Mechanisms of sleep-associated memory consolidation and next-day learning

Anna á Váli Guttesen

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Abstract

Sleep is linked to overnight memory consolidation and next-day learning. However, it is unclear which mechanisms of sleep support these memory processes. The Active Systems Consolidation model postulates that during sleep, newly formed hippocampus-dependent memories are reactivated and transformed into stable representations within neocortex. This transformation may, in turn, refresh new learning capacity within hippocampus. With a basis in these assumptions, the present thesis aimed to investigate how sleep facilitates offline consolidation and whether sleep-associated consolidation might contribute to learning the following day. Firstly, a targeted memory reactivation paradigm investigated the oscillatory signatures of reactivation during sleep elicited by verbal and non-verbal memory cues. Increases in theta and spindle power were linked to memory reactivation and stabilization during sleep, and furthermore, verbal cues evoked stronger spindle-mediated memory processes as compared to non-verbal memory cues. Secondly, three experiments investigated the benefits of sleeping before and after learning as compared to staying awake, either overnight or during the day. The results suggested that sleep benefits memory consolidation, and that losing sleep disrupts a neural signature of successful learning, namely, beta desynchrony. However, no benefits of sleeping prior to learning were observed when compared to daytime wakefulness. Addressing the novel hypothesis of a potential relationship between sleep-associated consolidation and next-day learning, three experiments consistently found no evidence to support this hypothesis. Surprisingly, an association was reported between forgetting during daytime wakefulness and subsequent learning of similar materials. Overall, this thesis provides insights into how sleep supports consolidation and raises novel questions about which processes during both sleep and wake may support new memory formation.

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Chapter 1:

General Introduction

The ability to remember is an essential part of our daily lives. Without memory, we would not be able to understand the world around us, nor have any sense of continuity from one moment to the next, as none of our experiences would be cognitively stored. When we initially form a memory, it is in a fragile state and, for it to become a long-term memory, it needs to undergo a process of transformation and strengthening – a process of consolidation. This consolidation process is thought to be supported by sleep (Stickgold, 2005; Walker & Stickgold, 2004), with recent work suggesting that sleep actively strengthens memories of recent experiences (Backhaus et al., 2008; Gais et al., 2006; Payne et al., 2012; Talamini et al., 2008). Additionally, sleeping prior to learning is found to support subsequent memory formation (Alberca-Reina et al., 2014; Cousins et al., 2018; Mander et al., 2011; Ong et al., 2020; Poh & Chee, 2017; Tempesta et al., 2016; Yoo et al., 2007). Thus, sleep seems to serve an important function for learning and consolidation.

This thesis aimed to address questions concerning the neurocognitive mechanisms through which sleep supports memory consolidation and next-day learning. The present chapter will therefore introduce theoretical models of memory consolidation and sleep, and review the evidence addressing the role of sleep for memory consolidation and next-day learning. Furthermore, I will evaluate the evidence suggesting that sleep loss disrupts neural signatures of learning. This chapter will conclude with an outline of thesis chapters and their research aims.

1.1 Memory consolidation

An episodic memory is often defined as a detailed memory of an experience (Tulving, 2002). During learning, it is thought that information is encoded in the hippocampal system and within neocortical networks. The information of the experience is processed across neocortical regions and the role of hippocampus is to integrate and bind the cortical information into a coherent representation (Eichenbaum, 2000, 2004). After learning, the process undergoes a process of stabilization on a synaptic level as well as systems level. Synaptic consolidation refers to the growth of new synaptic

connections as well as modifications to existing ones, and is thought to be complete within minutes to hours of learning. Systems consolidation builds on synaptic consolidation and refers to the gradual redistribution and reorganisation of memory traces across brain regions thought to take place over a longer time-scale (Dudai, 2004; Dudai et al., 2015). To provide an overview of the current accounts of memory consolidation, the following sections will cover two models, namely, the Standard Model of Systems Consolidation and the Multiple Trace Theory.

1.1.1 The Standard Model of Systems Consolidation

The Standard Model of Systems Consolidation posits that over time, memories become less dependent on hippocampal short-term store and are reorganised within neocortical networks for long-term storage. This transformation process is thought to rely on repeated reactivations of the memory trace within hippocampus and neocortex which strengthen the connectivity within cortical modules. In this manner, the retrieval of a memory trace eventually becomes fully independent of hippocampus. This has benefits for learning by maintaining hippocampal encoding capacity for new learning, and simultaneously reduces interference from new memories due to the integration within long-term memory stores (Frankland & Bontempi, 2005; McClelland et al., 1995; Squire & Alvarez, 1995; Squire & Bayley, 2007).

Much of the evidence in support of systems consolidation comes from neuropsychological studies (Scoville & Milner, 1957; Scoville & Milner, 2000; Squire & Alvarez, 1995). One well-known case is of patient H.M. who had large parts of his medial temporal lobe removed, including bilateral hippocampus. As a consequence, H.M. suffered from severe anterograde amnesia and could not form new declarative memories. Furthermore, H.M. showed signs of temporally graded retrograde amnesia, where he was unable to retrieve recently formed memories (encoded shortly before the surgery), but retained memories of earlier life experiences (Scoville & Milner, 1957; Scoville & Milner, 2000). These findings provided initial evidence of the role of hippocampus in recent rather than remote memories. Similarly, research in animals has addressed this in a more controlled environment,

and showed that monkeys with hippocampal lesions were severely impaired at remembering recently learned objects, while their memories of objects learned several weeks before the surgery was unaffected (Zola-Morgan & Squire, 1990). Note, there is also other evidence based on neuroimaging studies which will be discussed in Section 1.3.2 of this Chapter. Taken together, these neuropsychological studies suggest that over time, hippocampus-dependent memories are reorganised in neocortex and eventually become independent of hippocampus.

1.1.2 The Multiple Trace Theory

The time-limited involvement of hippocampus for episodic memories has been disputed in an alternative theory of consolidation (Nadel & Moscovitch, 1997; Nadel et al., 2000; Nadel et al., 2007). This model has been named the Multiple Trace Theory (MTT) and argues that retrieval of rich contextual details continues to rely on hippocampus over time, while neocortex stores a decontextualized (semantic) version of the memory which can be retrieved independently of hippocampus. In support of this theory, studies have shown that patients with hippocampal damage show severe and ungraded amnesia, while access to semantic memories mostly remain intact (Cipolotti et al., 2001; Rosenbaum et al., 2008; Spiers et al., 2001). For example, a patient showed a rich knowledge of words which could only have been learnt during the same period as their autobiographic episodic memories, suggesting that the retrieval of episodic memories continue to rely on the hippocampus, whilst semantic knowledge remains accessible within neocortex (McCarthy & Warrington, 1992; Verfaellie et al., 1995). Thus, the Multiple Trace Theory is in a better position than the Standard account to explain the cases showing non-graded (i.e. flat) retrograde amnesia following bilateral hippocampal damage.

There is some evidence that is less easily reconciled with the Multiple Trace account. Teng and Squire (1999) reported a patient with extensive damage to bilateral MTL including hippocampus, who was able to retrieve detailed episodic memories from his youth. These findings suggest that remote episodic memories may become fully independent of the hippocampus. More recently, models have

emerged from the standard systems consolidation account and MTT with a focus on how sleep may support the consolidation of memories.

1.2 Sleep and memory consolidation

Sleep is defined as a natural and reversible state of reduced responsiveness and is associated with a loss of consciousness (Rasch & Born, 2013). From an evolutionary perspective, the reduced responsiveness to the environment increases vulnerability and poses a danger to survival. In light of this, researchers have reasoned that the role of sleep must be essential, resulting in many theories on why we sleep (Siegel, 2005; Zielinski et al., 2016). Among these, sleep is suggested to serve a function for learning and memory (Maquet, 2001), whereby researchers have investigated whether there are specific components of sleep that support them.

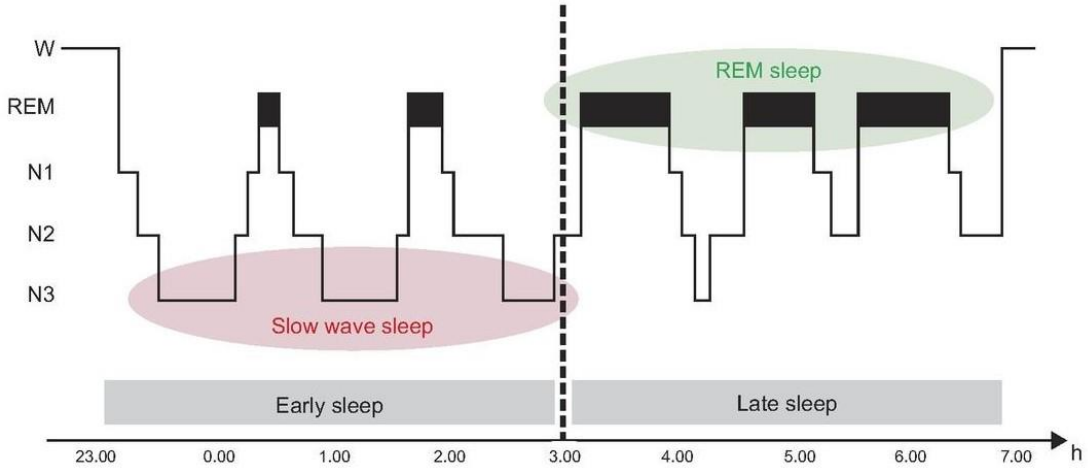

Figure 1.1. Sleep stages across a typical night. The stages alternate between NREM and REM. The early half of the night is dominated by SWS and the late half of the night is dominated by REM. Figure adapted from (Rasch & Born, 2013).

Human sleep is broadly divided into two main stages based on electroencephalography (EEG) oscillatory patterns: rapid eye-movement sleep (REM) and non-rapid eye-movement sleep (NREM). In addition to muscle atonia and rapid eye movements, REM sleep is marked by low-amplitude theta activity (4-8 Hz, Iber, 2007; Steriade, 2003). Furthermore, NREM is divided into three stages, N1, N2 and N3 (also referred to as slow-wave sleep, SWS), which alternate throughout the night with REM

sleep in cycles of around 90 minutes (Iber, 2007), although SWS dominates the first half of the night while REM sleep dominates the second half (Rasch & Born, 2013, see Figure 1.1). N1 is defined as the transition between wakefulness and sleep and is characterised by vertex sharp waves and oscillations in the alpha (8-12 Hz) and theta range (~4-8 Hz, Fuller et al., 2006). N2 is marked by the presence of sleep spindles and K-complexes: spindles are defined as short bursts of waxing and waning activity between ~10-16 Hz, while K-complexes often evoked by sensory stimuli characterised by brief negative voltage peaks high in amplitude followed by slow positive complexes and are thought to suppress arousal (Alger et al., 2014; Cash et al., 2009; Rasch & Born, 2013). Finally, slow-wave sleep is the deepest stage of sleep and is characterised by low frequency oscillations (0.5-4 Hz) high in amplitude (Genzel et al., 2014). In SWS, slow-oscillations (SOs, < 1 Hz) range across the whole brain along with thalamocortical spindles (~12-16 Hz) and hippocampal ripples (~100-300 Hz, Staresina et al., 2015).

Originally, sleep was suggested to passively protect memories from interference as compared to the increased interference during wakefulness (Jenkins & Dallenbach, 1924). More recent work has suggested that sleep actively strengthens memories of recent experiences (Backhaus et al., 2008; Gais et al., 2006; Payne et al., 2012; Talamini et al., 2008). Focusing on specific stages of sleep and their contributions to memory, early studies measured memory retention across the first half of the night (rich in SWS) and across the second half of the night (rich in REM sleep, see Figure 1.1). Participants in the early sleep condition would learn a memory task (word pairs) in the evening and then sleep for 3-4 h before being woken up to complete a memory test, whereas those in the late sleep condition would first sleep for ~3 h, complete the learning phase and then sleep for another 3-4 h before a memory test. These would be compared with control conditions where retention periods were kept the same, but with periods of wake rather than sleep. The studies found that retention across the first half of the night showed benefits for hippocampus-dependent declarative memories as compared with the latter half, hinting at a role of SWS (which dominates in the first half) for declarative memory consolidation (Fowler et al., 1973; Yaroush et al., 1971). Other studies with similar paradigms have

also suggested that REM sleep contributes to non-declarative memories (Plihal & Born, 1997). Although these paradigms provide rough measures of SWS (due to the additional sleep stages involved in each early and late halves) and there have been inconsistent findings using these paradigms (Gais et al., 2000; Rauchs et al., 2004), these studies contributed to theories predicting a role for SWS for memory consolidation.

