was averaged together, and a paired t-test was conducted between AM and PM sessions to assess a sleep effect.

MRI Acquisition

Participants were scanned at the Facility for Imaging and Brain Research at the University of California, Irvine on a 3 T Siemens Prisma MRI scanner (Siemens Medical Solutions), with a 32-channel head coil. High-resolution T1-weighted anatomical images were obtained using a standard MPRAGE sequence (TR = 2300ms, TE = 2 ms, flip angle = 8°, sagittal slices, 0.8 × 0.8 × 0.8 mm voxel size, field of view = 256 × 256 mm). Blood Oxygen Level Dependent (BOLD) functional scans (T2*-weighted) were acquired using an echo planar imaging (EPI) sequence (TR = 2240 ms, TE = 30 ms, flip angle = 90°, FOV = 216 × 216 mm, 40 transversal slices, slice thickness = 3 mm, dist factor = 10%, 3.4 × 3.4 × 3 mm voxel size, continuous bottom-up slice acquisition order). These parameters were chosen to ensure that residual gradient artifacts (in the slice repetition rate of ~ 17 Hz) did not compromise the sleep spindle frequency. Each run of the OSPAN task consisted of 216 volumes and 4 dummy samples were discarded during the initial acquisition due to equilibrium effects.

fMRI Preprocessing

EPI volumes were slice-time corrected, co-registered, realigned, and transformed to Montreal Neurological Institute (MNI) space using fMRIPrep 1.4.0, with several confounding time-series calculated (see supplemental methods for more details; https://github.com/nipreps/fmriprep). The fMRI data were then additionally preprocessed and analyzed using statistical parametric mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil. ion.ucl.ac.uk/) running on MATLAB

(MathWorks, Natick, Massachusetts, USA). Functional data were smoothed using a 5 mm full-width at half-maximum Gaussian smoothing kernel ('spm_smooth' function).

EEG Acquisition

EEG was acquired with an MR-compatible 12-channel EEG cap (BrainCap MR, Easy-Cap, Munich, Germany) according to the 10– 20 system (F3, F4, C3, C4, O1, O2, M1, M2). Skin resistance was kept below 5 kΩ (plus 5 kΩ safety resistors) using Abralyt HiCl electrode paste (Easycap) to ensure stable EEG recordings during the 2.5 hr sleep opportunity. Bipolar recordings of electrooculogram (outer canthi), electromyogram (chin), and electrocardiogram (on the backbone, ~ 25 cm below and above the heart) were acquired via MR-compatible Ag–AgCl cup electrodes with 10 kΩ safety resistors (EasyCap). FCz was used as the reference electrode and Cz was used as the ground electrode. The data were recorded using BrainAmp MR plus DC and bipolar BrainAmp ExG MR amplifiers and the BrainVision Recorder (BrainProducts, Munich, Germany) with a resolution of 0.5 μV/bit at 5 kHz and filtered between 0.016 and 250 Hz. To reduce the gradient artifact and ensure precise timing between EEG and fMRI data, we used the SyncBox (Brain Products, Munich, Germany), which synchronizes the clock of the BrainAmp MR amplifier with the clock driving the MRI scanner's gradient switching system.

EEG Preprocessing

Online MRI gradient and ballistocardiographic artifact correction (BrainVision RecView V.1.2; BrainProducts) allowed online sleep monitoring. Removal of these artifacts for subsequent analyses was performed offline by adaptive template subtraction (Allen et al., 1998, Allen et al., 2000) using windows of 100 volumes and 50 pulses, respectively (BrainVision Analyzer V. 2.0; BrainProducts). EEG data were re-referenced to contralateral mastoids (M1 and M2) and sleep stages were visually scored in 30-second epochs by one of the authors, according to standard AASM criteria. To ensure the NREM sleep analyzed further were continuous stable NREM without transitions, epochs with movements or arousal were scored as 'motion artifacts' instead of N2 or N3.

Slow Oscillations (SO) Detection

SO events individually detected in the EEG data were used as predictors in event-related fMRI analyses to assess fMRI activation during individual SO events (similar to Ilhan-Bayrakcı et al. 2022). SO troughs were detected for each channel automatically on MATLAB using the algorithm introduced by Dang-Vu et al., 2008 (Also used in Niknazar et al., 2022 PNAS and Chen et al. 2021 PNAS). EEG data were first band pass filtered with SO frequency range 0.7-1.4Hz using a Hamming windowed FIR filter. Hilbert filter were then applied to find phase and amplitude of the SO. Troughs (down-states) were detected when phase difference > 6. The up-states before and after each trough were then detected within 1.5 seconds window before and after the troughs. SO events were defined as the pre-trough up-states of SOs (event onset) through the post-trough up-states of SOs (defined as event offset) (Massimini et al., 2004; Mölle & Born, 2011; Zhang et al., 2020).

fMRI Analysis

General Linear Models (GLMs) were used to assess fMRI activation and functional connectivity. First-level analyses (Model specification and estimation) were performed using SPM12. Scans were corrected for low-frequency trends in the GLM (high-pass filter with cut-off period = 111.111 seconds). Motion scans were checked using framewise displacement from fMRIprep's 6 motion parameters (translation x y z; rotation x y z). Volumes with excessive framewise displacement (FD > 0.5mm) were accounted for by including nuisance regressors for each time point surrounding motion events (one TR before through to two TRs after FD > 0.5mm) (Power et al., 2015). Runs with excessive motion were not included in further analysis (% of excluded volumes greater than 2 standard deviations from the mean across all OSPAN task runs). Nuisance regressors were included as covariates in all GLMs (outputs from fMRIPrep): high motion volumes, 6 motion parameters (translation x y z; rotation x y z), the 1st derivative of the 6 motion parameters, and the top 8 anatomical CompCor (WM, CSF) components (Behzadi et al., 2007).

WM-related BOLD Activation

Task regressors were created for each OSPAN, Math and Baseline block for a total of 3 regressors (Math – Baseline, OSPAN- Baseline, Math – OSPAN). All of the 3 blocks have the same duration (28s), and onset times were calculated in 28s increments as the blocks alternate. To assess WM-related fMRI activation, e contrasted the OSPAN block with the Math block. The OSPAN vs Math contrast yielded regions likely associated with the high degree of cognitive control required during working memory tasks and the storage and retrieval of information. To assess WM-related activation regardless of the time of day (Figure 2a), OSPAN vs Math contrast beta maps were averaged across all 4 sessions (PM and AM sessions X 2 experimental visits) within each participant. To characterize pre vs post sleep working memory activations (Figure 2b), pre-sleep and post-sleep session beta maps across two visits were averaged within each participant, yielding an AM average and PM average. Sleep-dependent OSPAN changes (AM vs PM) were calculated using AM average – PM average within each participant.

The beta maps of task activation (average across all sessions, or pre vs. post sleep changes) were used for group level analysis using a one sample t-test. Family-wise error (FWE) correction was performed using Randomise (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/) with TFCE (threshold-free-cluster enhancement) methods and 50,000 permutations. Results are shown at the $p < 0.05$ level (FWE-corrected). The cerebellum was excluded in all analyses. We then defined data-driven WM areas as the regions showing significantly greater OSPAN vs Math activation from the whole-brain group level analysis (Figure 2a positive clusters). We next asked whether regions engaged during WM showed overnight changes in activation by testing the AM vs PM comparison within the data-driven WM areas. We then further probed areas (Precuneus) showing significant AM vs PM activation changes (Figure 2c) by assessing the functional connectivity during the OSPAN task and during SOs (using them as a seed region for Psychophysiological Interaction (PPI) analyses).

Sleep BOLD Activation

An event-related design was used to model brain activity associated with SO events vs non-SO NREM (N2+N3 sleep). Within each run of sleep scans, scans were corrected for low-frequency trends ('spm_filter' function; high-pass filter with cut-off period = 111.111 seconds). Next, to limit our analysis to stable NREM (N2+N3 sleep), artifact-free NREM epochs of duration > 100 TRs (224 seconds) were extracted and concatenated across runs (after low-frequency trends and the mean BOLD signal was removed). General Linear Models (GLMs) were performed upon the concatenated NREM data. SO event onsets were defined as the pre-trough up states of the slow oscillations, and event offsets were defined as the post-trough up states of the slow oscillations. A regressor was created to model activation related to SO events, based on these onsets and offsets. Nuisance regressors described above were included in these GLMs. The SO vs NREM contrast (Figure 4) yielded regions likely associated with the SO specific but not overall NREM processes.

Psychophysiological Interactions (PPI) analyses

To assess WM-related functional connectivity of regions showing overnight changes in thw OSPAN task, a PPI approach was used (implemented in SPM12). A GLM was built using the precuneus ROI as a seed region during the OSPAN task . The models included one regressor representing the task activation (OSPAN vs Math), one regressor representing the seed ROI time series, one regressor representing the PPI term (interaction between task and seed time series), and the covariates the same as the GLMs descripted above. Group-level one sample t-test was used on beta coefficient maps corresponding to the PPI term. As described above, FWE-correction was performed using randomise with TFCE (Figure 3a), to test where in the brain showed consistent PPI effects with the seed region. the same approach was applied to the NREM sleep data to assess changes in connectivity of the PPI seed during SO events. This was done by creating one regressor representing the SO events (SO vs NREM), one regressor representing the seed region, and one regressor representing the PPI term (Figure 3b).

Correlations between Overnight OSpan Changes and SO Activity

To assess whether changes in overnight WM activity may be related to neural processing during SOs, we examined correlations between these events using two distinct approaches. First, we asked whether variance in AM – PM OSPAN activity changes across individual sessions were related to variance in SO activation (Figure 5) on the voxel-wise level, using robust linear regression (the robustfit function in MATLAB) (Holland et al., 1977). Multiple comparisons were corrected using the Benjamini and Hochberg method with a false discovery rate $q < 0.05$. Next, significant clusters with > 5 voxels were extracted using FSL Cluster function. Figure 5 scatterplot illustrated the average contrasts across voxels in the significant clusters, with each data point indicate SO activation from one night and its corresponding AM – PM OSPAN activity changes across the night.