Other studies have found links between parameters of SWS and memory retention. There is some evidence that memory performance is associated with time spent in SWS (Alger et al., 2012; Backhaus et al., 2006; Diekelmann et al., 2012; Scullin, 2013) or NREM sleep (Wagner et al., 2007). Measuring EEG power in NREM sleep, some have found correlations between memory retention and slow-wave activity (SWA, Holz et al., 2012) as well as spindle activity (Holz et al., 2012; Schabus et al., 2004) or spindle density (Cox et al., 2012; Gais et al., 2002). However, recent efforts have failed to replicate these associations in larger samples (Ackermann et al., 2015; Cordi & Rasch, 2021), suggesting that the relationships between sleep parameters and memory consolidation might have been overestimated.

Researchers have gone beyond correlational approaches and manipulated slow oscillations to observe causal effects on memory. Using transcranial direct current stimulation (tDCS), which involves weak electrical stimulation to the scalp to briefly modify the membrane potential of neurons in the brain, researchers have induced slow oscillations (0.75 Hz) during post-learning sleep. Compared to the sham condition, stimulation enhanced slow oscillations and spindle activity (8-12 Hz) and benefitted memory retrieval of paired associates, whilst no such differences were observed for the procedural tasks. These findings suggested that slow oscillations facilitate declarative memory consolidation (Marshall et al., 2006; Marshall et al., 2004). However, using a similar approach, several studies have not found any benefits of tDCS on declarative memory retention (Bueno-Lopez et al., 2019; Eggert et al., 2013; Paßmann et al., 2016; Sahlem et al., 2015). Instead, some of these studies have reported more fragmented sleep compared to sham (Eggert et al., 2013; Paßmann et al., 2016), raising

questions about the specific conditions under which this stimulation paradigm is effective. More recently, researchers have developed an auditory stimulation paradigm which delivers stimuli in phase with the endogenous rhythmic occurrence of SO up-states. In their seminal study, Ngo et al. (2013) implemented this closed-loop auditory stimulation approach to boost SOs. Compared to the sham condition, they found that enhancing SO amplitude increased alignment with spindle activity and improved memory retention. From similar studies as well as correlational approaches, there is accumulating evidence that the temporal coupling between SOs and spindles is important for memory consolidation (Bar et al., 2020; Helfrich et al., 2018; Latchoumane et al., 2017; Leminen et al., 2017; Maingret et al., 2016; Mikutta et al., 2019; Mölle & Born, 2011; Ngo et al., 2013; Ong et al., 2016; Papalambros et al., 2017; Perl et al., 2016; Prehn-Kristensen et al., 2020; Schreiner et al., 2021), however, not all have been able to replicate these findings (Henin, Borges, et al., 2019). Overall, the evidence suggests that oscillations of SWS may support consolidation.

1.3 The Active Systems Model of Sleep-Dependent Memory Processing

The Active Systems Model of Sleep-Dependent Memory Processing builds on the Standard Model of Systems Consolidation by specifying the role of neural oscillations in sleep. Initially, memory traces are in a labile state and rely on the hippocampal system. In subsequent sleep, memories are repeatedly reactivated and gradually transformed into long-term representations within neocortex. This dialogue between the hippocampal and neocortical systems relies on interactions between the three cardinal oscillations of SWS, namely, neocortical slow oscillations (SOs), thalamocortical spindles and hippocampal ripples (see Figure 1.2, Staresina et al., 2015). SOs represent synchronous neuronal firing patterns across the neocortex, where the activity alternates between hyperpolarized down-states of neuronal quiescence and depolarized up-states of excitability. The SO up-states trigger reactivations of memories along with hippocampal ripples. Ripples and associated memory reactivations are nested within the troughs of spindles, which, in turn, are tightly coupled with the up-state of the SO. When spindles are tightly coupled with SO up-states, this facilitates the information transfer of the reactivated memory trace. Thus, reactivations and sleep oscillations are critical to the

gradual integration of memory traces within neocortex (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013). In this manner, reactivation and reorganisation are complementary processes mediating memory consolidation during sleep. The evidence directly investigating memory reactivation and reorganisation during sleep will be evaluated in this section.

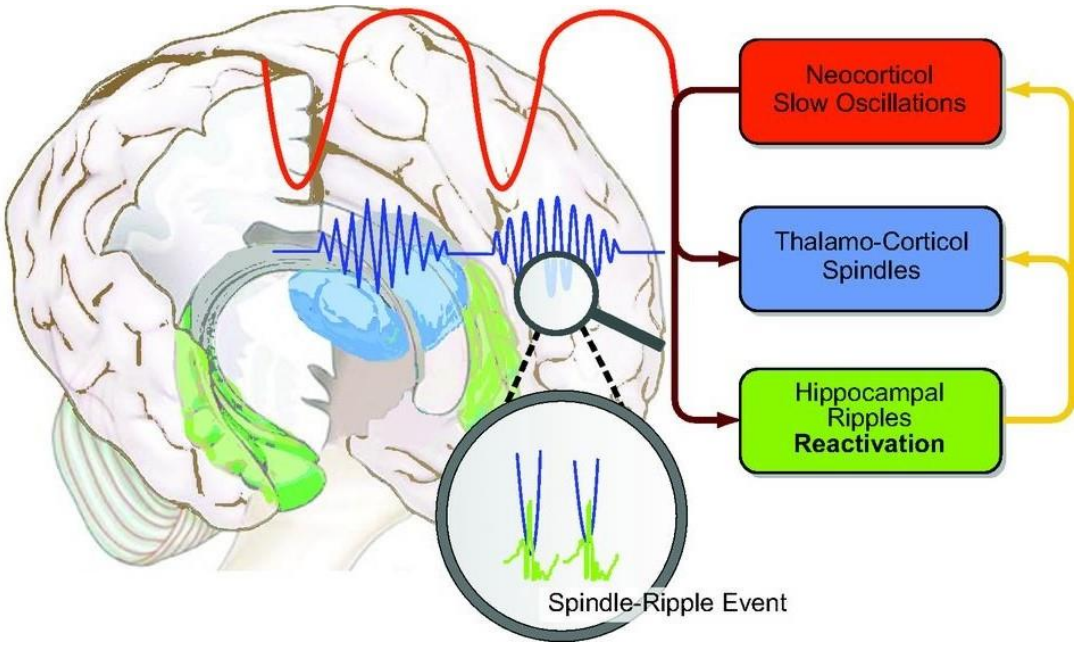

Figure 1.2. The role of oscillations in sleep for memory reactivation and redistribution. Newly formed memories are repeatedly reactivated in hippocampus and neocortex which drives their gradual redistribution to the long-term neocortical store. This process of systems consolidation is driven by oscillations of SWS which facilitate a dialogue between neocortex and hippocampus. The depolarizing up-states of the neocortical slow oscillations (red) drive the repeated reactivation of hippocampal memory representations along with hippocampal ripples (green) and thalamocortical spindles (blue). Spindle-ripple events (shown in larger scale) are defined as bursts of ripples and associated reactivated memory traces which are nested within the troughs of a spindle. Neocortical slow oscillation up-states drive these spindle-ripple events, thereby redistributing the reactivated memory trace for long-term storage. Figure adapted from Rasch and Born (2013).

1.3.1 Memory reactivation during sleep

A central tenet of the Active Systems Model of Sleep-Dependent Memory Processing is that memories are repeatedly reactivated during sleep. Memory reactivation is defined as the process that leads to the activation of a memory trace (Schreiner & Staudigl, 2020). Research on memory reactivation during sleep has come from animal and human studies.

1.3.1.1 Evidence on spontaneous reactivation from animal studies

Animal research has provided support for the notion that memories are replayed during sleep. Researchers have found that sequences of neuronal firing in rat hippocampus during wakeful learning spontaneously reoccur during NREM sleep, suggesting that memories formed during wakefulness are replayed in sleep (Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). In particular, hippocampal ripples during sleep have been tightly linked with memory reactivation (Pavlides & Winson, 1989; Wilson & McNaughton, 1994), whereby the extent of sharp wave ripple events is found to predict spatial memory performance in subsequent wakefulness (Dupret et al., 2010). In line with this, disrupting these oscillations impairs memory performance after sleep (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). In one study, researchers used auditory cues linked to the memory to bias memory replay and found evidence of a tight hippocampal-cortical interaction co-occurring with ripples and reactivation patterns (Bendor & Wilson, 2012; Rothschild et al., 2016). Together, these findings from rodent studies suggest that ripples and associated memory reactivation facilitate the consolidation of hippocampus-dependent memories.

1.3.1.2 Evidence on spontaneous reactivation from human studies

In humans, researchers have used electrophysiological (EEG) and functional neuroimaging measures to investigate which neural signatures of human sleep support memory reactivation. In earlier attempts to investigate reactivation during sleep, researchers investigated whether the brain regions involved during wakeful encoding were also activated in subsequent sleep (Bergmann et al., 2012; Peigneux et al., 2004). Using simultaneous EEG and functional magnetic resonance imaging (fMRI),

Bergmann et al. (2012) recorded while participants learned either a face-scene association or a control visuomotor task (on separate days). In subsequent sleep, they observed a stronger hippocampal and neocortical activation after the face-scene task compared to after the control task, suggesting that learning-related activity occurred in sleep. These increases were temporally coupled with spindle events and correlated with pre-sleep behavioural performance, indicating that spindles are linked to reactivation-like patterns. However, without a measure of retention, it remained unclear whether this pattern of reactivation and spindle activity had any bearing on the consolidation process.

More recent work has tracked the emergence of memory replay by studying the content of reactivated memory traces. Schönauer et al. (2017) investigated whether they could determine the type of images (faces or houses) presented during learning by using a multivariate pattern analysis (MVPA) based on EEG recordings of ensuing sleep. While they found evidence of memory reprocessing during both REM and NREM sleep, only reactivation strength during NREM sleep predicted later memory benefits. The researchers also found links between increases in spindle activity and the accuracy with which they could classify memory replay as a face or a house, again hinting at a role of spindles for reactivation. However, considering the importance of temporal coupling between SOs and spindles for memory consolidation, these data could not provide insights into how these neural interactions supported reactivation to strengthen the memory trace. To further investigate the role of oscillations for reactivation, recent work has demonstrated that endogenous reactivation patterns were precisely timed with SO-spindle complexes (Schreiner et al., 2021). On separate experimental days, participants learned to associate words with images of objects or scenes before going to sleep with EEG monitoring. Based on the EEG data from a subsequent task when participants viewed new images of objects or scenes (on separate sessions), the researchers could train a classifier to distinguish patterns of objects or scenes on the sleep EEG data, thereby identifying whether reactivation patterns reflected the type of material learnt before sleep. They found that during SO-spindle complexes, activation patterns were biased towards the previously learnt material. Furthermore, the strength of the reactivation pattern predicted memory retention. With this study, they highlighted the importance of

SO-spindle coupling in endogenously reactivating and consolidating recently formed memories. Linking this back to the Active Systems account, the precise timing between SOs, spindles and ripples may enable the replay of hippocampus-dependent memories to neocortical long-term storage (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013).

1.3.1.3 Evidence from targeted memory reactivation during human sleep

The evidence from the previous section addressed memory reactivation occurring spontaneously. An alternative line of work has sought to directly manipulate which memory is being reactivated using TMR. In a pioneering study by Rasch et al. (2007), participants firstly learned object-location associations while smelling a rose odour. The participants then slept, and when they reached SWS the researchers again administered rose-scented air for some of the participants. Participants who had received odours during SWS had improved memory recall. These effects were not observed in the control conditions where participants either received the odours during rapid eye movement (REM) sleep or did not receive any odours. These findings suggested that reinstating the learning context during SWS improves memory retention. Others have since investigated whether cueing during sleep can selectively reactivate individual memories. Rudoy and colleagues (2009) addressed this question of specificity by pairing the learned stimuli with various environmental sounds. In ensuing sleep, half of these sounds were replayed and upon waking, they exhibited a higher memory accuracy for those items that had been cued compared to those that had not. Thus, they demonstrated that memory reactivation can be triggered in SWS using auditory cues and that cueing can influence a select subset of specific newly formed memories.

Building upon this work, others have also found TMR benefits when using various types of auditory stimuli (Antony et al., 2018; Cairney et al., 2016; Cairney et al., 2017; Göldi et al., 2019; Schechtman et al., 2021; Schönauer, Geisler, et al., 2014; Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2015). Schreiner and Rasch (2015) tested whether cueing with verbal cues during sleep would improve vocabulary learning. Participants learned Dutch words along with their translations and in subsequent

non-REM sleep, half of the learnt words were cued. Indeed, the cued words led to improved memory performance compared to the non-cued words. Taken together with similar studies using spoken words (Cairney et al., 2016; Farthouat et al., 2017; Göldi et al., 2019; Lehmann et al., 2016; Schreiner, Göldi, et al., 2015), the evidence suggests that memories can also be reactivated and strengthened with complex verbal stimuli during non-REM sleep. However, little is known about how the memory effects of different types of auditory cues compare.