In addition to the data-driven approach mentioned above, we also used a network-driven approach to examine relationships between overnight changes in WM activity and

SO activity. The goal of this analysis to examine whether variance in overnight WM activation changes across brain regions is related to SO activation in those brain regions. To do so we focused on pre-defined attention networks. Specifically, we looked at the Ventral Attention Network, defined using the 7-network parcellation of the human cerebral cortex from Yeo et al. (2011), shown on Figure 6a. We first ensured that this network is engaged in our WM task by examining the OSPAN vs Math contrast using Ventral Attention Network as an ROI. Next, we computed the AM – PM change in activation (contrast value) and SO vs NREM activation (contrast value), averaged across participants, for each voxel in the Ventral Attention Network. After averaging across participants, we performed robust linear regression to assess the correlation between overnight WM activity changes and SO activation across voxels within the Ventral Attention Network (Figure 6c). Statistical significance of the observed correlation was assessed using a non-parametric permutation test. Specifically, we created a null distribution by shuffling the labels between the AM and PM sessions and re-computing the correlation (N = 1000 permutations). The p value of correlation in Figure 6c was computed by comparing the observed correlation values to the null distribution.

Results

Minutes	Mean(SD)
TIB	139.71(42.08)
TST	95.67(36.62)
SOL	11.34(12.73)
N1	10.64(12.79)
N2	46.15(22.59)
SWS	36.30(26.24)
REM	1.87(6.97)
WASO	16.42(23.99)
SE(%)	69.98(21.93)

Table 3 Sleep architecture during EEG-fMRI recording

Minutes	Mean(SD)
TIB	493.24(73.78)
TST	366.06(108.39)
Light	197.28(58.12)
Deep	140.01(46.07)
REM	74.33(132.95)
WASO	49.46(32.01)

Table 4 Sleep architecture throughout the night (in scanner + out of the scanner measured by OURA)

Sleep Architecture

On average, participants had 95.67 min (SD=36.62) total sleep time in the MRI scanner (Table 1). The average sleep latency was 11.34 min (SD=12.73). The average duration of N2 sleep was 46.15 min (SD=22.59) and 36.3 min (SD=26.24) for SWS. NREM sleep from 34 participants (67 nights) were included in the analyses (for individual sleep architecture, see Supplemental table 2).

Throughout the night, participants on average were in bed for 493.24 min (SD=73.78), with a total sleep time of 366.06 min (SD=108.39). OURA categorizes NREM sleep into Light and Deep sleep, which we combined with N2 and N3, respectively (table 2).

Behavioral Results

Performance on the OSPAN task was significantly better during AM test (0.74+-0.15) compared to PM test (0.77+-0.17) (t40=-2.12, p=0.04). When comparing the two visits, participants had lower accuracy at visit 1 (0.71+_0.16) compared to visit 2 (0.76+_0.17) at PM test (t33=-3.00, p=0.005). For AM test, the two visits (visit 1 0.76+_0.18, visit 2 0.77+_0.19) had similar performance (t33=-0.67, p=0.51). There was no significant difference between the two visits on the overnight performance change (t33 = 1.38, p=0.18). Average RTs for the math equations were 2121.73 ms (SD=364.99) for the OSPAN blocks and 2093.09ms (SD=383.22) for the math blocks, which were consistent with prior studies (Faraco et al., 2011; Kondo et al., 2004).

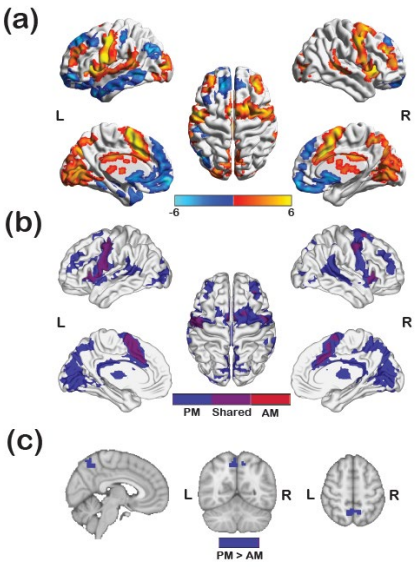

Figure 4-2 Task-related BOLD activation. (a) across all 4 sessions, (b) for PM and AM tests separately, and (c) change overnight

Working Memory-related Activation

To extract regions associated with WM (WM-related regions), we first examined the OSPAN vs Math contrast in the whole brain across all 4 sessions. During OSPAN compared to Math blocks, there was increased activation in several cortical and subcortical areas, including bilateral putamen, bilateral precentral, primary motor cortex, cingulate, bilateral caudate, bilateral insular, occipital area, and reduced activation in frontal and parietal areas, as well as subcortical regions including insular and precuneus (figure 2a, FWE corrected at $p<0.05$).

To assess whether WM-related activation may differ between PM and AM sessions, we first analyzed each session separately. At PM test, we found widespread activation during OSPAN vs math encompassing the frontal and parietal areas, including the frontal pole, inferior frontal gyrus, supplementary motor cortex, the precuneus, cingulate, insular, putamen, pallidum, caudate, intracalcarine cortex, and supramarginal gyrus (figure 2b, FWE corrected at $p<0.05$). During AM test, overall less

WM-related activation was present, including regions in the frontal area (supplementary motor cortex, inferior frontal gyrus), the precentral gyrus, and subcortical regions including cingulate, left pallidum, and left putamen (figure 2b, FWE corrected at $p<0.05$).

To determine whether WM activation changed with sleep, we assessed the change in OSPAN vs Math contrast between the AM test and PM test within regions engaged during OSPAN vs. Math blocks (shown in Fig 2a). The precuneus region (MNI: 29.5, 22.2, 40.4) showed a significant decrease in activation overnight (FWE corrected at p<0.05). The reduced recruitment of this area during WM task over a night of sleep may suggest there is increase WM efficiency. We, therefore, defined this significant cluster in the precuneus as our Sleep Seed for subsequent PPI analyses.

Functional connectivity between the Sleep Seed and working memory-related regions

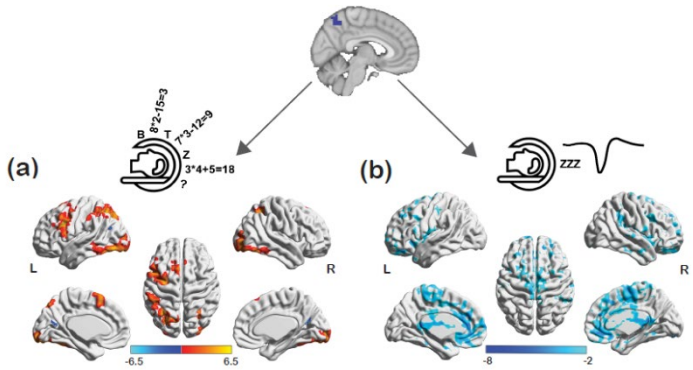

Figure 4-3 PPI between the precuneus and task-related regions during (a) the WM task and (b) NREM SOs.

To investigate how the overnight change in precuneus associated with WM-related areas, we examined connectivity between our Sleep Seed in the precuneus and other WM regions in the OSPAN vs Math contrast (figure 3a, FWE corrected at $p<0.05$). In the OSPAN vs Math contrast, we found increased connectivity between precuneus and the occipital and frontal areas, including fusiform gyrus, precentral gyrus, middle frontal area, and supplementary motor cortex, but decreased connectivity between the precuneus and bilateral precuneus and lateral occipital area (figure 3a, FWE corrected at $p<0.05$).

We also looked at the connectivity between our Sleep Seed and WM-related regions during SOs (the SO vs non-SO NREM contrast) to examine how SOs modulate WM-related regions (figure 3b, FWE corrected at $p<0.05$). In the SOs vs Non-SO NREM contrast (figure 3b), we saw decreased connectivity between the precuneus and frontal and parietal areas, while only the supplementary motor cortex survived multiple comparisons correction (FWE corrected at $p<0.05$), suggesting SO might play a role in reorganizing the WM network.

Working memory BOLD Activation during SO

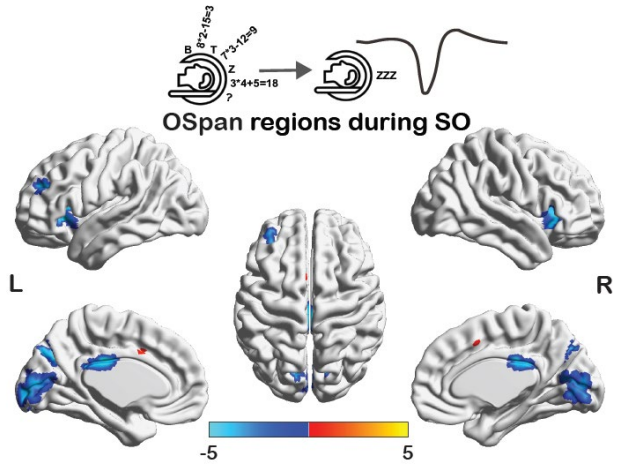

Figure 4-4 BOLD activation during individual SO events.

To better understand the relation between SO activation patterns and WM-related regions, we examined if these WM-regions were reactivated during SO events. We observed increased BOLD activation in WM-related subcortical regions during SO events compared to non-SO NREM. Specifically, there was an increased activation in the cingulate and right thalamus, and a decrease in activation in the insular, putamen, precuneus and intracalcarine cortex (figure 4, FWE corrected at $p<0.05$). These data suggest that WM-related regions are modulated during SOs, which begs the question of how task-related activations might be associated with the activations during SO.

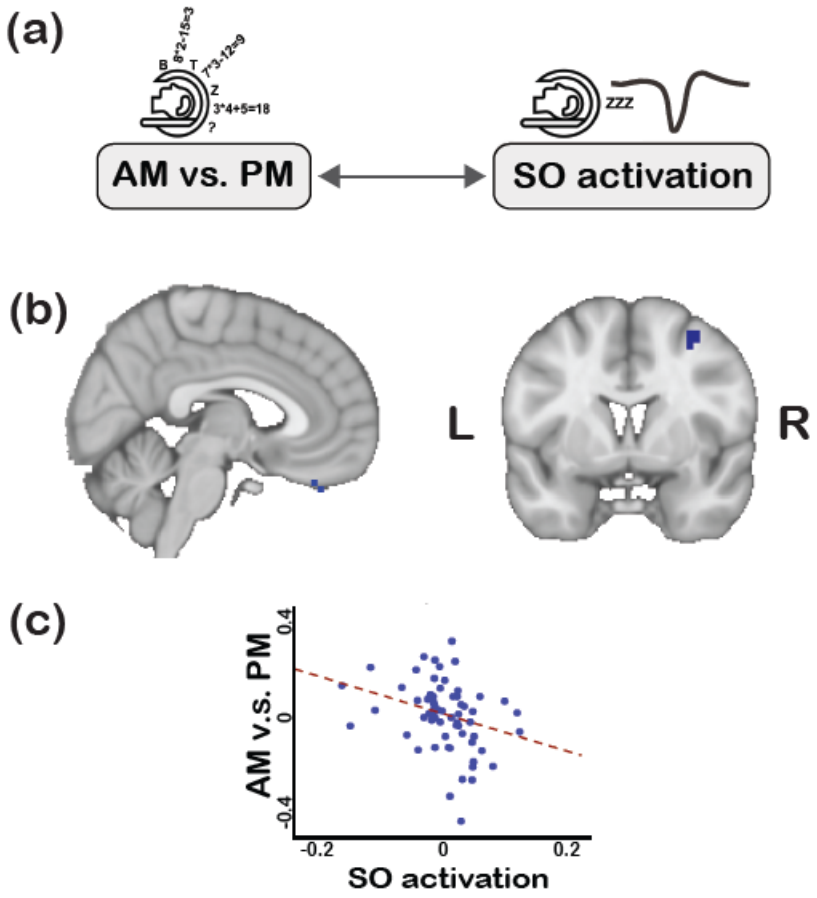

Figure 4-5 Correlation between activation during the WM task and SO.

Correlation between working memory and SO BOLD activation across sessions

To establish a link between SO-related and WM-related functional changes, we asked whether the variance in WM activation overnight changes across sessions was correlated with SO-related activity. We found a negative correlation between WM overnight changes (AM-PM) and activation during SOs compared to non-SO NREM in 2 clusters, the vmPFC and the premotor cortex (figure 5, FWE corrected at $p<0.05$, cluster >5 voxels). In other words, sessions with greater activity in these areas during SO had reduced activation during the task after a night of sleep, suggesting a role for SOs in increasing neural efficiency associated with WM improvement.

Correlation between working memory and SO BOLD activation across the Ventral Attention Network

The network-driven approach allows us to investigate the activity of pre-defined networks involved in WM; specifically, we looked at the ventral attention network (figure

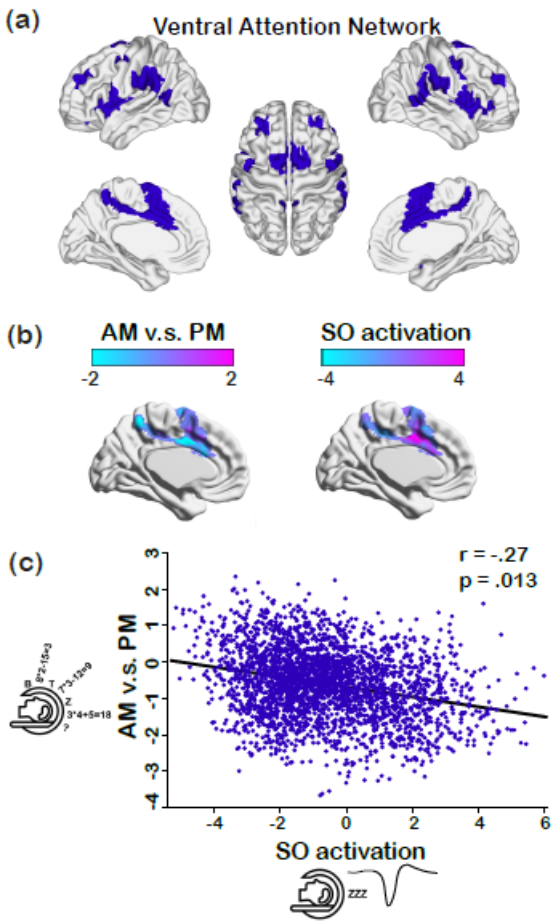

Figure 4-6 (a), schematic of the ventral attention network; (b), activation during task (left) and SO (right) in the ventral attention network; (c), correlation between overnight change during task and activation during SOs within the ventral attention network

6a). We first ensured that the ventral attention network was significantly activated during OSPAN vs math (p=0.0045, t=3.02) when averaging across all 4 sessions.

To investigate the potential role of SO-related functional activity in modulating the overnight changes in this network during our WM task, we then examined relationships between the AM-PM OSpan change and SO vs NREM BOLD activation contrasts (figure 6b). Across voxels in the ventral attention network, there was a negative correlation between the AM-PM and SO vs NREM BOLD activation contrasts (r=-0.27, p=0.01, permutation test). This indicates that voxels with more increased overnight efficiency during working memory task execution show more activation during SO. Ventral attention network activity during SO might facilitate increased neural efficiency of WM across a night of sleep.

Discussion

The aim of our study is to investigate the neural basis of WM improvement during sleep using simultaneous EEG-fMRI. To our knowledge, this is the first study to show a direct role of sleep events, specifically SOs, in WM-induced functional changes in the brain. Our findings reveal several important insights into the neural mechanism of WM over a night of sleep. Namely, overnight sleep is associated with an increase in WM-related neural efficiency, as shown by a decrease in precuneus recruitment overnight during the WM task. Moreover, the functional connectivity between the precuneus and other WM-related regions was modulated by sleep. Namely, there was increased connectivity between the precuneus and frontal as well as occipital areas decreased connectivity with other parts of the precuneus and lateral occipital area during OSPAN vs math overnight. During SO vs non-SO NREM sleep, there was decreased connectivity between the precuneus and frontal area. We also found a negative correlation between SO-induced WM activation and overnight WM activation changes in task-related areas that are specific to our dataset as well as the Ventral Attention Network.

Consistent with prior literature implicating the precuneus in WM processes, this region showed a significant reduction in activation during the OSPAN task after sleep in our study. WM tasks have consistently led to the activation in the posterior parietal area (Baddeley, 1992; Honey et al., 2000; Smith & Jonides, 1998). For example, one study showed that precuneus is the most predominantly activated area during a spatial WM task compared to other structures in the posterior parietal region (Wallentin et al., 2008). The precuneus is significant activated in a meta-analysis of 11 fMRI studies using a n-back WM paradigm(Owen et al., 2005) as well as in a MEG study using a similar task (Costers et al., 2020). Moreover, the precuneus has been shown to reflect the cognitive demand of WM. Those who found the task more difficult and responded with a slower reaction time had more activation in the precuneus during a n-back WM task (Honey et al., 2000). Similarly, patients with schizophrenia showed hypoactivations in the precuneus and poorer performance during a n-back WM task, suggesting dysfunction of the precuneus impairs WM performance (Schneider et al., 2007). Studies have established a direct role of the precuneus in WM via transcranial magnetic stimulation (TMS). Specifically, TMS applied to the midline parietal site centered around the precuneus led to improved WM performance, whereas TMS applied to other regions such as frontal or occipital sites did not have such benefit (Luber et al., 2007). Our finding adds to this field by showing that overnight sleep may enhance WM via reduced need for precuneus recruitment during the OSPAN task. This reduction in precuneus recruitment may reflect a more efficient use of neural resources, allowing for WM improvement.

After showing sleep led to increased neural efficiency for WM, the next logical question is: What are the specific neural mechanisms during sleep that led to increased neural efficiency during WM? To this end, our findings suggest that NREM SOs may play a role in reorganizing WM network. During SOs, we found a broad decrease in activation in the WM-related areas and a decrease in precuneus connectivity with other WM-related regions. The decrease in precuneus connectivity may reflect a shift in the decoupling of the precuneus from the network of WM-related regions. Indeed, improved WM performance is associated with distinct changes in different networks. A prior study reported improved WM performance after a 6-week WM training is associated with reduced functional connectivity in the default mode network including the precuneus, and increased functional connectivity in the frontoparietal network (Jolles et al., 2013). Furthermore, a reduction in brain activity during SOs is consistent with prior findings showing a broad decrease in activation in frontal and parietal areas as well as subcortical areas including the precuneus during NREM sleep using fMRI (Kaufmann et al., 2006) and PET (Maquet et al., 1997). SWS has been thought of as a state of quiescence due to the studies showing that brain oxygen metabolism, cerebral blood flow, and glucose metabolism are decreased during this time in comparison to wakefulness and REM sleep (Czisch et al., 2004; Sawaya & Ingvar, 1989; Townsend et al., 1973). It is worth noting that we found increased activation in the cingulate and right thalamus during SOs compared to non-SO NREM periods, suggesting SOs modulate WM-related network by selectively activating specific areas while silencing others.

Importantly, when probing the direct association between brain activity during SOs and during WM processing, we found that the more WM-related areas were activated

during SOs, the less they were activated after sleep compared to pre-sleep, suggesting that less resources were needed to perform the WM task. We observed this negative correlation between SOs-related activation and task-related activation using a WM-related mask derived from our data as well as a pre-defined WM-related network, the Ventral Attention Network, using two methods, across sessions and across brain regions within the Ventral Attention Network, respectively. Moreover, similar to our finding in SO-related increase in activation in selective subcortical areas, a study employing simultaneous EEG-fMRI reported significant BOLD signal increases in cortical areas including the inferior frontal, medial prefrontal, precuneus, and posterior cingulate during SWA (<4Hz), suggesting slow wave during NREM sleep might be associated with increased transient brain activities that are critical for memory.