Moreover, with TMR, it is possible to gain insight into neural mechanisms of reactivation by investigating oscillatory response to memory cues. Spindles have repeatedly been linked to memory reactivation induced by TMR (Antony et al., 2018; Cox, Hofman, et al., 2014; Farthouat et al., 2017; Groch et al., 2017; Laventure et al., 2018; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). For example, Cairney et al. (2018) compared the evoked response to memory cues with that of previously unheard control cues, and found a significant increase in spindle power (~13-16 Hz) ~1.7 – 2.3 s after stimulus onset. Interestingly, based on this time-window of spindle increase, they were furthermore able to decode the categorical features of the reactivated memories, suggesting that spindles may mediate information processing of newly formed memories. Furthermore, the level of distinction between the categorical features also predicted how well participants remembered the cued items (vs. the non-cued items) at later test, supporting the idea that spindles serve an important function for memory consolidation. In line with these findings, other studies have cued memories associated with left- or right-hand movements and showed evidence of lateralized reactivation. Additionally, the strength of this reactivation signal has been linked to spindle power as well as memory retention (Cox, van Driel, et al., 2014; Wang et al., 2019). Thus, localized spindle activity after learning may reflect memory reinstatement which supports offline consolidation. A recent framework reconciles these empirical findings and argues that spindles support consolidation by mediating the reinstatement and reprocessing of memory traces within local networks (Antony et al., 2019).

Theta power (4-8 Hz) has also been linked to memory reactivation. A working model posits complementary roles of theta and spindle activity, whereby theta supports the reinstatement of memory representations and is paralleled or immediately followed by spindles which support the reprocessing and stabilization of the reactivated memory trace (Schreiner & Rasch, 2017). In support of this model, increases in theta power following the onset of a memory cue have been reported in several TMR studies (Farthouat et al., 2017; Groch et al., 2017; Joensen et al., 2022; Laventure et al., 2018; Lehmann et al., 2016; Oyarzún et al., 2017; Schechtman et al., 2021; Schreiner et al., 2018; Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2015). Schreiner et al. (2018) found that theta activity which occurred during wakeful retrieval reoccurred during TMR in subsequent sleep. Based on this, they suggested that theta supports memory reinstatement irrespective of sleep or wake. Beyond correlational evidence, blocking theta and spindle activity after reactivation with auditory feedback also blocked the behavioural benefit of cueing (Schreiner, Lehmann, et al., 2015). In this manner, theta and spindle power may act in concert to reinstate and stabilize newly formed memory traces.

1.3.2 Evidence from memory reorganisation during sleep

The Active Systems account suggests that sleep supports memory reorganisation (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013, see Figure 1.3). Combining behavioural and neuroimaging techniques, Takashima et al. (2009) tested the hypothesis that memories undergo a systems-level change during sleep. On the first experimental day, participants learned to associate faces with locations. The second session took place 24 h later (including a whole night of sleep) during which participants learned a new set of face-location pairings followed by a retrieval phase inside the MRI scanner. At retrieval, participants performed a cued recall test for the first set of face-location pairings (remote memories) and the second set (recent memories). They found that hippocampal activity during retrieval decreased with consolidation and that neocortical activity increased. Furthermore, they found a stronger functional connectivity between hippocampus and neocortex

(within regions linked to face and place processing) for the retrieval of recent compared to the remote associations, suggesting that hippocampus binds neocortically distributed information for the retrieval of recent memories and that this link decreases with consolidation. Together, these results supported the hypothesis that a delay of 24 h including sleep supports the migration of declarative memories from hippocampus to neocortex.

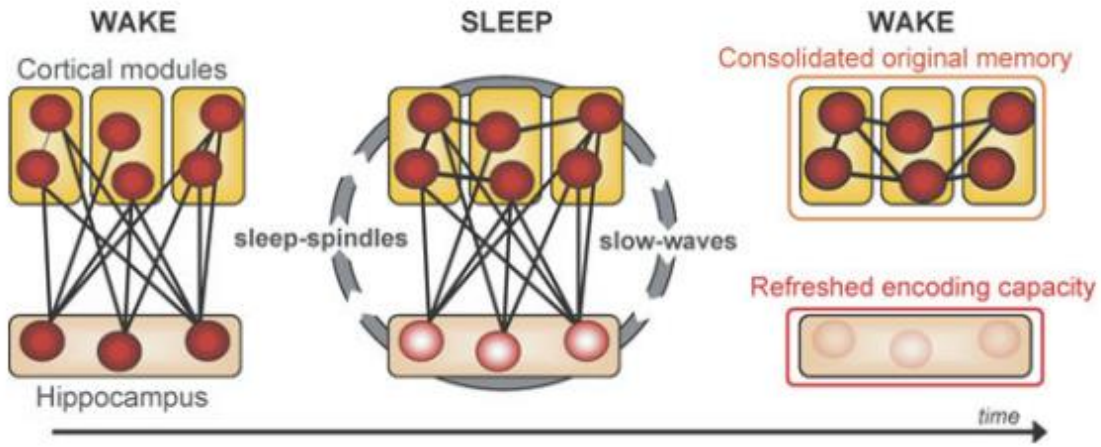

Figure 1.3. Memory reorganisation during sleep. During encoding, the hippocampus rapidly integrates information within distributed cortical modules. In subsequent sleep, reactivation of this hippocampal-cortical network leads to incremental strengthening of cortico-cortical connections, which over time, allow these memories to become independent of the hippocampus and gradually integrated with pre-existing cortical memories, thereby refreshing encoding capacity within hippocampus. Figure adapted from Walker (2009).

Other work has more directly investigated the role of sleep in systems consolidation. Researchers have found that a nap is sufficient to reduce hippocampal involvement at retrieval (Himmer et al., 2019; Takashima et al., 2006). Some have investigated how sleep architecture supports consolidation and found supporting evidence that sleep facilitates a shift in dependency away from the hippocampus. These studies have reported a link between the amount of SWS following learning and the level of hippocampal decrease at later retrieval (Cairney et al., 2015; Takashima et al., 2006). Beyond

declarative learning, similar findings have been observed with statistical learning (Durrant et al., 2013). In line with the Active Systems model, these studies show that SWS actively contributes to hippocampal-to-neocortical reorganisation of memories.

There is some conflicting evidence regarding at which point hippocampus becomes disengaged at retrieval. In a within-subjects study by Gais et al. (2007), participants learned and retrieved word pairs and then either slept or remained awake overnight (i.e. they were sleep deprived). After a 48 h delay, including a night of recovery sleep, participants returned and completed another memory test. Six months later, participants returned for a follow-up memory test. During all learning and retrieval phases, brain activity was measured with fMRI. When comparing brain activity between the sleep and wake conditions elicited at 48 h, the researchers found that when participants slept after learning, hippocampus was more strongly engaged during retrieval after sleep. Furthermore, they found increased functional connectivity between hippocampus and medial prefrontal cortex during retrieval. Six months later, there was evidence of increased hippocampal-neocortical connectivity for the sleep condition compared to the sleep deprivation condition. Based on these findings, they suggested that the initial increase in hippocampal activity reflected an early consolidation process during sleep, and in the long term, these initiated processes transform the memory trace to become more reliant on neocortical systems. Similar findings have been observed after 72 h (Sterpenich et al., 2007). Notably, the finding of hippocampal increase during retrieval after sleep conflicted with other studies showing instead a decrease after a nap (Himmer et al., 2019; Takashima et al., 2006) or after 24 h including sleep (Cairney et al., 2015; Takashima et al., 2009). One possible explanation for these inconsistent findings is simply that some materials may be more rapidly consolidated than others. Indeed, there is evidence indicating that pre-existing knowledge and rehearsal increases the speed of consolidation (Himmer et al., 2019; Tse et al., 2007). Thus, the time-scale of memory reorganisation may vary depending on such factors at learning.

1.3.3 Sleep and subsequent learning

As a consequence of memory reorganisation, sleep accordingly facilitates the shift in dependency away from the hippocampus, thereby refreshing hippocampal capacity for new learning (Walker, 2009). In line with this, sleep is found to facilitate new learning of hippocampus-dependent memories (Antonenko et al., 2013; Mander et al., 2011; Ong et al., 2020; Ong et al., 2018; Van Der Werf et al., 2009). Some have argued that the same processes that mediate memory reorganisation during sleep, may also benefit subsequent learning (Walker, 2009). Indeed, the neural oscillations linked to overnight memory retention have also been linked to new learning in hippocampus, suggesting that these processes may rely on overlapping mechanisms. In Section 1.2 of this chapter, I reviewed the literature on the oscillations of SWS that are linked to memory consolidation. To briefly reiterate, SOs and spindles were considered the prime candidates supporting consolidation and are thought to facilitate the redistribution of memory traces from hippocampus to neocortex (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). To evaluate whether the sleep-associated mechanisms supporting consolidation and subsequent learning overlap, the present section will review the evidence finding associations between oscillations of sleep and subsequent learning.

There is some evidence that slow-wave activity (SWA, 0.5-4 Hz, sometimes separated into SOs, < 1 Hz, and delta waves, 1-4 Hz) is linked to subsequent learning. In a within-subjects overnight study, researchers delivered sounds to disrupt SWA in thirteen elderly participants in one condition (Van Der Werf et al., 2009). The same participants also completed the control condition consisting of a typical night of sleep with the same sleep duration as the disruption condition. The following day, participants completed a learning task inside the MRI scanner. Based on performance at a subsequent test, they found that participants performed worse on an image recognition task when learning took place after SWA disruption compared to a typical night of sleep. Additionally, they found that, during encoding, the hippocampal response was reduced in SWA disruption condition. Thus, disrupting SWA had detrimental effects on learning. Furthermore, considering that they found no difference in implicit

task performance (serial reaction time task), disrupting SWA seemed to only impair encoding of hippocampus-dependent memories (Van Der Werf et al., 2009). In line with this, boosting SWA or SOs has also shown beneficial effects on declarative learning (Antonenko et al., 2013; Ong et al., 2018). Using a stimulating current to boost SWA during a nap, the researchers found a benefit in all hippocampus-dependent (pictures, word-pairs and word-lists) but not hippocampus independent (finger-tapping) tasks when they compared performance between stimulation and sham conditions (Antonenko et al., 2013). Similarly, enhancing SO by delivering sounds simultaneously as the SO peaks occurred, resulted in a positive correlation between SO enhancement and declarative learning, however, they did not find an overall group benefit for learning (Ong et al., 2018). Taken together, the evidence suggests that SWA may play an important role for subsequent hippocampus-dependent learning. Considering that SOs are also thought to support memory reorganisation, these overlaps hint at a link between sleep-associated reorganisation and subsequent learning.

In addition to SWA, spindles have repeatedly been linked to memory retention (Antony et al., 2018; Cairney, Guttesen, et al., 2018; Cox et al., 2012; Creery et al., 2015; Farthouat et al., 2017; Fuentemilla et al., 2013; Göldi et al., 2019; Groch et al., 2017; Lehmann et al., 2016; Schabus et al., 2004; Schreiner et al., 2021) and have also been linked to subsequent declarative learning (Antonenko et al., 2013; Mander et al., 2011; Ong et al., 2020). Mander et al. (2011) found that napping only benefitted performance on a declarative (face-name pair) task, not a procedural motor-skill learning task and, importantly, spindle activity was associated with declarative learning performance after sleep, suggesting that spindles may support subsequent memory formation. Considering the role of spindles for memory consolidation, the researchers argued that this could be interpreted in light of the Active Systems model: without sleep, the temporary hippocampal store had not had the opportunity to redistribute previous memories and was therefore poor at encoding new declarative memories. This study provided some indirect evidence that oscillations that support consolidation may also support post-sleep learning. If these mechanisms supporting memory consolidation and subsequent learning

are indeed shared, one would expect to observe a relationship between the two processes. However, this relationship has not been empirically tested.

1.4 Alternative theories of sleep and consolidation

Besides the Active Systems, there exist other accounts of how sleep benefits memory. Two prominent theories are the Contextual Binding account and the Synaptic Homeostasis model.