The specific neural mechanism underlying SOs' role in modulating WM-networks remains to be explored, here we present two potential ways. Studies have shown that SOs in SWS promote synaptic downscaling, which involves the weakening of synaptic connections that have been strongly activated during wakefulness (Tononi & Cirelli, 2006). This downscaling process helps to maintain the stability and efficiency of neural networks, preventing them from becoming overloaded, and it can potentially facilitate cognitive functioning including WM by freeing up capacities for the encoding of new information during the upcoming wake period (Raven et al., 2018). The second potential mechanism of how SOs modulate WM-networks is through glymphatic clearance. The glymphatic system is responsible for brain-wide delivery of nutrients and clearance of waste via influx of cerebrospinal fluid (CSF) alongside perivascular spaces and through the brain (Jessen et al., 2015). Specifically, SWS is associated with glymphatic clearance, as studies have reported that SOs are temporally coupled with and precede cerebrospinal glymphatic clearance(Fultz et al., 2019; Hablitz et al., 2019). The glymphatic system's primary function is to clear metabolic waste products and toxic substances that accumulate in the brain. By facilitating the removal of these waste products, the glymphatic system may help maintain the optimal functioning of the brain, including the networks involved in WM. Therefore, SOs are linked to synaptic downscaling and glymphatic clearance, which could be important for a range of cognitive functioning, including WM. SOs are mostly prevalent in the frontal area (Massimini et al., 2004), an area important for executive functioning and WM.

Our studies have several limitations. The limited sleep duration and the amount of recorded sleep events during the scan made it impossible to differentiate between SOs in N2 and SWS. It remains to be explored how SOs modulate WM-related areas throughout the night as we were only able to collect EEG-fMRI data for the first sleep cycle. Moreover, our study focuses on WM-related functional changes during sleep. Previous studies have shown WM and episodic memory might compete for limited resources during sleep, and particularly SOs (Chen et al., 2022). Therefore, it will be interesting to investigate how SOs modulate episodic memory networks.

In conclusion, our findings suggest that overnight sleep plays a critical role in the consolidation of WM by increasing neural efficiency and reorganizing the WM network. Our study highlights the importance of SOs in this process and suggests that task-related

reactivation during SOs might benefit neural efficiency during the task. These findings provide a basis to develop theoretic models on sleep-dependent memory benefit across different cognitive domains. It may also have implications for the development of sleep-based interventions aimed at improving WM performance.

CHAPTER 5 Concluding Remarks

In this dissertation work, I present a novel investigation into the neural mechanisms of sleep-dependent memory improvement across different domains utilizing multi-modal brain-imaging techniques. In the first study examining how sleep protects episodic memory against interference, I found that sleep rescues memories after interference has already occurred, and this effect is associated with SWA. In the second study, I established a causal role of sleep spindles and spindle-SO coupling in episodic memory consolidation overnight by enhancing sleep spindles pharmacologically. Then, I investigated how SOs and sleep spindles contribute to different memory domains and how they modulate specific memory networks, which is the goal for study 3. I reported that overnight sleep increases WM neural efficiency by decreasing the precuneus recruitment during a WM task. Specifically, SOs modulate the WM network by increasing activation in precentral and postcentral gyrus and decreasing activation in other WM-related areas. These three experimental studies suggest a theoretical hypothesis that sleep oscillations of a similar frequency could contribute to different memory domains.

The three studies build on each other to provide a richer understanding of the neural mechanisms underlying sleep-dependent memory benefits across different cognitive domains. The findings suggest that while both WM and episodic memory rely on SOs, they may be supported by distinct neural mechanisms. One question that arises is how these different memory domains share the same resources during the night? Prior studies have found a positive correlation between WM and LTM, indicating that WM can boost LTM recognition while also constraining LTM encoding capacity (Cotton & Ricker, 2022; Forsberg et al., 2021). However, a study by Hoskin et al. (2019) demonstrated that memory reactivation during wakefulness can interfere with WM maintenance, suggesting that coordinated activity patterns triggered by memory reactivation across cortical regions, including the prefrontal cortex (PFC), could compete for resources needed for WM maintenance. These findings suggest that WM and episodic memory may be supported by separate neural mechanisms.

In addition, studies from our group and others have reported behavioral trade-off between episodic LTM and WM. For example, one study demonstrated that cortical oscillations in the spindle range suppressed vagal autonomic activity using effective connectivity estimation, which is critical for WM performance (Friston, 1994, 2011). Our study showed that spindle activity was associated with a trade-off between enhanced post-sleep episodic LTM at the cost of reduced WM improvement. Specifically, we found zolpidem, a GABA-a agonist, can enhance spindle activity and episodic LTM consolidation while impairing WM improvement compared to placebo (Chen et al., 2021b). Additionally, spindle-SO coupling was associated with a similar behavioral trade-off, with greater spindle-SO coupling associated with less WM improvement (Chen et al., 2021b).

These interesting findings led my colleagues and I to propose the Sleep Oscillation Switch (SOS) model, for how these memory domains may interact during sleep. The SOS model posits that the brain toggles between the two memory processes, WM and LTM, via a complex interaction at the synaptic, systems, and mechanistic levels. We propose that sleep

is a competitive arena in which both memory domains vie for limited resources, and we have experimentally supported this hypothesis by showing that boosting one system leads to a functional trade-off in electrophysiological and behavioral outcomes in another, During the Long-Term Memory state, consolidation occurs via spindle-coupled SOs, which leads to reduced autonomic vagal-dependent activity and less WM improvement. During the Working Memory state, greater efficiency occurs during uncoupled SOs associated with increased autonomic vagal-dependent activity, which leads to reduced central spindle dependent activity and less LTM consolidation.

Based on the SOS model, one could hypothesize that WM-related regions would be activated during uncoupled SOs to increase neural efficiency overnight. At the same time, episodic-related regions would be activated during spindle-coupled SOs to facilitate neural efficiency in the LTM network. In Chapter 3, I showed that spindle-SOs coupling is critical for episodic memory consolidation. The study described in Chapter 4 provides the initial support showing SOs modulate WM networks, and future studies are needed to compare the different functional changes associated with spindle-coupled SOs and uncoupled SOs. The pivotal role of SOs in memory consolidation is evident in both WM and episodic memory. However, upon closer examination, it becomes possible that the specific impact of SOs on each memory type varies, contingent upon the distinct networks they modulate. The possibility of dividing neural oscillations of similar frequency into more re-fined subdivisions based on their functional impact has been explored by recent studies. For example, Ngo and colleagues (2019) demonstrated a functional dissociation between delta and SOs, with delta waves facilitating forgetting while SOs are more likely to couple with spindles and promote episodic long-term memory consolidation (Kim et al. 2019, Ngo et al. 2019). Additionally, Malerba and colleagues have categorized SOs into different categories using spatiotemporal characteristics demonstrating global, local, and frontal SOs (Malerba et al., 2018). Importantly, global SOs are more likely to couple with sleep spindles (Malerba et al., 2022), and be more related to episodic memory improvement (Niknazar et al., 2022). Together with my research, these findings suggest that what may initially appear as a singular wave, in this case SOs, can actually represent multiple distinct waves, each potentially contributing to specific memory networks.

Here, I present several lines of research investigating how specific sleep events modulate different brain networks to contribute to episodic and WM. I highlight the importance of incorporating not only the temporal profile but also the spatial and functional characteristics when categorizing specific sleep events, as it will provide valuable insights into the intricate interplay among diverse cognitive domains during sleep. Specifically, I propose a potential subdivision of SOs into coarse categories based on the functional changes in specific structures, with SOs coupled with spindles as related to hippocampal reactivations critical for episodic memory, whereas uncoupled SOs related to WM networks. Categorizing sleep events based on not only the temporal profile, but also spatial and functional characteristics will help us understand the complex interplay between different cognitive domains during sleep. Understanding the neural mechanisms of sleep-dependent memory benefits across different cognitive domains is essential for us to gain insights in memory models.

REFERENCE

Andrade, K. C., Spoormaker, V. I., Dresler, M., Wehrle, R., Holsboer, F., Sämann, P. G., & Czisch, M. (2011). Sleep Spindles and Hippocampal Functional Connectivity in Human NREM Sleep. *The Journal of Neuroscience*, *31*(28), 10331–10339. https://doi.org/10.1523/JNEUROSCI.5660-10.2011

Antony, J. W., Piloto, L., Wang, M., Pacheco, P., Norman, K. A., & Paller, K. A. (2018). Sleep Spindle Refractoriness Segregates Periods of Memory Reactivation. *Current Biology: CB*, *28*(11), 1736-1743.e4. https://doi.org/10.1016/j.cub.2018.04.020

Asplund, C. L., Todd, J. J., Snyder, A. P., & Marois, R. (2010). A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. *Nature Neuroscience*, *13*(4), Article 4. https://doi.org/10.1038/nn.2509

Backhaus, J., Hoeckesfeld, R., Born, J., Hohagen, F., & Junghanns, K. (2008). Immediate as well as delayed post learning sleep but not wakefulness enhances declarative memory consolidation in children. *Neurobiology of Learning and Memory*, *89*(1), 76–80. https://doi.org/10.1016/j.nlm.2007.08.010

Baddeley, A. (1992). Working Memory. *Science*, *255*(5044), 556–559. https://doi.org/10.1126/science.1736359

Baddeley, A. (2010). Long-term and working memory: How do they interact? In *Memory, aging and the brain: A Festschrift in honour of Lars-Göran Nilsson* (pp. 7–23). Psychology Press.

Bailes, C., Caldwell, M., Wamsley, E. J., & Tucker, M. A. (2020). Does sleep protect memories against interference? A failure to replicate. *PLOS ONE*, *15*(2), e0220419. https://doi.org/10.1371/journal.pone.0220419

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300.