1.4.1 Contextual Binding account of consolidation

The recently developed Contextual Binding account builds on the Multiple Trace Theory by arguing that sleep benefits memory merely by reducing contextual interference (Yonelinas et al., 2019). This contextual binding account is similar to the Multiple Trace account in that memories rich in detail continue to depend on hippocampus, whilst neocortex supports semantic and decontextualized knowledge. The hippocampus binds item-related and context-related information during encoding and contextual changes in time and space contribute to forgetting of encoded items. Unlike the Active Systems account which posits that sleep supports reactivation and stabilization, the contextual binding account suggests that any replay of memories merely reflects residual activity due to the context. Furthermore, if the spatial or temporal context changes, this residual activity will decrease. In this manner, sleep has a passive role for memory retention by reducing contextual interference.

A range of evidence supports the tenets of the Contextual Binding model. Similar to the Multiple Trace Theory, the Contextual Binding theory can account for the studies showing that hippocampal damage results in severe and ungraded amnesia (Cipolotti et al., 2001; Rosenbaum et al., 2008; Spiers et al., 2001), which are not well explained by the Active Systems account. Furthermore, the model focuses on the reduced interference during sleep and can explain some evidence from the sleep and memory literature. For example, work observing rapid benefits of napping after learning compared to staying awake on declarative memory retention (Tucker et al., 2006) supports the notion that sleep reduces contextual interference and thereby reduces forgetting. While these rapid effects could also be

explained by synaptic consolidation during sleep (Dudai, 2004; Dudai et al., 2015), this account provides a different perspective on how sleep supports memory consolidation.

There is some evidence from sleep and memory studies that is not fully explained by the Contextual Binding account. Although they argue that SWS is beneficial for memory retention due to the deeper stage of sleep as compared with REM, recent findings of the close interplay between oscillations and memory stabilization are more difficult to reconcile with the model (Bar et al., 2020; Helfrich et al., 2018; Latchoumane et al., 2017; Leminen et al., 2017; Maingret et al., 2016; Mikutta et al., 2019; Mölle & Born, 2011; Ngo et al., 2013; Ong et al., 2016; Papalambros et al., 2017; Perl et al., 2016; Prehn-Kristensen et al., 2020; Schreiner et al., 2021). For example, the findings by Schreiner et al. (2021) whereby SO-spindle coupling and reactivation were linked to improved memory performance suggest an active rather than passive process of sleep for memory transformation and stabilization.

1.4.2 Synaptic Homeostasis Hypothesis

The Synaptic Homeostasis model proposes that sleep is essential for brain plasticity. During waking, synapses require more energy to form connections. If synaptic strength continues to increase, this will lead to saturated neural signalling, which affects learning and memory. Slow waves during sleep are necessary to downscale the synapses to a baseline level, preparing them for new learning. In addition, by improving signal-to-noise ratio, synaptic homeostasis indirectly benefits consolidation (Tononi & Cirelli, 2012, 2014).

Findings from animal and human studies have provided evidence in support for synaptic downscaling during sleep. During wakefulness, synapses potentiate and synaptic strength is increased. If this continues, this will lead to saturated neural signalling and this will impair learning and memory due to saturation of upregulated synapses. During the subsequent period of sleep, SWA downscales the potentiated synapses to a baseline level, preparing them for new learning (Bushey et al., 2011; de Vivo et al., 2017; Gilestro et al., 2009; Huber et al., 2013; Liu et al., 2010; Spano et al., 2019; Vyazovskiy et al., 2008). In a human transcranial magnetic stimulation (TMS) and EEG study, excitability in the human

frontal cortex increased with time awake and was reset to baseline following sleep (Huber et al., 2013). Furthermore, synaptic number and strength during wake is thought to drive the amplitude of slow waves (Esser et al., 2007; Riedner et al., 2007). In humans, theta activity, an EEG marker for wakeful learning, is thought to be a predictor of SWA in subsequent sleep (Finelli et al., 2000; Huber et al., 2007; Huber et al., 2004). Hence, it seems increases in learning during wake predict SWA during sleep, which in turn help downscale synapses to baseline levels. Importantly, downscaling is thought to benefit memory and learning as renormalisation of synapses prevents saturation. Thereby meaningful signal is separated from unwanted interference (Tononi & Cirelli, 2012, 2014). Behaviourally, this would mean that memory performance would be worse after wake than sleep, which is the case for sleep deprivation studies (Ashton et al., 2020; Gais et al., 2006; Yang et al., 2012). In addition, the amount of SWA is found to predict memory performance after sleep (Huber et al., 2004). In this way, renormalisation of synapses has been related to improved memory retention after sleep.

The central role of SWS for memory consolidation is a feature of both the Synaptic Homeostasis model as well as the Active Systems model. While the Synaptic Homeostasis model best explains sleep-associated consolidation on a synaptic level, the Active Systems model accounts for memory benefits which have been linked to memory reactivation and hippocampal-neocortical interactions during sleep. Indeed, these processes are not considered mutually exclusive leading researchers to integrate the two models into unified theories of sleep-dependent consolidation (Genzel et al., 2014; Klinzing et al., 2019; Rasch & Born, 2013).

1.5 Sleep loss and cognition

On the flip side of the idea that sleep supports subsequent learning, researchers have investigated how an absence of sleep affects next-day cognitive performance. Extended wakefulness can have detrimental consequences for attention and working memory whereby networks become unstable (Krause et al., 2017). Attentional networks are particularly sensitive to increases in sleep pressure which increase with time spent awake. With increasing sleep pressure, attentional lapses, also referred to as microsleeps, are more likely to occur, resulting in unstable task performance (Borbély,

1982; Borbély et al., 2016; Durmer & Dinges, 2005). Working memory is also impaired by sleep deprivation (Drummond et al., 2012). In particular, reductions in the dorsolateral prefrontal cortex and posterior parietal regions correlate with deficits in attention and working memory task performance after sleep deprivation (Chee & Choo, 2004; Chee & Chuah, 2007; Choo et al., 2005). Some have also found evidence of compensatory neural processing during learning after sleep restriction (Chee & Choo, 2004; Drummond et al., 2004). This section will cover the literature focusing on the effects of sleep deprivation on next-day declarative learning and will subsequently introduce the neural signatures of learning.

1.5.1 Sleep deprivation impairs subsequent learning

Sleep deprivation has detrimental effects on forming new hippocampus-dependent memories (Alberca-Reina et al., 2014; Cousins et al., 2018; Kaida et al., 2015; McDermott et al., 2003; Poh & Chee, 2017; Saletin et al., 2016; Tempesta et al., 2016; Yoo et al., 2007). For example, an influential study by Yoo et al. (2007) investigated the effects of overnight sleep deprivation on encoding new memories the next day. Twenty-eight participants either stayed awake or slept overnight before encoding face-image associations while undergoing fMRI. When they were tested two days later, after recovery sleep, the researchers found that participants who had stayed awake were significantly worse at recognising the images compared to those who had slept. The researchers also found reduced hippocampal activity during successful memory formation for the sleep-deprived participants compared to the sleep group. Based on these results, they suggested that sleep is important for committing new hippocampus-dependent information to memory the following day.

Along similar lines, Alberca-Reina et al. (2014) presented participants with images of semantically related and unrelated face-face associations after a night of either sleep (control) or 4-hour sleep restriction. Based on later memory tests, they found that the participants who had been sleep deprived before learning had a lower memory accuracy of semantically unrelated associations compared to semantically related ones, whereas no such differences were observed for the control

sleep group. They suggested that due to pre-existing knowledge during encoding of semantically related (congruent) materials, the hippocampus might be less involved than when the materials are unrelated (incongruent). In line with previous studies, sleep restriction seemed to impair learning of hippocampus-dependent memories. Furthermore, the extent of this learning impairment following sleep loss is found to vary across individuals. A study found that hippocampal morphology could predict vulnerability to learning impairments after sleep deprivation (Saletin et al., 2016). In summary, the evidence suggests that the hippocampus is particularly vulnerable to sleep deprivation, and that the extent of these effects may differ between individuals. However, less is known about how fluctuations in brain rhythms reflecting successful learning are affected by sleep loss.

1.5.2 Neural signatures of successful memory formation

To understand the neural correlates of successful learning, researchers typically compare neural activity during encoding for items that are remembered at a later test, as compared to those that are forgotten. The effects observed are referred to as a subsequent memory effects (SMEs). This approach can provide insights into the mechanisms of effective encoding. In particular, the hippocampus and prefrontal regions are thought to support memory formation. Using functional neuroimaging, researchers found an increased activation in the hippocampus during learning for items and associations that were subsequently remembered compared to those that were forgotten (Davachi & Wagner, 2002). In addition to MTLs (including hippocampus), similar findings have been reported for inferior prefrontal regions during successful learning (Weis et al., 2004).

Using EEG, it is possible to investigate neural interactions of learning on a faster timescale than is possible with fMRI. When contrasting subsequently remembered to forgotten trials, increases in theta (~4-8 Hz) and gamma (> 30 Hz) power (sometimes referred to as synchrony) are found to support successful memory formation (Hanslmayr et al., 2009; Henin, Shankar, et al., 2019; Kirov et al., 2009; Klimesch, 1999; Mölle et al., 2002; Osipova et al., 2006; Staudigl & Hanslmayr, 2013). Theta and gamma oscillations are thought to support memory formation through long-term potentiation (LTP)

and spike-timing-dependent plasticity (a type of LTP dependent on the timing of presynaptic and postsynaptic firing), respectively (Nyhus & Curran, 2010). Furthermore, recent evidence suggests that the close temporal coupling between theta and gamma oscillations facilitate the binding of information into one memory representation (Friese et al., 2013; Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021; Benjamin J. Griffiths et al., 2019; Köster et al., 2018).

Recently, decreases in neocortical alpha (8-12 Hz) and beta (12-20 Hz) power (sometimes referred to as desynchrony) have received more attention as a marker of successful learning. Alpha/beta decreases have consistently been associated with subsequent remembered items (Fellner et al., 2019; Griffiths et al., 2016; Griffiths, Martín-Buro, Staresina, Hanslmayr, et al., 2021; Hanslmayr et al., 2014; Klimesch et al., 1996). In particular, beta desynchrony is thought to reflect semantic processing (Fellner et al., 2013; Hanslmayr et al., 2009). Researchers manipulated the level of semantic encoding by asking one group of participants to study semantic features of images, whereas the other group studied non-semantic features of the same materials. When comparing the oscillations between the two encoding tasks, they observed decreases in the beta range during semantic encoding for those items later remembered (vs. forgotten) whilst no such decreases were observed for the non-semantic task (Hanslmayr et al., 2009). Building on this, simultaneous EEG and fMRI recordings during word list encoding revealed that beta power decreases correlated with increased BOLD response in the left inferior frontal cortex (Hanslmayr et al., 2011) – a region linked to semantic memory processing (Gabrieli et al., 1998; Jackson, 2021). In the same study, they also observed increases in theta power (see Figure 1.3). On the other hand, alpha is often considered a correlate of attention, with decreases in alpha going hand-in-hand with increases in attention (Jensen & Mazaheri, 2010; Klimesch et al., 1998; Klimesch et al., 2007). Taken together, alpha and beta power desynchronization during encoding are thought to reflect attentional and semantic processes, respectively, and to contribute to successful memory formation.

Recent evidence suggests that hippocampal theta/gamma synchrony and neocortical alpha/beta desynchrony serve distinct functions in episodic memory formation. In their neurocognitive framework, Hanslmayr et al. (2016) argue that neocortical alpha/beta desynchrony represent the content of the encoded episode and hippocampal theta/gamma synchrony supports the binding of the episode. In a recent MEG study, researchers tested this idea (Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021). To disentangle oscillations of information processing and mnemonic binding, participants were first presented with images of objects, patterns and scenes separately (sequence perception/information processing), and subsequently asked to create a mental image incorporating the three stimuli (mnemonic binding), thus attempting to divide the processes temporally into two separate windows. During the sequence perception window (but not the mnemonic binding window), they found that neocortical alpha/beta power decreased from baseline and the level of decrease correlated with the number of items later recalled. During mnemonic binding (but not sequence perception), they instead found evidence of hippocampal theta/gamma coupling which correlated with the number of items recalled at later test. In this manner, alpha/beta desynchrony and theta/gamma synchrony may have dissociable, yet complementary, roles in successful episodic memory formation, one supporting item representation whilst the other supports mnemonic binding, respectively.