Benson, K., & Feinberg, I. (1977). The Beneficial Effect of Sleep in an Extended Jenkins and Dallenbach Paradigm. *Psychophysiology*, *14*(4), 375–384. https://doi.org/10.1111/j.1469-8986.1977.tb02967.x

Bergmann, T. O., Mölle, M., Diedrichs, J., Born, J., & Siebner, H. R. (2012). Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. *NeuroImage*, *59*(3), 2733–2742. https://doi.org/10.1016/j.neuroimage.2011.10.036

Binder, S., Rawohl, J., Born, J., & Marshall, L. (2014). Transcranial slow oscillation stimulation during NREM sleep enhances acquisition of the radial maze task and modulates cortical network activity in rats. *Frontiers in Behavioral Neuroscience*, *7*. https://doi.org/10.3389/fnbeh.2013.00220

Borbély, A. A., Daan, S., Wirz-Justice, A., & Deboer, T. (2016). The two-process model of sleep regulation: A reappraisal. *Journal of Sleep Research*, *25*(2), 131–143. https://doi.org/10.1111/jsr.12371

Born, J., & Wilhelm, I. (2012). System consolidation of memory during sleep. *Psychological Research*, *76*(2), 192–203. http://dx.doi.org/10.1007/s00426-011-0335-6

Buzsáki, G. (1989). Two-stage model of memory trace formation: A role for "noisy" brain states. *Neuroscience*, *31*(3), 551–570. https://doi.org/10.1016/0306-4522(89)90423-5
Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron*, *33*(3), 325–340.
Cabeza, R., Ciaramelli, E., & Moscovitch, M. (2012). Cognitive contributions of the ventral parietal cortex: An integrative theoretical account. *Trends in Cognitive Sciences*, *16*(6), 338–352. https://doi.org/10.1016/j.tics.2012.04.008
Cairney, S. A., Durrant, S. J., Power, R., & Lewis, P. A. (2015). Complementary Roles of Slow-Wave Sleep and Rapid Eye Movement Sleep in Emotional Memory Consolidation. *Cerebral Cortex*, *25*(6), 1565–1575. https://doi.org/10.1093/cercor/bht349
Cairney, S. A., Guttesen, A. á V., El Marj, N., & Staresina, B. P. (2018). Memory Consolidation Is Linked to Spindle-Mediated Information Processing during Sleep. *Current Biology*, *28*(6), 948-954.e4. https://doi.org/10.1016/j.cub.2018.01.087
Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., Berger, M. S., Barbaro, N. M., & Knight, R. T. (2006). High Gamma Power Is Phase-Locked to Theta Oscillations in Human Neocortex. *Science*, *313*(5793), 1626–1628. https://doi.org/10.1126/science.1128115
Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working Memory From the Psychological and Neurosciences Perspectives: A Review. *Frontiers in Psychology*, *9*. https://www.frontiersin.org/articles/10.3389/fpsyg.2018.00401
Chen, P.-C., Niknazar, H., Alaynick, W. A., Whitehurst, L. N., & Mednick, S. C. (2021a). Competitive dynamics underlie cognitive improvements during sleep. *Proceedings of the National Academy of Sciences*, *118*(51), e2109339118. https://doi.org/10.1073/pnas.2109339118
Chen, P.-C., Niknazar, H., Alaynick, W. A., Whitehurst, L. N., & Mednick, S. C. (2021b). Competitive dynamics underlie cognitive improvements during sleep. *Proceedings of the National Academy of Sciences*, *118*(51). https://doi.org/10.1073/pnas.2109339118
Chen, P.-C., Whitehurst, L. N., & Mednick, S. C. (2020). Autonomic activity during a daytime nap facilitates working memory improvement. *BioRxiv*, 2020.04.22.056580. https://doi.org/10.1101/2020.04.22.056580
Chen, P.-C., Zhang, J., Thayer, J. F., & Mednick, S. C. (2022). Understanding the roles of central and autonomic activity during sleep in the improvement of working memory and episodic memory. *Proceedings of the National Academy of Sciences*, *119*(44), e2123417119. https://doi.org/10.1073/pnas.2123417119
Choi, S. H., Kwon, H. B., Jin, H. W., Yoon, H., Lee, M. H., Lee, Y. J., & Park, K. S. (2021). Weak closed-loop vibrational stimulation improves the depth of slow-wave sleep and declarative memory consolidation. *Sleep*, *44*(6). https://doi.org/10.1093/sleep/zsaa285
Cirelli, C. (2017). Sleep, synaptic homeostasis and neuronal firing rates. *Current Opinion in Neurobiology*, *44*, 72–79. https://doi.org/10.1016/j.conb.2017.03.016
Clemens, Z., Fabó, D., & Halász, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience*, *132*(2), 529–535. https://doi.org/10.1016/j.neuroscience.2005.01.011
Clemens, Z., Mölle, M., Erőss, L., Jakus, R., Rásonyi, G., Halász, P., & Born, J. (2011). Fine-tuned coupling between human parahippocampal ripples and sleep spindles.

European Journal of Neuroscience, *33*(3), 511–520. https://doi.org/10.1111/j.1460-9568.2010.07505.x

Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., & Noll, D. C. (1994). Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping*, *1*(4), 293–304. https://doi.org/10.1002/hbm.460010407

Conway, A. R. A., Cowan, N., Bunting, M. F., Therriault, D. J., & Minkoff, S. R. B. (2002). A latent variable analysis of working memory capacity, short-term memory capacity, processing speed, and general fluid intelligence. *Intelligence*, *30*(2), 163–183. https://doi.org/10.1016/S0160-2896(01)00096-4

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Cordi, M. J., & Rasch, B. (2021). How robust are sleep-mediated memory benefits? *Current Opinion in Neurobiology*, *67*, 1–7. https://doi.org/10.1016/j.conb.2020.06.002

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews. Neuroscience*, *3*(2), 153–160. https://doi.org/10.1038/nrn726

Costers, L., Van Schependom, J., Laton, J., Baijot, J., Sjøgård, M., Wens, V., De Tiège, X., Goldman, S., D'Haeseleer, M., D'hooghe, M. B., Woolrich, M., & Nagels, G. (2020). Spatiotemporal and spectral dynamics of multi-item working memory as revealed by the n-back task using MEG. *Human Brain Mapping*, *41*(9), 2431–2446. https://doi.org/10.1002/hbm.24955

Cotton, K., & Ricker, T. J. (2022). Examining the relationship between working memory consolidation and long-term consolidation. *Psychonomic Bulletin & Review*, *29*(5), 1625–1648. https://doi.org/10.3758/s13423-022-02084-2

Czisch, M., Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Pollmächer, T., & Auer, D. P. (2004). Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. *European Journal of Neuroscience*, *20*(2), 566–574. https://doi.org/10.1111/j.1460-9568.2004.03518.x

Dang-Vu, T. T., Schabus, M., Desseilles, M., Albouy, G., Boly, M., Darsaud, A., Gais, S., Rauchs, G., Sterpenich, V., Vandewalle, G., Carrier, J., Moonen, G., Balteau, E., Degueldre, C., Luxen, A., Phillips, C., & Maquet, P. (2008). Spontaneous neural activity during human slow wave sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(39), 15160–15165. https://doi.org/10.1073/pnas.0801819105

Dang-Vu, T. T., Schabus, M., Desseilles, M., Sterpenich, V., Bonjean, M., & Maquet, P. (2010). Functional Neuroimaging Insights into the Physiology of Human Sleep. *Sleep*, *33*(12), 1589–1603. https://doi.org/10.1093/sleep/33.12.1589

Davachi, L., & Wagner, A. D. (2002). Hippocampal Contributions to Episodic Encoding: Insights From Relational and Item-Based Learning. *Journal of Neurophysiology*, *88*(2), 982–990. https://doi.org/10.1152/jn.2002.88.2.982

Deliens, G., Schmitz, R., Caudron, I., Mary, A., Leproult, R., & Peigneux, P. (2013). Does Recall after Sleep-Dependent Memory Consolidation Reinstate Sensitivity to Retroactive Interference? *PLOS ONE*, *8*(7), e68727. https://doi.org/10.1371/journal.pone.0068727

Demanuele, C., Bartsch, U., Baran, B., Khan, S., Vangel, M. G., Cox, R., Hämäläinen, M., Jones, M. W., Stickgold, R., & Manoach, D. S. (2017). Coordination of Slow Waves With Sleep Spindles Predicts Sleep-Dependent Memory Consolidation in Schizophrenia. *Sleep*, *40*(1). https://doi.org/10.1093/sleep/zsw013

D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies. *Experimental Brain Research*, *133*(1), 3–11. https://doi.org/10.1007/s002210000395

Diekelmann, S. (2014). Sleep for cognitive enhancement. *Frontiers in Systems Neuroscience*, *8*. http://dx.doi.org/10.3389/fnsys.2014.00046

Diekelmann, S., & Born, J. (2010a). The memory function of sleep. *Nature Reviews Neuroscience*, *11*(2), 114–126. https://doi.org/10.1038/nrn2762

Diekelmann, S., & Born, J. (2010b). The memory function of sleep. *Nature Reviews Neuroscience*, *11*, 114–126. https://doi.org/10.1038/nrn2762

Diep, C., Ftouni, S., Manousakis, J. E., Nicholas, C. L., Drummond, S. P. A., & Anderson, C. (2020). Acoustic slow wave sleep enhancement via a novel, automated device improves executive function in middle-aged men. *Sleep*, *43*(zsz197). https://doi.org/10.1093/sleep/zsz197

Diep, C., Garcia-Molina, G., Jasko, J., Manousakis, J., Ostrowski, L., White, D., & Anderson, C. (2021). Acoustic enhancement of slow wave sleep on consecutive nights improves alertness and attention in chronically short sleepers. *Sleep Medicine*, *81*, 69–79. https://doi.org/10.1016/j.sleep.2021.01.044

Dijk, D. J., James, L. M., Peters, S., Walsh, J. K., & Deacon, S. (2010). Sex differences and the effect of gaboxadol and zolpidem on EEG power spectra in NREM and REM sleep. *Journal of Psychopharmacology (Oxford, England)*, *24*(11), 1613–1618. https://doi.org/10.1177/0269881109105788

Diwadkar, V. A., Carpenter, P. A., & Just, M. A. (2000). Collaborative Activity between Parietal and Dorso-Lateral Prefrontal Cortex in Dynamic Spatial Working Memory Revealed by fMRI. *NeuroImage*, *12*(1), 85–99. https://doi.org/10.1006/nimg.2000.0586

Drosopoulos, S., Schulze, C., Fischer, S., & Born, J. (2007). Sleep's function in the spontaneous recovery and consolidation of memories. *Journal of Experimental Psychology. General*, *136*(2), 169–183. https://doi.org/10.1037/0096-3445.136.2.169

Drover, D. R. (2004). Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: Zaleplon, zolpidem and zopiclone. *Clinical Pharmacokinetics*, *43*(4), 227–238. https://doi.org/10.2165/00003088-200443040-00002

Ellenbogen, J. M., Hulbert, J. C., Stickgold, R., Dinges, D. F., & Thompson-Schill, S. L. (2006). Interfering with theories of sleep and memory: Sleep, declarative memory, and associative interference. *Current Biology: CB*, *16*(13), 1290–1294.