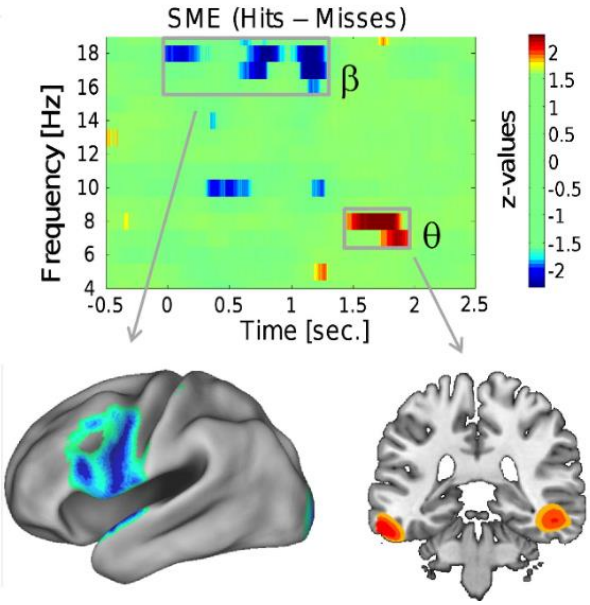

Figure 1.4. Oscillatory subsequent memory effects in during encoding. Time-frequency representations show the difference in oscillatory power (4-20 Hz) between later remembered and later forgotten items (Hanslmayr et al., 2011). Source localizations revealed that beta power decreases (blue) were generated in the left inferior prefrontal cortex, and theta power increases (red) were generated in lateral and medial temporal lobe regions. Figure adapted from Hanslmayr and Staudigl (2014).

1.6 Thesis chapters

1.6.1 Chapter 2

In Chapter 2, I addressed outstanding questions about the neural mechanisms of memory reactivation. Little is known about how memory cueing with spoken words compares with that of environmental sounds. This is an important question as it addresses the neural pathways through which linguistic and non-linguistic stimuli evoke offline memory reactivations and how this is linked to sleep-associated consolidation. Chapter 2 addressed this gap in the literature by exploring the neural underpinnings of memory reactivation by observing the oscillatory responses to verbal and non-verbal memory cues and previously unheard control cues. The analysed data was taken from a study for which the behavioural findings have been published (Cairney et al., 2017), whilst Chapter 2 focused on the evoked EEG response. Across two experiments, participants learned word-sound associations before a night of TMR in the lab. During slow-wave sleep, verbal and non-verbal sounds from the previously

learnt associations were repeatedly played. For a subset of the participants, the speaker of the verbal cues was mismatched between learning and TMR. Considering that spoken words engage phonological and semantic processes, whilst environmental sounds may not (Gaskell & Mirkovic, 2016), Chapter 2 directly compared the oscillatory response to verbal and non-verbal memory cues. Furthermore, this chapter explored whether acoustic matching between learning and TMR has any effects on the neural oscillations during reactivation. Overall, Chapter 2 aimed to provide novel insights into the mechanisms of cued memory reactivation during sleep when the cues vary in linguistic and acoustic content.

1.6.2 Chapter 3

Chapter 3 addressed the novel question of whether sleep-associated consolidation is linked to subsequent learning. By measuring memory retention across the night and subsequent learning of new materials the following morning, I investigated whether there was a relationship between sleep-associated consolidation of visuospatial memories and next-day learning of word-image pairs. This question was addressed in a within-subjects design where participants either slept or stayed awake overnight in the laboratory.

Because neuroimaging research on sleep deprivation and learning has so far mainly employed fMRI (with poor temporal resolution), little is known about how extended wakefulness impacts the neural mechanisms of encoding on a finer temporal scale. To address this gap in the literature, Chapter 3 additionally observed the effects of sleep deprivation on the neural signatures of successful memory formation. On separate experimental nights, participants either slept or stayed awake in the laboratory and then learned word-image pairings while EEG was recorded for which they completed a test two days later (after recovery sleep). By separating the EEG data during encoding into subsequently remembered and forgotten trials, Chapter 3 investigated how the neural signatures of successful learning are affected by sleep deprivation.

1.6.3 Chapter 4

Chapter 4 complemented the previous study with two between-subjects experiments conducted online. In contrast to the previous chapter, these experiments consisted of 12 h delays including either overnight sleep or daytime wakefulness. Furthermore, the indices of consolidation and subsequent learning were both based on the same task. Similar to Chapter 3, Chapter 4 investigated whether the processes thought to support memory reorganisation and stabilization might pave the way for next-day learning by assessing whether there is a link between overnight consolidation and next-day learning.

1.6.4 Summary of Research Objectives

The overarching aim of this theses was to investigate the mechanisms by which sleep supports memory consolidation as well as next-day learning. The mechanisms of sleep-associated consolidation were investigated by observing the neural markers of targeted memory reactivation (Chapter 2) and by comparing memory retention across a night of sleep to a day or a night awake (Chapters 3 and 4). The ways in which sleep supports next-day learning were investigated by comparing the learning performance after a night of sleep to a day or a night awake (Chapters 3 and 4) and by observing the neural signatures of learning after sleep deprivation (Chapter 3). Furthermore, Chapters 3 and 4 addressed the novel question of whether there is a relationship between sleep-associated consolidation and next-day learning. Together, the thesis chapters provide insights into the role of sleep for memory consolidation and memory formation.

Chapter 2:

The sleeping brain's response to verbal and non-verbal memory cues

Anna á V. Guttesen[1], M. Gareth Gaskell[1,2] & Scott A. Cairney[1,2]

[1] Department of Psychology, University of York, York, UK

[2] York Biomedical Research Institute, University of York, York, UK

Note for examiners

The EEG data in this chapter is from a secondary data resource and the behavioural data has been published as:

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2.1 Abstract

Sleep supports memory consolidation via the reactivation of newly formed memory traces. One way to investigate memory reactivation in sleep is by re-exposing the sleeping brain to auditory stimuli that are linked to newly learned information; a paradigm known as targeted memory reactivation. In the current study, fifty-one healthy male participants learned to associate visually-presented words with spoken words (verbal cues) and environmental sounds (non-verbal cues). Subsets of the verbal and non-verbal cues were then replayed during sleep, alongside previously unheard control cues. For a subset of the participants (N = 23), the voice of the verbal cues was mismatched between sleep and learning. In this secondary analysis (behavioural data published in Cairney et al., 2017), we explored how verbal and non-verbal memory cues affect oscillatory activity during non-rapid eye movement sleep. Memory cues (relative to control cues) prompted an initial increase in theta/alpha and spindle power, and a subsequent decrease in spindle/beta power. Moreover, verbal memory cues were associated with a stronger increase in spindle power than non-verbal memory cues. There were no significant differences between the matched and mismatched voice conditions when analysing verbal memory cues in isolation. Our findings demonstrate that memory cues delivered in sleep evoke increases in theta and spindle power, which have both been implicated in sleep-associated memory consolidation. Verbal memory cues might also be more effective than non-verbal memory cues for triggering memory reactivation in sleep, as indicated by an amplified spindle response.

2.2 Introduction

Sleep supports memory consolidation. Initially, sleep was thought to passively protect memories from interference, as compared to the increased interference during wakefulness (Jenkins & Dallenbach, 1924). However, more recent work has suggested that sleep plays an active role in memory consolidation (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013). According to this view, newly formed hippocampus-dependent memories are initially unstable and prone to interference. In subsequent sleep, memory traces are repeatedly reactivated and gradually integrated within pre-existing representations – a process whereby labile memories become stable long-term memories.

Oscillations of slow-wave sleep (SWS) are thought to support the reactivation and stabilization of memories. Spindles (~12-16 Hz) are defined as waxing and waning waves (Rasch & Born, 2013). Importantly, spindle events are closely linked to memory reactivation (Bergmann et al., 2012; Cairney, Guttesen, et al., 2018; Schönauer et al., 2017; Schreiner et al., 2021; Wang et al., 2019). They are found to gate Ca^{2+} influx into dendrites of pyramidal cells facilitating synaptic plasticity (Rosanova & Ulrich, 2005; Seibt et al., 2017). Thus, repeated memory reactivation along with spindle-induced synaptic modifications helps strengthen and stabilize memory traces (Genzel et al., 2014). According to the Active Systems Consolidation view, spindles are also implicated in the redistribution of memory traces from hippocampus to neocortex through close interactions with neocortical slow-oscillations (SOs) (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013). Theta power (4-8 Hz) has also been linked to reactivation (Schreiner, Göldi, et al., 2015). Unlike spindles, the role of theta oscillations for sleep-associated memory consolidation is less clear. A recent working model postulates that theta activity reflects the reinstatement of memory representations during both wakefulness and sleep (Schreiner & Rasch, 2017). During sleep, theta coordinates the reactivation of memories formed in previous wakefulness through reinstatement (Schreiner et al., 2018) and is paralleled or immediately followed by spindles, which through reprocessing support the stabilization and integration of the reactivated memory representation (Schreiner & Rasch, 2017).

Researchers have developed a method of manipulating memory reactivation in sleep – this paradigm is known as targeted memory reactivation (TMR). In a typical TMR study, participants learn new information associated with sounds and in subsequent sleep, some of those sounds are replayed to trigger reactivation of the memories. By measuring the changes in memory performance before and after sleep for memories that have or have not been cued with TMR, researchers are able to investigate the effects of memory reactivation on memory consolidation. In an influential study by Rudoy and colleagues (2009), participants firstly learned object locations paired with environmental sounds. During non-REM sleep, half of these sounds were replayed and upon waking they exhibited a memory benefit for those items that had been cued compared to those that had not. With this study, they showed that auditory stimulation is effective for TMR and that cueing can influence a select subset of specific newly formed memories. Others have since replicated these findings and also found memory benefits of TMR using environmental auditory cues (Antony et al., 2018; Schechtman et al., 2021; Schönauer, Geisler, et al., 2014).

Researchers have also triggered memory reactivation via TMR when the auditory stimuli consist of more complex information, for instance, spoken words. Schreiner and Rasch (2015) tested whether cueing with verbal cues during sleep would improve vocabulary learning. Participants learned Dutch words along with their translations and in subsequent non-REM sleep, half of the learnt words were cued. Indeed, the cued words led to improved memory performance compared to the non-cued words. Taken together with similar studies using spoken words (Cairney et al., 2016; Farthouat et al., 2017; Göldi et al., 2019; Lehmann et al., 2016; Schreiner, Göldi, et al., 2015), the evidence suggests that memories can also be reactivated and strengthened with complex verbal stimuli during non-REM sleep. However, little is known about how the memory effects of different types of auditory cues compare.

In addition to observing changes in memory performance, TMR enables researchers to understand neural mechanisms of reactivation by investigating oscillatory responses to memory cues. EEG studies

in humans have repeatedly shown a relationship between spindles and memory reactivation induced by TMR (Antony et al., 2018; Cox, Hofman, et al., 2014; Farthouat et al., 2017; Groch et al., 2017; Laventure et al., 2018; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). Cairney et al. (2018) compared the evoked response to memory cues with that of previously unheard control cues, and found a significant increase in spindle power (~13-16 Hz) ~1.7 – 2.3 s after stimulus onset. Furthermore, they were able to decode the categorical features of the reactivated memories based on the same time as the evoked spindle response. Importantly, the level of distinction between the categorical features also predicted how well participants remembered the cued items (vs the non-cued items) at a later test. This evidence points to an important role of spindles for memory-related information processing whereby spindles facilitate synaptic changes and thereby strengthen the memory traces.

Theta power has also been linked to successful memory cueing by TMR (Farthouat et al., 2017; Groch et al., 2017; Joensen et al., 2022; Laventure et al., 2018; Lehmann et al., 2016; Oyarzún et al., 2017; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015; Schreiner & Rasch, 2015). Schreiner et al. (2018) found that increases in theta power occurred during wakeful retrieval and TMR during sleep. Based on this, they suggested that theta supports memory reinstatement irrespective of sleep or wake. Beyond correlational evidence, blocking theta and spindle activity after reactivation with auditory feedback also blocked the behavioural benefit of cueing (Schreiner, Lehmann, et al., 2015). Taken together, theta and spindles may work together to reactivate and stabilize memories, whereby theta initially supports reinstatement of the memory representation and subsequent spindle activity facilitates the stabilization of the memory traces (Schreiner & Rasch, 2017). While there is substantial evidence of how memory reactivation is supported by oscillatory activity, an outstanding question concerns the pathways through which verbal and non-verbal cues reactivate memories in sleep and, to date, no study has directly compared the oscillatory response to verbal and non-verbal memory cues. This is important as it addresses how memories are retrieved during sleep. To extract meaning from spoken words, the waking brain engages phonological and semantic processes (Gaskell &

Mirkovic, 2016). In contrast, environmental sounds may involve fewer high-level processes. Little is known about whether the sleeping brain engages multilevel decoding to retrieve memories.

Cairney et al. (2017) set out to address this gap in the literature. Across two experiments, participants learned word-sound associations before a night of TMR in the lab. During slow-wave sleep, verbal and non-verbal sounds from the previously learnt associations were repeatedly played. Based on the memory performance before and after sleep, they found that the participants were better at retaining the pairs that had been cued during sleep compared to the non-cued pairs. The memory benefits of cueing were comparable for verbal and non-verbal cues, however, it remained unclear whether the behavioural benefits were achieved through distinct neural processes. Additionally, they investigated whether the acoustic matching of verbal cues between learning and sleep had any impact on the memory effects of TMR. In the first experiment, the speaker of the verbal cues was the same between learning and TMR (matched), while in the second experiment the speaker was changed (mismatched). When the speaker was matched, they found better retention for the cued compared to the non-cued pairings. However, when the speaker was mismatched, they found an overall retention benefit for both cued and non-cued verbal pairs when compared with non-verbal pairs. These findings suggest that when the acoustics do not match between learning and sleep, cues may reactivate memories more generally, possibly reactivating multiple memories from the previous learning context. In line with this idea, recent evidence suggests that cueing not only benefits retention of the items specifically linked to the cue, but also benefits those contextually linked to it (Schechtman et al., 2022). Furthermore, delta-theta and spindle power modulations are seemingly sensitive to how many objects are linked to the cued item (Schechtman et al., 2021).

In the present paper, we conducted secondary analyses of the EEG data from Cairney et al. (2017) to examine the neural correlates of memory reactivation triggered by verbal and non-verbal cues. To identify the time-locked oscillatory markers of memory reactivation in sleep, we firstly compared the memory cues with the unheard control cues. Secondly, we explored whether there were any

oscillatory differences between memory reactivation when the cues consisted of verbal and non-verbal information. Finally, we compared the neural response of when the speaker was matched to when they were mismatched. With these analyses, we aimed to provide insights into the neural correlates of memory processing with varying cue information and, more broadly, the mechanisms of cued memory reactivation in sleep.

2.3 Materials and Methods

The EEG data analysed in this paper were collected as a part of an earlier study that examined the behavioural effects of TMR on memory performance and whether the information in the memory cue (i.e. verbal or non-verbal, matched or mismatched) had any effect on the consolidation process (Cairney et al., 2017). Participants learned word-sound associations before a night of sleep in the lab. The sounds consisted of spoken words (verbal) and environmental sounds (non-verbal). During slow-wave sleep (SWS), a subset of the learned sounds (memory cues) was then replayed along with previously unheard control cues. In Experiment 2, the voice of the verbal cues was mismatched between learning and sleep. After waking, participants were tested on their memory of all the pairings. For clarity, the full procedure is reported here, however, only the EEG data were analysed (behavioural data published in (Cairney et al., 2017).

2.3.1 Participants

Data from 51 healthy males (mean ± SD age: 20.61 ± 1.97) were analysed (N = 28 from Experiment 1, mean ± SD age: 20.32 ± 1.54, and N = 23 from Experiment 2, mean ± SD age: 20.96 ± 2.38). Screening questionnaires indicated that the participants had no history of sleep, neurological or psychiatric disorders, were non-smokers, were not using any psychoactive medications, and had not consumed alcohol nor caffeine for 24 hours prior to the study. As indicated by the Pittsburgh Sleep Quality Index (Buysse et al., 1989), all participants had obtained a normal pattern of sleep in the month prior to the study. Participants provided written and informed consent and the study was approved by the Research Ethics Committee of the Department of Psychology, University of York.

2.3.2 Stimuli

Verbal auditory cues

Thirty-five monosyllabic and disyllabic words (mean ± SD syllable count: 1.54 ± 0.51) were taken from the University of South Florida (USF) word association, rhyme, and word fragment norms to use as spoken verbal cues for the verbal pairings (Maki et al., 2004; Nelson et al., 1998). The words were recorded using two separate speakers, one male and one female which were matched in duration (mean duration ± SD ms: male = 769.29 ± 104.95, female = 774.80 ± 99.14, $t(34) = 0.49$; $p = .63$). Additionally, a distinct and abstract word ("surface") was taken from the USF norms to serve as the control verbal cue (male duration: 990 ms; female duration: 950 ms).

Non-verbal auditory cues

Thirty-five environmental sounds were taken from previous studies (Oudiette & Paller, 2013; Rudoy et al., 2009) and from freesound.org to use as non-verbal cues for the non-verbal pairings and were similar in length to the male and female spoken word durations (mean duration ± SD ms: 740.97 ± 156.29, $F(2,102) = 0.76$; $p = .47$). Additionally, the sound of a guitar strum (524 ms) was taken from Rudoy et al. (2009) to serve as the non-verbal control cue.

Verbal and non-verbal pairings

Seventy monosyllabic and disyllabic words (mean ± SD syllable count: A = 1.34 ± 0.48, B = 1.34 ± 0.48, $t(34) = 0.00$, $p = 1.00$) were taken from the USF norms. These were used as verbal and non-verbal pair targets and were divided into two sets, set A and set B, which were matched for concreteness (mean ± SD: A = 5.76 ± 0.62, B = 5.68 ± 0.54, $t(34) = 0.63$, $p = .54$), frequency (mean ± SD: A = 30.37 ± 39.21, B = 29.83 ± 38.31, $t(34) = 0.06$, $p = .96$), and length (mean ± SD: A = 4.94 ± 0.76, B = 4.94 ± 0.84, $t(34) = 0.00$, $p = 1.00$). Within the sets, each word was paired with a verbal cue and a non-verbal cue. For the behavioural task, the verbal pairings (i.e. verbal cue paired with visual word) were taken from one

set while the non-verbal pairings (i.e. non-verbal cue paired with visual word) were taken from the other set (counterbalanced across participants). The pairings did not contain a clear semantic link.

2.3.3 Procedure

Experiment 1

Pre-sleep session

Participants arrived at the sleep laboratory (Department of Psychology, University of York) at 9:30 pm (± 30 minutes). They were informed that the study was about the role of sleep in memory consolidation, but were unaware of the TMR manipulation during sleep. Participants were fitted with sleep EEG (see below). Immediately before starting the tasks, participants completed the Stanford Sleepiness Scale (Hoddes et al., 1973). Following this, they completed training of the pairings, which included a learning phase followed by a test phase. There was separate training of the verbal pairings and non-verbal pairings (order counterbalanced across participants). During learning, each trial began with a black fixation cross presented for 1500 ms, which then turned blue to indicate the onset of an auditory stimulus. After 500 ms, a randomly selected verbal cue or non-verbal cue was presented. Verbal cues were presented in either a male or female voice (counterbalanced across participants). After 1500 ms, a visual word was presented on one of four locations of the screen quadrant (top or bottom to the left or right). Participants were asked to form mental images of the visually presented word and auditory stimulus interacting and informed that a test would follow immediately after learning. They completed 35 trials of both types of pairs: 3 practice trials, 28 experimental trials and 4 filler trials divided between the beginning and end to serve as primacy and recency buffers, respectively. The 28 experimental trials were equally distributed across the four quadrants of the screen. Participants were informed that a memory test for the words would follow immediately after learning and that they would not be tested on the word locations but to attend to the quadrant on the screen that the word appeared.

During the test phase, each trial started with a 1500 ms black fixation cross, which turned blue for 500 ms before the onset of the auditory stimulus (either verbal or non-verbal cue depending on the training phase). After 500 ms, a rectangular box appeared and participants were asked to type the target word associated with the cue within 12 s and press the Enter key to submit their response. Participants were asked to provide their responses in singular, lower case and spelled correctly. They were advised that they could use the Backspace key for any corrections prior to submitting the response. Immediately following the response submission, participants were asked to indicate which quadrant of the screen the word had appeared by pressing the corresponding board number key (1 = bottom left, 3 = bottom right, 7 = top left, 9 = top right) within 5 seconds. The test sets each consisted of 31 trials: 3 practice trials (same pairs as during learning) followed by 28 experimental trials. If the participants incorrectly recalled >40% of the experimental trials, the training was repeated. Participants were excluded if they did not reach criterion within four training rounds.

After completing these two training phases (verbal and non-verbal), participants completed the main test, where they were tested on all 56 pairs of verbal and non-verbal pairings. The test followed the same procedures as during training, with the exception that all 56 pairs were included in random order. The 6 practice trials (3 verbal pairings and 3 non-verbal pairings) were also included at the beginning of the test (62 trials in total). This test provided a pre-sleep index of memory recall for the two types of pairings. They were informed that they would complete another test in the morning.

TMR setup

For each participant, all incorrect verbal and non-verbal pairs from the pre-sleep test were firstly excluded. Of the correct pairs, half of the verbal cues and half of the non-verbal cues were randomly selected for TMR. The remaining halves of verbal and non-verbal pairs served as controls for the morning test (i.e. no TMR). For example, if 20 verbal pairings were correctly recalled and 18 non-verbal pairings were correctly recalled, there would be 10 verbal cues in the verbal TMR set and 9 non-verbal cues in the non-verbal TMR set (with an equal number serving as no-TMR pairs for the verbal and non-

verbal, respectively). This ensured that performance before sleep was identical for cued and non-cued items and controlled for inter-individual differences in learning. The maximum number of cues was 28 for 100% memory performance in the pre-sleep test (14 verbal cues and 14 non-verbal cues). With a > 60% performance criterion, it ensured that there was a minimum of 8 verbal cues and 8 non-verbal cues. On occasions where there was an odd number of correctly recalled pairs, the additional item was either included in the TMR set or included in the no-TMR set (this assignment was counterbalanced across participants). The verbal and non-verbal cues assigned to TMR, henceforth referred to as memory cues, were intermixed in a random order. Two additional control cues were also randomly interspersed within the list of the memory cues. The verbal control cue was the spoken word "surface" while the non-verbal cue was the sound of a guitar strum. The control cues were played the same number of times as their corresponding verbal and non-verbal cues. With the inclusion of these control cues, we could observe the evoked oscillatory response from auditory stimuli that had been associated with a word immediately before sleep (memory cues) to those that had not (control cues). Additionally, the control cues were played four times (2 verbal and 2 non-verbal, intermixed) at the beginning before the start of the TMR list to ensure that the auditory stimulation would not disturb the participants' sleep.

Sleep and TMR

Participants went to bed at ~11 pm. Throughout the night, white noise was played through a speaker above the bed (39 dB) to habituate participants to auditory stimulation. Once participants had showed continuous SWS for 2 minutes (as scored with online sleep EEG recordings), TMR began (see Figure 2.1). Cues were played at 5 s intervals and white noise intensity was lowered during the replay of each cue to promote acoustic clarity. However, because the number of memory cues varied across participants, null events (i.e. events with no stimulation) were randomly interspersed within the list so that each round of TMR (the full list of cues) always lasted 290 s. The rounds of TMR were repeated throughout SWS with 1-minute intervals. Cueing was stopped immediately if SWS stopped or

participants showed signs of microarousals, but was restarted if they returned to SWS. Participants were woken up at ~ 7 am, unless they were in SWS or REM, in which case they were allowed to continue sleeping until they woke up or reached N1 or N2. To account for sleep inertia, participants were given a ~20-minute break between waking up and the start of the post-sleep session, during which electrodes were removed.

Post-sleep session

In a post-sleep session, participants completed the Stanford Sleepiness Scale again. They then completed another memory test which was identical to the pre-sleep test (i.e. they were tested on all verbal and non-verbal pairings). Participants were then informed of the study aims and asked if they had been aware of the auditory stimuli during sleep (none reported being aware). Finally, they completed a discrimination task of all the 56 auditory cues (28 verbal and 28 non-verbal), during which they were asked to indicate using the keyboard whether they thought the cue had been played in sleep or not.

Experiment 2

Experiment 2 followed identical procedures to Experiment 1, with the exception that verbal cues were always spoken by a male speaker in training and test, but were spoken by a female speaker during sleep TMR and the discrimination task. The non-verbal cues remained identical throughout the study (i.e. at training, test and during sleep).