Ellenbogen, J. M., Payne, J. D., & Stickgold, R. (2006). The role of sleep in declarative memory consolidation: Passive, permissive, active or none? *Current Opinion in Neurobiology*, *16*(6), 716–722. https://doi.org/10.1016/j.conb.2006.10.006

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General*, *128*, 309–331. https://doi.org/10.1037/0096-3445.128.3.309

Farhadian, N., Khazaie, H., Nami, M., & Khazaie, S. (2021). The role of daytime napping in declarative memory performance: A systematic review. *Sleep Medicine*. https://doi.org/10.1016/j.sleep.2021.05.019

Feld, G. B., & Diekelmann, S. (2015). Sleep smart—Optimizing sleep for declarative learning and memory. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.00622

Fernandez, L. M. J., & Lüthi, A. (2020). Sleep Spindles: Mechanisms and Functions. *Physiological Reviews*, *100*(2), 805–868. https://doi.org/10.1152/physrev.00042.2018

Ferrarelli, F., Kaskie, R., Laxminarayan, S., Ramakrishnan, S., Reifman, J., & Germain, A. (2019). An increase in sleep slow waves predicts better working memory performance in healthy individuals. *NeuroImage*, *191*, 1–9. https://doi.org/10.1016/j.neuroimage.2019.02.020

Forsberg, A., Adams, E. J., & Cowan, N. (2021). Chapter One - The role of working memory in long-term learning: Implications for childhood development. In K. D. Federmeier (Ed.), *Psychology of Learning and Motivation* (Vol. 74, pp. 1–45). Academic Press. https://doi.org/10.1016/bs.plm.2021.02.001

Fowler, M. J., Sullivan, M., & Ekstrand, B. R. (1973). Sleep and Memory. *Science*, *179*(4070), 302–304. https://doi.org/10.1126/science.179.4070.302

Fox, S. E., Wolfson, S., & Ranck, J. B. (1986). Hippocampal theta rhythm and the firing of neurons in walking and urethane anesthetized rats. *Experimental Brain Research*, *62*(3), 495–508. https://doi.org/10.1007/bf00236028

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*(1-2), 56–78. https://doi.org/10.1002/hbm.460020107

Friston, K. J. (2011). Functional and Effective Connectivity: A Review. *Brain Connectivity*, *1*(1), 13–36. https://doi.org/10.1089/brain.2011.0008

Fuentemilla, L., Barnes, G. R., Düzel, E., & Levine, B. (2014). Theta oscillations orchestrate medial temporal lobe and neocortex in remembering autobiographical memories. *NeuroImage*, *85*, 730–737. https://doi.org/10.1016/j.neuroimage.2013.08.029

Gais, S., & Born, J. (2004). Declarative memory consolidation: Mechanisms acting during human sleep. *Learning & Memory*, *11*(6), 679–685. https://doi.org/10.1101/lm.80504

Gais, S., Lucas, B., & Born, J. (2006). Sleep after learning aids memory recall. *Learning & Memory*, *13*(3), 259–262. https://doi.org/10.1101/lm.132106

Gais, S., Mölle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *22*(15), 6830–6834. https://doi.org/20026697

Greenblatt, D. J., Harmatz, J. S., Singh, N. N., Steinberg, F., Roth, T., Moline, M. L., Harris, S. C., & Kapil, R. P. (2014). Gender differences in pharmacokinetics and pharmacodynamics of zolpidem following sublingual administration. *The Journal of Clinical Pharmacology*, *54*(3), 282–290. https://doi.org/10.1002/jcph.220

Groch, S., Preiss, A., McMakin, D. L., Rasch, B., Walitza, S., Huber, R., & Wilhelm, I. (2017). Targeted Reactivation during Sleep Differentially Affects Negative Memories in Socially Anxious and Healthy Children and Adolescents. *Journal of Neuroscience*, *37*(9), 2425–2434. https://doi.org/10.1523/JNEUROSCI.1912-16.2017

Hale, S., Rose, N. S., Myerson, J., Strube, M. J., Sommers, M., Tye-Murray, N., & Spehar, B. (2011). The Structure of Working Memory Abilities across the Adult Life Span. *Psychology and Aging*, *26*(1), 92–110. https://doi.org/10.1037/a0021483

Hall-Porter, J. M., Schweitzer, P. K., Eisenstein, R. D., Ahmed, H. A. H., & Walsh, J. K. (2014). The Effect of Two Benzodiazepine Receptor Agonist Hypnotics on Sleep-Dependent Memory Consolidation. *Journal of Clinical Sleep Medicine*, *10*(01), 27–34. https://doi.org/10.5664/jcsm.3352

Headley, D. B., & Paré, D. (2017). Common oscillatory mechanisms across multiple memory systems. *Npj Science of Learning*, *2*(1), Article 1. https://doi.org/10.1038/s41539-016-0001-2

Helfrich, R. F., Mander, B. A., Jagust, W. J., Knight, R. T., & Walker, M. P. (2018). Old Brains Come Uncoupled in Sleep: Slow Wave-Spindle Synchrony, Brain Atrophy, and Forgetting. *Neuron*, *97*(1), 221-230.e4. https://doi.org/10.1016/j.neuron.2017.11.020

Honey, G. D., Bullmore, E. T., & Sharma, T. (2000). Prolonged Reaction Time to a Verbal Working Memory Task Predicts Increased Power of Posterior Parietal Cortical Activation. *NeuroImage*, *12*(5), 495–503. https://doi.org/10.1006/nimg.2000.0624

Hu, X., Cheng, L. Y., Chiu, M. H., & Paller, K. A. (20200206). Promoting memory consolidation during sleep: A meta-analysis of targeted memory reactivation. *Psychological Bulletin*, *146*(3), 218. https://doi.org/10.1037/bul0000223

Hutchison, I. C., & Rathore, S. (2015). The role of REM sleep theta activity in emotional memory. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01439

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences*, *105*(19), 6829–6833. https://doi.org/10.1073/pnas.0801268105

Jenkins, J. G., & Dallenbach, K. M. (1924). Obliviscence during sleep and waking. *The American Journal of Psychology*, *35*(4), 605–612. https://doi.org/10.2307/1414040

Jolles, D. D., van Buchem, M. A., Crone, E. A., & Rombouts, S. A. R. B. (2013). Functional brain connectivity at rest changes after working memory training. *Human Brain Mapping*, *34*(2), 396–406. https://doi.org/10.1002/hbm.21444

Karakaş, S., Çakmak, E. D., Bekçi, B., & Aydın, H. (2007). Oscillatory responses representing differential auditory processing in sleep. *International Journal of Psychophysiology*, *65*(1), 40–50. https://doi.org/10.1016/j.ijpsycho.2007.02.010

Kaufmann, C., Wehrle, R., Wetter, T. C., Holsboer, F., Auer, D. P., Pollmächer, T., & Czisch, M. (2006). Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: An EEG/fMRI study. *Brain*, *129*(3), 655–667. https://doi.org/10.1093/brain/awh686

Kim, J., Gulati, T., & Ganguly, K. (2019). Competing Roles of Slow Oscillations and Delta Waves in Memory Consolidation versus Forgetting. *Cell*, *179*(2), 514-526.e13. https://doi.org/10.1016/j.cell.2019.08.040

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2), 169–195. https://doi.org/10.1016/S0165-0173(98)00056-3

Klimesch, W., Schimke, H., & Schwaiger, J. (1994). Episodic and semantic memory: An analysis in the EEG theta and alpha band. *Electroencephalography and Clinical Neurophysiology*, *91*(6), 428–441. https://doi.org/10.1016/0013-4694(94)90164-3

Kopp, C., Rudolph, U., & Tobler, I. (2004). Sleep EEG changes after zolpidem in mice. *Neuroreport*, *15*(14), 2299–2302. https://doi.org/10.1097/00001756-200410050-00031

Kuriyama, K., Mishima, K., Suzuki, H., Aritake, S., & Uchiyama, M. (2008). Sleep Accelerates the Improvement in Working Memory Performance. *The Journal of Neuroscience*, *28*(40), 10145. https://doi.org/10.1523/JNEUROSCI.2039-08.2008

Lacourse, K., Yetton, B., Mednick, S. C., & Warby, S. C. (n.d.). *Massive Online Data Annotation (MODA): Crowdsourcing to generate high-quality sleep spindle annotations from EEG data*.

Landolt, H. P., Finelli, L. A., Roth, C., Buck, A., Achermann, P., & Borbély, A. A. (2000). Zolpidem and sleep deprivation: Different effect on EEG power spectra. *Journal of Sleep Research*, *9*(2), 175–183.