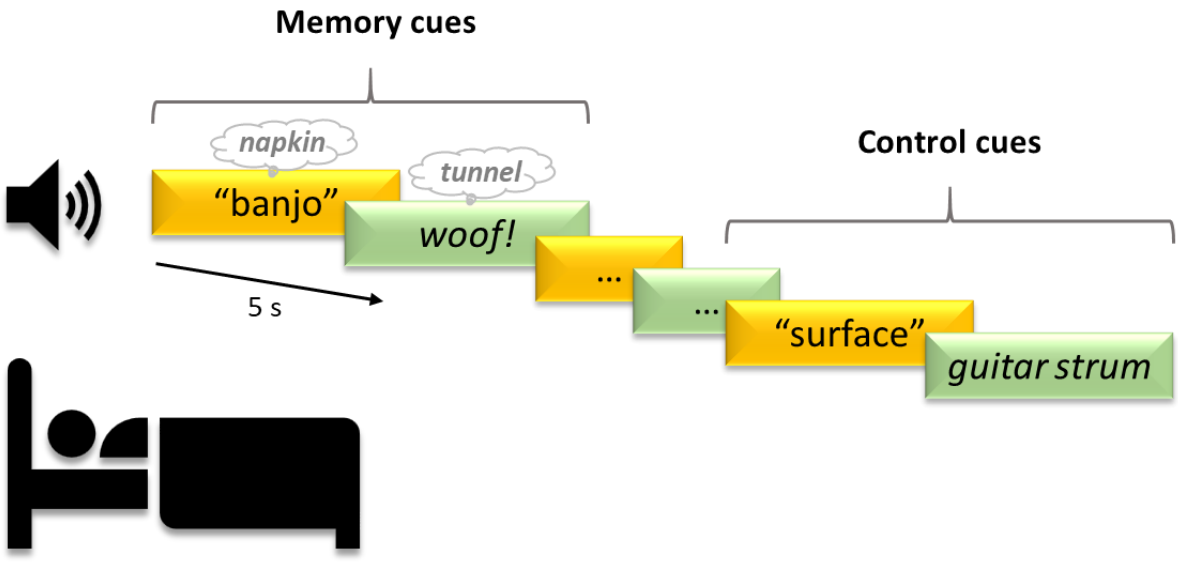

Figure 2.1. Cue examples. Examples of memory cues and control cues consisting of verbal (yellow) or non-verbal (green) auditory stimuli, which were played during overnight slow-wave sleep. All memory cues had previously been associated with a visually presented word (e.g. *napkin*, *tunnel,* etc.). Control cues consisted of the verbal cue "surface" and the non-verbal sound of a guitar strum. In Experiment 1, cues were presented by the same speaker as during learning (matched), and in Experiment 2, the speaker was different between learning and sleep (mismatched). Cues were presented in a random order, one at a time (ITI = 5 s).

2.3.4 Equipment

Behavioural tasks

All behavioural tasks were implemented on a PC with E-Prime (v. 2.0, Psychology Software Tools, Inc.) using headphones (Beyerdynamic DT 234 PRO) and a flat screen positioned at eye level ~0.5m from the participant (23" LCD monitor, resolution = 1920 x 1080 pixels).

Sleep EEG

Sleep EEG recordings were administered with two Embla N7000 systems and REMLogic (v. 3.4) software. Gold-plated electrodes were attached to the scalp using EC2 electrode cream (Grass Technologies). Electrodes were attached according to the international 10-20 system at frontal (F3 and F4), central (C3 and C4) and occipital (O1 and O2) locations, and were each referenced to the

contralateral mastoid (M1 and M2, for recording only). Left and right electrooculography electrodes were attached, as were electromyography electrodes at the mentalis and submentalis bilaterally, and a ground electrode was attached to the forehead. Each electrode had a connection impedance of < 5 kΩ and all online signals were digitally sampled at 200 Hz. Online sleep scoring was conducted on the referenced central electrodes (C3 and C4). For offline scoring, data were partitioned into 30 s epochs and scored in RemLogic (v. 3.4) according to standardised criteria (Iber, 2007).

TMR

TMR was implemented with Presentation version 17.0 (Neurobehavioral Systems, Inc.). Auditory cues were played via a speaker placed ~1.5m above the bed, which was connected to an amplifier in a separate control room.

2.3.5 EEG analyses

All data preprocessing and analyses were conducted in Matlab (v. 2019a) using FieldTrip toolbox (Oostenveld et al., 2011, v. 10/04/18).

Preprocessing

Sleep EEG data from both experiments were re-referenced to linked mastoids (average of M1 and M2), notch filtered at 49-51 Hz, high-pass filtered at 0.5 Hz and then segmented into trials (-1s to 3.5 s around cue onset). Using FieldTrip's Databrowser, channels were visually inspected and no noisy channels were identified. In order to keep artifact rejection as consistent as possible across participants, artifacts were first removed using FieldTrip's automated artifact rejection function (*ft_artifact_zvalue*). Muscle artifacts at 15-32 Hz (Brunner et al., 1996) were exaggerated using filters and z-transformations (0.1 s padding on each side of the artifact) and removed (mean ± SD trials rejected across all participants in both experiments: 3.96 ± 2.26). Subsequently, additional artifacts were manually rejected based on visual inspection using FieldTrip's databrowser (mean ± SD noisy trials rejected across all participants in both experiments: 4.14 ± 5.23, note these were in addition to

the trials rejected in the previous automated process). Finally, trials that fell outside of N2 and SWS were excluded prior to analyses (mean ± SD trials: 7.55 ± 10.84). For later analyses (see *Statistics*), information about the type of cue was added to each trial, i.e. whether the trial consisted of a memory cue or control cue, whether they were verbal or non-verbal, and whether they were presented by a matched or mismatched speaker (see Table 2.1 for number of trials for each condition).

Table 2.1. Mean ± SD of TMR trials per condition that were included in the analyses (i.e. after artifact rejection). The speaker identity of the verbal cues was matched to the training session in Experiment 1 and mismatched in Experiment 2.

	Memory cues		**Control cues**	
	Experiment 1 (matched)	**Experiment 2**	**Experiment 1 (mismatched)**	**Experiment 2**
Verbal (N)	89.68 ± 35.60	78.22 ± 29.37	108.50 ± 41.81	97.17 ± 33.82
Non-verbal (N)	88.57 ± 38.85	79.57 ± 32.18	107.64 ± 46.83	97.70 ± 37.45
Total (N)	169.02 ± 66.58		206.55 ± 78.93	

Time-frequency analyses

Time-frequency representations (TFRs) were calculated for frequencies ranging from 4-30 Hz. Data were convolved with a 5-cycle Hanning taper in 0.5 Hz frequency steps and 5 ms time steps using adaptive window-length (i.e. where window length decreases with increasing frequency, e.g. 1.25 s at 4 Hz, 1 s at 5 Hz etc). TFRs were converted into % power change relative to a -300 to -100 ms pre-cue

baseline window. This window was chosen to mitigate baseline contamination by post-stimulus activity while preserving proximity to cue onset (Cairney, Guttesen, et al., 2018).

Event-related potentials

For event-related potentials (ERPs), data were high-pass filtered at 0.5 Hz and low-pass filtered at 30 Hz. Data were baseline-corrected with a pre-cue window from -200 ms to 0 ms (Cairney, Guttesen, et al., 2018).

Statistics

ERP and TFR analyses were performed as dependent samples analyses and corrected for multiple comparisons using FieldTrip's nonparametric cluster-based permutation method with 1000 randomisations (when the standard deviation of the p-value crossed the alpha-value, this was increased to 1500 in order to improve accuracy (Meyer et al., 2021). All time-frequency clusters were defined by channel * time * frequency (4-30 Hz, cluster threshold $p < .050$, two-tailed). Based on previous findings, the time window of interest in the TFR was set from 0.3-2.5 s (Cairney, Guttesen, et al., 2018; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). ERP clusters were defined by time (averaged across channels) and based on a time-window of interest from 0 to 2.5 s (4-30 Hz, cluster threshold $p < .050$, two-tailed).

A factorial approach was used to assess the effects of verbal cues (vs non-verbal cues) on the oscillatory activity of memory reactivation in sleep: we calculated the grand average difference for memory cues > control cues within each condition (verbal cues and non-verbal cues), and then entered these contrasts into the cluster-based permutation analysis (verbal cues$^{memory>control}$ > non-verbal cues$^{memory>control}$). A similar approach was used in Experiment 2, when comparing effects of changing the speaker between learning and TMR (i.e. matched speaker$^{memory>control}$ > mismatched speaker$^{memory>control}$). Cohen's d_z effect sizes were based on the largest identified clusters by averaging power across time, frequency and channels which contributed to the clusters at any point.

2.4 Results

2.4.1 Memory cues compared to control cues

To study the overall differences in evoked EEG responses between memory cues and control cues, we firstly collapsed the data across Experiments 1 and 2. There were significant differences between the oscillatory response to the memory cues (Figure 2.2a) compared to the control cues (Figure 2.2b, (memory cue > control cue, $p < .050$). The identified clusters showed an initial increase for memory cues (vs control cues) in theta/alpha power in both hemispheres (~4-11.5 Hz, ~0.3-0.9 s, left: $d_z = .52$, right: $d_z = .48$) followed by an increase in spindle/beta power in both hemispheres (~10.5-20 Hz, ~0.8-1.7 s, left: $d_z = .51$, right: $d_z = .56$). Furthermore, there was a later power decrease ranging across a wider spindle/beta band in both hemispheres (~12-26 Hz, ~1.8-2.5 s, left: $d_z = -.38$, right: $d_z = -.46$, Figure 2.2c and 2.2d). To distinguish between this early increase (~10.5-20 Hz) and later decrease which encompasses a wider frequency range (~12-26 Hz), we will henceforth refer to these as spindle and spindle/beta, respectively. However, it should be noted that the spindle label encompasses higher frequencies than which would normally be considered spindles. The ERP evoked by memory cues (Figure 2.2a) was also significantly stronger to that evoked by the control cues (Figure 2.2b, $p < .050$). This corresponded to three clusters, a negative cluster at ~0.4-0.7 s ($d_z = -.70$), followed by a positive cluster ~0.9-1.3 s ($d_z = .59$) and another negative cluster at ~1.4-1.8 s ($d_z = -.64$).

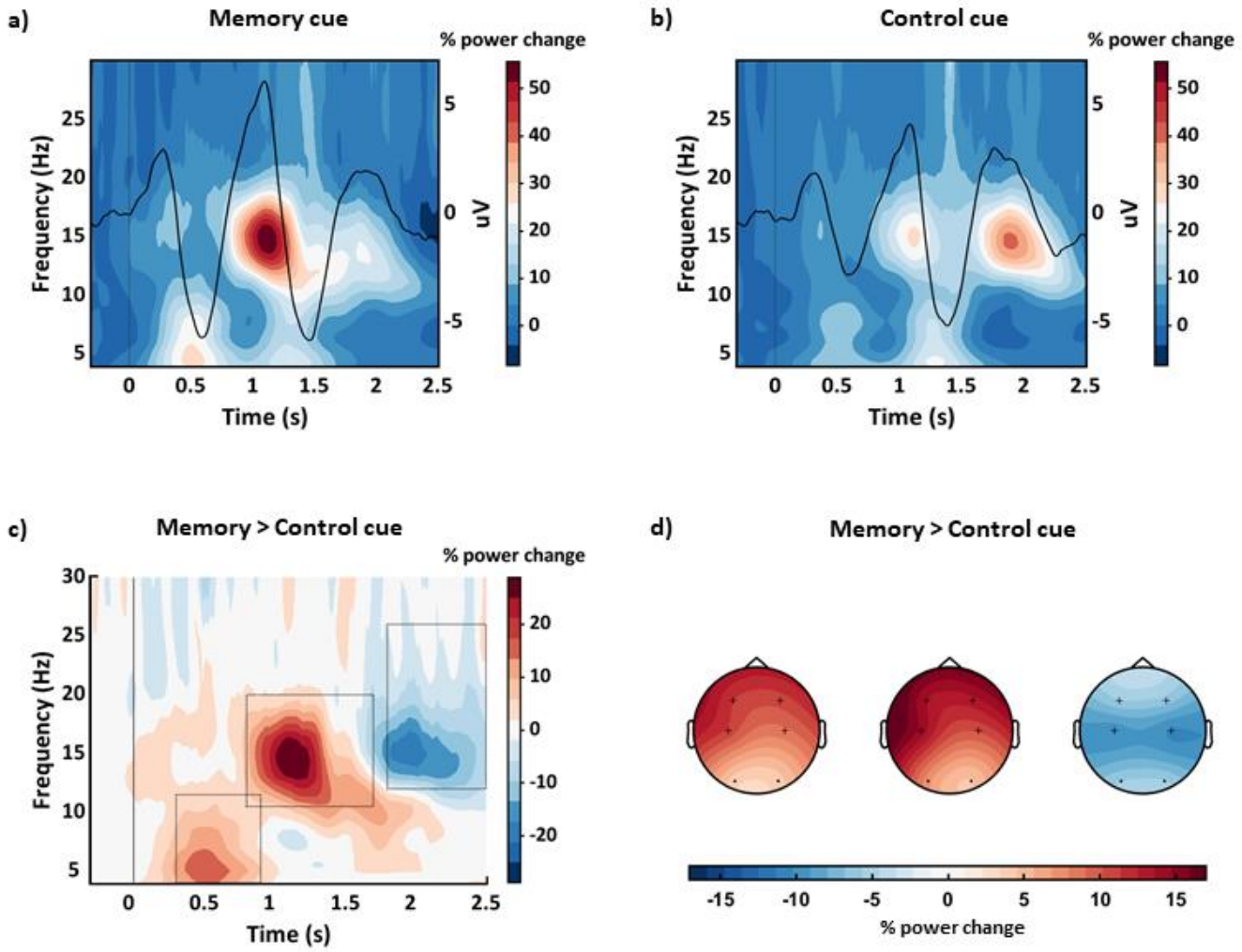

Figure 2.2. Memory cues and control cues. Grand average time-frequency representations with superimposed event-related potentials (baseline corrected and averaged across all channels) for **a)** memory cue, **b)** control cue. **c)** Time-frequency representation and **d)** topographical representations for memory > control cue. The rectangles in **c)** illustrate timing and frequency windows of topographical distribution in **d)** presented in the same order as the rectangles (left to right). Crosses represent the channels contributing to largest clusters.