Latchoumane, C.-F. V., Ngo, H.-V. V., Born, J., & Shin, H.-S. (2017a). Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms. *Neuron*, *95*(2), 424-435.e6. https://doi.org/10.1016/j.neuron.2017.06.025

Latchoumane, C.-F. V., Ngo, H.-V. V., Born, J., & Shin, H.-S. (2017b). Thalamic Spindles Promote Memory Formation during Sleep through Triple Phase-Locking of Cortical, Thalamic, and Hippocampal Rhythms. *Neuron*, *95*(2), 424-435.e6. https://doi.org/10.1016/j.neuron.2017.06.025

Lau, E. Y. Y., Wong, M. L., Lau, K. N. T., Hui, F. W. Y., & Tseng, C. (2015). Rapid-Eye-Movement-Sleep (REM) Associated Enhancement of Working Memory Performance after a Daytime Nap. *PLOS ONE*, *10*(5), e0125752. https://doi.org/10.1371/journal.pone.0125752

Lega, B. C., Jacobs, J., & Kahana, M. (2012). Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus*, *22*(4), 748–761. https://doi.org/10.1002/hipo.20937

Levy, R., & Goldman-Rakic, P. S. (2000). Segregation of working memory functions within the dorsolateral prefrontal cortex. *Experimental Brain Research*, *133*(1), 23–32. https://doi.org/10.1007/s002210000397

Lin, F., L. Heffner, K., Ren, P., & Tadin, D. (2017). A Role of the Parasympathetic Nervous System in Cognitive Training. *Current Alzheimer Research*, *14*(7), 784–789. https://doi.org/10.2174/1567205014666170203095128

Luber, B., Kinnunen, L. H., Rakitin, B. C., Ellsasser, R., Stern, Y., & Lisanby, S. H. (2007). Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: Frequency- and time-dependent effects. *Brain Research*, *1128*, 120–129. https://doi.org/10.1016/j.brainres.2006.10.011

Lundahl, J., Deacon, S., Maurice, D., & Staner, L. (2012). EEG spectral power density profiles during NREM sleep for gaboxadol and zolpidem in patients with primary insomnia. *Journal of Psychopharmacology (Oxford, England)*, *26*(8), 1081–1087. https://doi.org/10.1177/0269881111424457

Lustenberger, C., Boyle, M. R., Alagapan, S., Mellin, J. M., Vaughn, B. V., & Fröhlich, F. (2016). Feedback-controlled transcranial alternating current stimulation reveals functional role of sleep spindles in motor memory consolidation. *Current Biology : CB*, *26*(16), 2127–2136. https://doi.org/10.1016/j.cub.2016.06.044

Lustenberger, C., Maric, A., Dürr, R., Achermann, P., & Huber, R. (2012). Triangular Relationship between Sleep Spindle Activity, General Cognitive Ability and the Efficiency of Declarative Learning. *PLoS One; San Francisco*, *7*(11), e49561. http://dx.doi.org/10.1371/journal.pone.0049561

Majerus, S., Attout, L., D'Argembeau, A., Degueldre, C., Fias, W., Maquet, P., Martinez Perez, T., Stawarczyk, D., Salmon, E., Van der Linden, M., Phillips, C., & Balteau, E. (2012). Attention Supports Verbal Short-Term Memory via Competition between Dorsal and Ventral Attention Networks. *Cerebral Cortex*, *22*(5), 1086–1097. https://doi.org/10.1093/cercor/bhr174

Majerus, S., Péters, F., Bouffier, M., Cowan, N., & Phillips, C. (2018). The Dorsal Attention Network Reflects Both Encoding Load and Top–down Control during Working Memory. *Journal of Cognitive Neuroscience*, *30*(2), 144–159. https://doi.org/10.1162/jocn_a_01195

Majerus, S., Poncelet, M., Van der Linden, M., Albouy, G., Salmon, E., Sterpenich, V., Vandewalle, G., Collette, F., & Maquet, P. (2006). The left intraparietal sulcus and verbal short-term memory: Focus of attention or serial order? *NeuroImage*, *32*(2), 880–891. https://doi.org/10.1016/j.neuroimage.2006.03.048

Malerba, P., Whitehurst, L., & Mednick, S. C. (2022). The space-time profiles of sleep spindles and their coordination with slow oscillations on the electrode manifold. *Sleep*, *45*(8), zsac132. https://doi.org/10.1093/sleep/zsac132

Malerba, P., Whitehurst, L. N., Simons, S. B., & Mednick, S. C. (2018). Spatio-temporal structure of sleep slow oscillations on the electrode manifold and its relation to spindles. *Sleep*, *42*(1). https://doi.org/10.1093/sleep/zsy197

Maquet, P., Degueldre, C., Delfiore, G., Aerts, J., Péters, J.-M., Luxen, A., & Franck, G. (1997). Functional Neuroanatomy of Human Slow Wave Sleep. *Journal of Neuroscience*, *17*(8), 2807–2812. https://doi.org/10.1523/JNEUROSCI.17-08-02807.1997

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, *164*(1), 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024

Marr, D. (1971). Simple memory: A theory for archicortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *262*(841), 23–81. https://doi.org/10.1098/rstb.1971.0078

Marshall, L., Helgadóttir, H., Mölle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature*, *444*(7119), 610–613. https://doi.org/10.1038/nature05278

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The Sleep Slow Oscillation as a Traveling Wave. *Journal of Neuroscience*, *24*(31), 6862–6870. https://doi.org/10.1523/JNEUROSCI.1318-04.2004

McDevitt, E. A., Duggan, K. A., & Mednick, S. C. (2015). REM sleep rescues learning from interference. *Neurobiology of Learning and Memory*, *122*, 51–62. https://doi.org/10.1016/j.nlm.2014.11.015

Mednick, S. C., Cai, D. J., Shuman, T., Anagnostaras, S., & Wixted, J. T. (2011). An opportunistic theory of cellular and systems consolidation. *Trends in Neurosciences*, *34*(10), 504–514. https://doi.org/10.1016/j.tins.2011.06.003

Mednick, S. C., McDevitt, E. A., Walsh, J. K., Wamsley, E., Paulus, M., Kanady, J. C., & Drummond, S. P. A. (2013). The critical role of sleep spindles in hippocampal-

dependent memory: A pharmacology study. *The Journal of Neuroscience*, *33*(10), 4494–4504. http://dx.doi.org/10.1523/JNEUROSCI.3127-12.2013
Meléndez, J., Galli, I., Boric, K., Ortega, A., Zuñiga, L., Henríquez-Roldán, C. F., & Cárdenas, A. M. (2005). Zolpidem and triazolam do not affect the nocturnal sleep-induced memory improvement. *Psychopharmacology*, *181*(1), 21–26. https://doi.org/10.1007/s00213-005-2228-0
Melton, A. W. (1963). Implications of short-term memory for a general theory of memory. *Journal of Verbal Learning and Verbal Behavior*, *2*(1), 1–21. https://doi.org/10.1016/S0022-5371(63)80063-8
Miller, J. A., Tambini, A., Kiyonaga, A., & D'Esposito, M. (2022). Long-term learning transforms prefrontal cortex representations during working memory. *Neuron*, *110*(22), 3805-3819.e6. https://doi.org/10.1016/j.neuron.2022.09.019
Mölle, M., Bergmann, T. O., Marshall, L., & Born, J. (2011). Fast and Slow Spindles during the Sleep Slow Oscillation: Disparate Coalescence and Engagement in Memory Processing. *Sleep*, *34*(10), 1411–1421. https://doi.org/10.5665/SLEEP.1290
Mölle, M., & Born, J. (2011). Chapter 7—Slow oscillations orchestrating fast oscillations and memory consolidation. In E. J. W. Van Someren, Y. D. Van Der Werf, P. R. Roelfsema, H. D. Mansvelder, & F. H. Lopes Da Silva (Eds.), *Progress in Brain Research* (Vol. 193, pp. 93–110). Elsevier. https://doi.org/10.1016/B978-0-444-53839-0.00007-7
Mölle, M., Eschenko, O., Gais, S., Sara, S. J., & Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *The European Journal of Neuroscience*, *29*(5), 1071–1081. https://doi.org/10.1111/j.1460-9568.2009.06654.x
Mukahirwa, J., Eun, S., Kang, M., Yoon, T., & Park, K. (2021). Deactivation of the attention-shifting ventromedial prefrontal cortex during the encoding and hold phases predicts working memory performance. *NeuroReport*, *32*(18), 1408–1415. https://doi.org/10.1097/WNR.0000000000001744
Müller, G., & Pilzecker, A. (1900). Experimentelle Beiträge zur Lehre vom Gedächtniss. *Zeitschrift Für Psychologie*, *Ergänzungsband*(1), 1–300.
Ngo, H.-V. V., Martinetz, T., Born, J., & Mölle, M. (2013). Auditory Closed-Loop Stimulation of the Sleep Slow Oscillation Enhances Memory. *Neuron*, *78*(3), 545–553. https://doi.org/10.1016/j.neuron.2013.03.006
Ngo, H.-V. V., & Staresina, B. P. (2022). Shaping overnight consolidation via slow-oscillation closed-loop targeted memory reactivation. *Proceedings of the National Academy of Sciences*, *119*(44), e2123428119. https://doi.org/10.1073/pnas.2123428119
Niethard, N., Ngo, H.-V. V., Ehrlich, I., & Born, J. (2018). Cortical circuit activity underlying sleep slow oscillations and spindles. *Proceedings of the National Academy of Sciences*, *115*(39), E9220–E9229. https://doi.org/10.1073/pnas.1805517115
Niknazar, H., Malerba, P., & Mednick, S. C. (2022). Slow oscillations promote long-range effective communication: The key for memory consolidation in a broken-down network. *Proceedings of the National Academy of Sciences*, *119*(26), e2122515119. https://doi.org/10.1073/pnas.2122515119
Niknazar, M., Krishnan, G. P., Bazhenov, M., & Mednick, S. C. (2015). Coupling of Thalamocortical Sleep Oscillations Are Important for Memory Consolidation in Humans. *PLoS ONE*, *10*(12). https://doi.org/10.1371/journal.pone.0144720

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM Sleep, Prefrontal Theta, and the Consolidation of Human Emotional Memory. *Cerebral Cortex*, *19*(5), 1158–1166. https://doi.org/10.1093/cercor/bhn155

Nyhus, E., & Curran, T. (2010). Functional role of gamma and theta oscillations in episodic memory. *Neuroscience & Biobehavioral Reviews*, *34*(7), 1023–1035. https://doi.org/10.1016/j.neubiorev.2009.12.014

Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nature Neuroscience*, *7*(1), Article 1. https://doi.org/10.1038/nn1165

Oudiette, D., & Paller, K. A. (2013). Upgrading the sleeping brain with targeted memory reactivation. *Trends in Cognitive Sciences*, *17*(3), 142–149. https://doi.org/10.1016/j.tics.2013.01.006

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping*, *25*(1), 46–59. https://doi.org/10.1002/hbm.20131

Paller, K. A., & Voss, J. L. (2004). Memory reactivation and consolidation during sleep. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *11*(6), 664–670. https://doi.org/10.1101/lm.75704

Payne, J. D., Tucker, M. A., Ellenbogen, J. M., Wamsley, E. J., Walker, M. P., Schacter, D. L., & Stickgold, R. (2012). Memory for Semantically Related and Unrelated Declarative Information: The Benefit of Sleep, the Cost of Wake. *PLOS ONE*, *7*(3), e33079. https://doi.org/10.1371/journal.pone.0033079

Plihal, W., & Born, J. (1997a). Effects of Early and Late Nocturnal Sleep on Declarative and Procedural Memory. *Journal of Cognitive Neuroscience*, *9*(4), 534–547. https://doi.org/10.1162/jocn.1997.9.4.534

Plihal, W., & Born, J. (1997b). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*, *9*(4), 534–547. https://doi.org/10.1162/jocn.1997.9.4.534

Poe, G. R. (2017). Sleep Is for Forgetting. *The Journal of Neuroscience*, *37*(3), 464–473. https://doi.org/10.1523/JNEUROSCI.0820-16.2017

Poe, G. R., Nitz, D. A., McNaughton, B. L., & Barnes, C. A. (2000). Experience-dependent phase-reversal of hippocampal neuron firing during REM sleep. *Brain Research*, *855*(1), 176–180. https://doi.org/10.1016/s0006-8993(99)02310-0

Pöhlchen, D., Pawlizki, A., Gais, S., & Schönauer, M. (2021). Evidence against a large effect of sleep in protecting verbal memories from interference. *Journal of Sleep Research*, *30*(2), e13042. https://doi.org/10.1111/jsr.13042

Pugin, F., Metz, A. J., Wolf, M., Achermann, P., Jenni, O. G., & Huber, R. (2015). Local Increase of Sleep Slow Wave Activity after Three Weeks of Working Memory Training in Children and Adolescents. *Sleep*, *38*(4), 607–614. https://doi.org/10.5665/sleep.4580

Ramanathan, D. S., Gulati, T., & Ganguly, K. (2015). Sleep-Dependent Reactivation of Ensembles in Motor Cortex Promotes Skill Consolidation. *PLOS Biology*, *13*(9), e1002263. https://doi.org/10.1371/journal.pbio.1002263

Rasch, B., & Born, J. (2008). Reactivation and consolidation of memory during sleep. *Current Directions in Psychological Science*, *17*(3), 188–192. http://dx.doi.org/10.1111/j.1467-8721.2008.00572.x

Rasch, B., & Born, J. (2013). About Sleep's Role in Memory. *Physiological Reviews*, *93*(2), 681–766. https://doi.org/10.1152/physrev.00032.2012

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques, and scoring system for the sleep stages of human subjects* (Vol. 1).

Rosanova, M., & Ulrich, D. (2005). Pattern-Specific Associative Long-Term Potentiation Induced by a Sleep Spindle-Related Spike Train. *Journal of Neuroscience*, *25*(41), 9398–9405. https://doi.org/10.1523/JNEUROSCI.2149-05.2005

Ruch, S., Markes, O., Duss, S. B., Oppliger, D., Reber, T. P., Koenig, T., Mathis, J., Roth, C., & Henke, K. (2012). Sleep stage II contributes to the consolidation of declarative memories. *Neuropsychologia*, *50*(10), 2389–2396. https://doi.org/10.1016/j.neuropsychologia.2012.06.008

Sattari, N., Whitehurst, L. N., Ahmadi, M., & Mednick, S. C. (2019). Does working memory improvement benefit from sleep in older adults? *Neurobiology of Sleep and Circadian Rhythms*, *6*, 53–61. https://doi.org/10.1016/j.nbscr.2019.01.001

Sawaya, R., & Ingvar, D. H. (1989). Cerebral blood flow and metabolism in sleep. *Acta Neurologica Scandinavica*, *80*(6), 481–491. https://doi.org/10.1111/j.1600-0404.1989.tb03915.x

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeitlhofer, J. (2004a). Sleep Spindles and Their Significance for Declarative Memory Consolidation. *Sleep*, *27*(8), 1479–1485. https://doi.org/10.1093/sleep/27.7.1479

Schabus, M., Gruber, G., Parapatics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeitlhofer, J. (2004b). Sleep spindles and their significance for declarative memory consolidation. *Sleep*, *27*(8), 1479–1485.

Schneider, F., Habel, U., Reske, M., Kellermann, T., Stöcker, T., Shah, N. J., Zilles, K., Braus, D. F., Schmitt, A., Schlösser, R., Wagner, M., Frommann, I., Kircher, T., Rapp, A., Meisenzahl, E., Ufer, S., Ruhrmann, S., Thienel, R., Sauer, H., … Gaebel, W. (2007). Neural correlates of working memory dysfunction in first-episode schizophrenia patients: An fMRI multi-center study. *Schizophrenia Research*, *89*(1), 198–210. https://doi.org/10.1016/j.schres.2006.07.021

Schreiner, T., Doeller, C. F., Jensen, O., Rasch, B., & Staudigl, T. (2018). Theta Phase-Coordinated Memory Reactivation Reoccurs in a Slow-Oscillatory Rhythm during NREM Sleep. *Cell Reports*, *25*(2), 296–301. https://doi.org/10.1016/j.celrep.2018.09.037

Sherin, J. E., Elmquist, J. K., Torrealba, F., & Saper, C. B. (1998). Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *18*(12), 4705–4721.

Smith, E. E., & Jonides, J. (1998). Neuroimaging analyses of human working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(20), 12061–12068. https://doi.org/10.1073/pnas.95.20.12061

Staresina, B. P., Bergmann, T. O., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C. E., Axmacher, N., & Fell, J. (2015). Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. *Nature Neuroscience*, *18*(11), 1679–1686. https://doi.org/10.1038/nn.4119

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature*, *437*(7063), 1272–1278. https://doi.org/10.1038/nature04286

Talamini, L. M., Nieuwenhuis, I. L. C., Takashima, A., & Jensen, O. (2008). Sleep directly following learning benefits consolidation of spatial associative memory. *Learning & Memory*, *15*(4), 233–237. https://doi.org/10.1101/lm.771608

Townsend, R. E., Prinz, P. N., & Obrist, W. D. (1973). Human cerebral blood flow during sleep and waking. *Journal of Applied Physiology*, *35*(5), 620–625. https://doi.org/10.1152/jappl.1973.35.5.620

Tucker, M. A., Hirota, Y., Wamsley, E. J., Lau, H., Chaklader, A., & Fishbein, W. (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiology of Learning and Memory*, *86*(2), 241–247. https://doi.org/10.1016/j.nlm.2006.03.005

Ulrich, D. (2016). *Sleep Spindles as Facilitators of Memory Formation and Learning* [Research article]. Neural Plasticity. https://doi.org/10.1155/2016/1796715

Uygun, D. S., Ye, Z., Zecharia, A. Y., Harding, E. C., Yu, X., Yustos, R., Vyssotski, A. L., Brickley, S. G., Franks, N. P., & Wisden, W. (2016). Bottom-Up versus Top-Down Induction of Sleep by Zolpidem Acting on Histaminergic and Neocortex Neurons. *The Journal of Neuroscience*, *36*(44), 11171–11184. https://doi.org/10.1523/JNEUROSCI.3714-15.2016

Van Der Werf, Y. D., Van Der Helm, E., Schoonheim, M. M., Ridderikhoff, A., & Van Someren, E. J. W. (2009). Learning by observation requires an early sleep window. *Proceedings of the National Academy of Sciences*, *106*(45), 18926–18930.

Wallentin, M., Weed, E., Østergaard, L., Mouridsen, K., & Roepstorff, A. (2008). Accessing the mental space—Spatial working memory processes for language and vision overlap in precuneus. *Human Brain Mapping*, *29*(5), 524–532. https://doi.org/10.1002/hbm.20413

Wamsley, E. J., Shinn, A. K., Tucker, M. A., Ono, K. E., McKinley, S. K., Ely, A. V., Goff, D. C., Stickgold, R., & Manoach, D. S. (2013). The effects of eszopiclone on sleep spindles and memory consolidation in schizophrenia: A randomized placebo-controlled trial. *Sleep*, *36*(9), 1369–1376. https://doi.org/10.5665/sleep.2968

Warby, S. C., Wendt, S. L., Welinder, P., Munk, E. G. S., Carrillo, O., Sorensen, H. B. D., Jennum, P., Peppard, P. E., Perona, P., & Mignot, E. (2014). Sleep spindle detection: Crowdsourcing and evaluating performance of experts, non-experts, and automated methods. *Nature Methods*, *11*(4), 385–392. https://doi.org/10.1038/nmeth.2855

Wei, Y., Krishnan, G. P., & Bazhenov, M. (2016). Synaptic Mechanisms of Memory Consolidation during Sleep Slow Oscillations. *The Journal of Neuroscience*, *36*(15), 4231–4247. https://doi.org/10.1523/JNEUROSCI.3648-15.2016

Woo, C.-W., Krishnan, A., & Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. *NeuroImage*, *91*, 412–419. https://doi.org/10.1016/j.neuroimage.2013.12.058

Yin, S., Bi, T., Chen, A., & Egner, T. (2021). Ventromedial Prefrontal Cortex Drives the Prioritization of Self-Associated Stimuli in Working Memory. *Journal of Neuroscience*, *41*(9), 2012–2023. https://doi.org/10.1523/JNEUROSCI.1783-20.2020

Zhang, J., Yetton, B., Whitehurst, L. N., Naji, M., & Mednick, S. C. (2020). The Effect of Zolpidem on Memory Consolidation Over a Night of Sleep. *Sleep*. https://doi.org/10.1093/sleep/zsaa084

Zhao, J., Wang, J., Huang, C., & Liang, P. (2022). Involvement of the dorsal and ventral attention networks in visual attention span. *Human Brain Mapping*, *43*(6), 1941–1954. https://doi.org/10.1002/hbm.25765

Zinke, K., Noack, H., & Born, J. (2018). Sleep augments training-induced improvement in working memory in children and adults. *Neurobiology of Learning and Memory*, *147*, 46–53. https://doi.org/10.1016/j.nlm.2017.11.009