2.4.2 Verbal memory cues compared to non-verbal memory cues

Next, we examined whether verbal and non-verbal memory cues evoke distinct patterns of oscillatory activity during sleep. With the data collapsed across Experiments 1 and 2, we first subtracted the

control cue response (Figure 2.3b and 2.3d) from the memory cue response (Figure 2.3a and 2.3c) separately for verbal and non-verbal cues leading to a 2x2 factorial design ($verbal^{memory - control}$ > $non\text{-}verbal^{memory - control}$). There was a significant difference ($p < .050$) corresponding to a cluster showing an increase in the spindle band for $verbal^{memory > control}$ > $non\text{-}verbal^{memory > control}$ (~10.5-16.5 Hz, ~0.5-1 s, d_z = .27, Figure 2.3e and 2.3f). Channels contributing to the cluster were in the right hemisphere (Figure 2.3f). Interestingly, post-hoc tests of the cluster revealed a stronger response to verbal memory cues compared to both non-verbal memory cues ($p = .008$) and verbal control cues ($p < .001$). We observed no such differences between the non-verbal memory and control cues ($p = .800$) nor the control cues ($p = .129$, all Bonferroni corrected, Figure 2.3g). Using a similar factorial approach for the ERP, we observed significantly stronger evoked potential for $verbal^{memory > control}$ compared to $non\text{-}verbal^{memory > control}$, $p < .050$. This corresponded to two clusters, one positive cluster at ~0.8-1 s (d_z = .47) followed by a negative cluster at ~1.2-1.5 s (d_z = -.50).

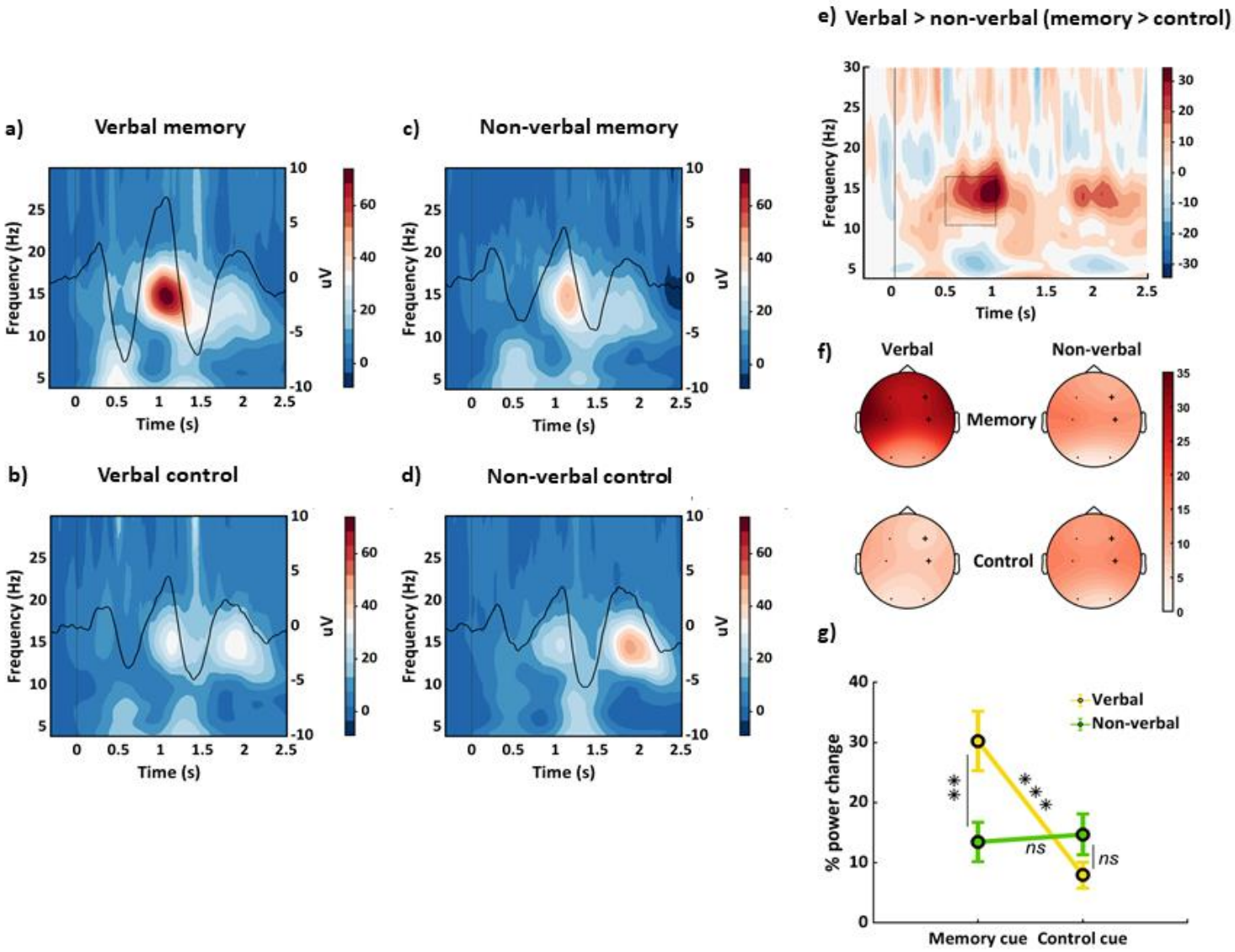

Figure 2.3. Verbal cues > Non-verbal cues (memory > control). Grand average time-frequency representations with superimposed event-related potentials (baseline corrected and averaged across all channels) for **a)** verbal memory cues, **b)** verbal control cues, **c)** non-verbal memory cues and **d)** non-verbal control cues. **e)** Grand average difference between verbal > non-verbal [memory – control]. The rectangle illustrates the timing (~0.5-1 s) and frequency (~10.5-16.5 Hz) of topographical distributions in **f)** which contributed to the largest cluster. Crosses represent the channels contributing to largest clusters. Colour bars represent % change. **g)** Average (±SEM) power change of the identified cluster by cue type (averaged across timing and frequency included in the rectangle in **e)**, ~0.5-1 s and ~10.5-16.5 Hz and channels highlighted in **f)**, F4 and C4). ** = p < .010, *** = p < .001, ns = p > .0125. Note, because the time-frequency in **e)** is averaged across all channels, and the cluster analysis was based on time*frequency*channel, the rectangle does not represent the channel dimension of the cluster – this dimension is shown in **f)**.

2.4.3 Verbal cues compared between the same and different speaker

Similar to the other factorial analyses, we first subtracted the evoked EEG response for the control cues from that for the memory cues separately for the matched (Experiment 1) and the mismatched speaker conditions (Experiment 2) leading to a 2x2 factorial design (matched$^{memory > control}$ > mismatched$^{memory > control}$). Cluster-based permutation analyses showed no significant differences when changing the speaker in Experiment 2 (matched$^{memory > control}$ > mismatched$^{memory > control}$, $p > .050$, Figure 2.4). Similarly, we observed no ERP differences between the conditions (matched$^{memory > control}$ > mismatched$^{memory > control}$, $p > .050$).

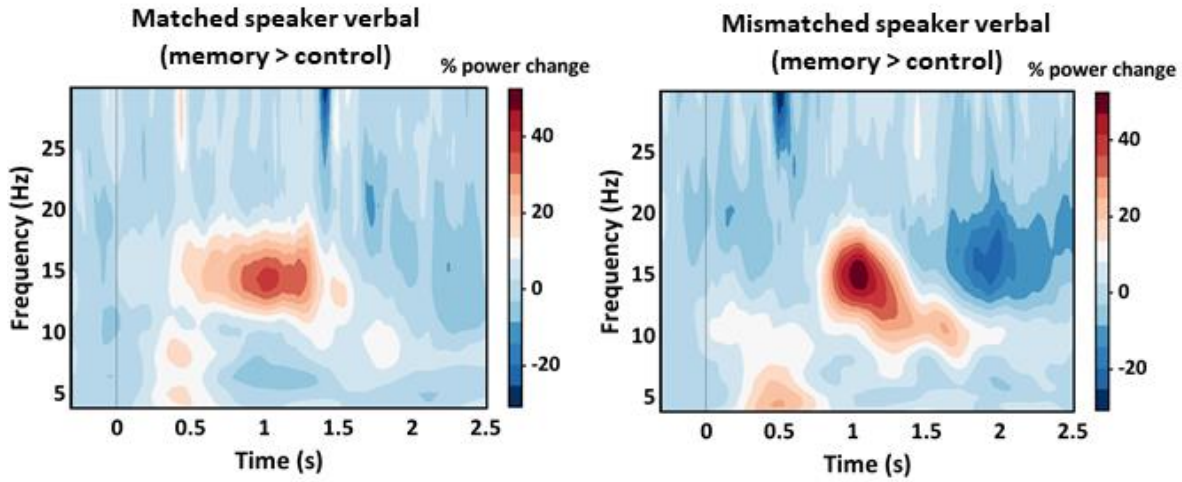

Figure 2.4. Changing the speaker identity during verbal cueing. Grand average time-frequency representations (power differences between memory cues vs. control cues averaged across all channels) for the matched speaker in Experiment 1 (left) and the mismatched speaker in Experiment 2 (right). The cluster-based permutation analysis revealed no significant differences when changing the speaker ($p > .05$).

2.5 Discussion

This was the first study to directly compare the oscillatory responses of verbal to that of non-verbal memory cueing in sleep. We carried out exploratory analyses of sleep EEG data to investigate the

neural markers of targeted memory reactivation during slow-wave sleep (SWS). We explored whether verbal memory cues would evoke differential neural oscillations compared to non-verbal memory cues. Furthermore, we set out to test whether we would observe any oscillatory differences when the speaker of the verbal cues was matched or mismatched between learning and TMR. Memory cues delivered in SWS evoked an initial increase in theta/alpha and spindle power and a subsequent decrease in spindle/beta power, as compared to unheard control cues. Verbal memory cues elicited a stronger spindle response than non-verbal memory cues. The data also suggest that there was a spindle response for verbal memory cues compared to control cues, but this effect was not apparent for the non-verbal memory cues compared to control cues. Finally, we did not find any significant differences in the oscillatory response when the speaker of the verbal cues was matched or mismatched between learning and TMR.

What might these neural responses reflect? We found that memory cues (vs. control cues) elicited an initial increase in theta/alpha power followed by an increase in spindle power. Our findings complement a number of prior studies that observed an initial memory cue-induced increase in theta power accompanied by an increase in fast spindle power (Cairney, Guttesen, et al., 2018; Göldi et al., 2019; Groch et al., 2017; Laventure et al., 2018; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). Considering that these studies used various types of stimuli (verbal auditory, non-verbal auditory and olfactory) and analysis approaches, these oscillatory patterns of TMR appear relatively robust and might reflect a general memory reactivation process during sleep.

Prior work suggests that theta and spindle oscillations have complementary roles in memory reactivation during sleep. Theta oscillations are thought to support the reinstatement of the memory representation, whilst subsequent spindle activity enables reduced disruption during reprocessing of the reactivation, which facilitates the strengthening and stabilization of the memories (Schreiner & Rasch, 2017). The idea that theta supports reinstatement is based on evidence of increases in theta power during wakeful retrieval as well as sleep TMR (Schreiner et al., 2018). Furthermore, blocking

theta and subsequent spindle power immediately after TMR also blocks the memory benefits of the cued items at later test (Schreiner, Lehmann, et al., 2015). Thus, the present increases in theta/alpha power followed by increases in spindle power for the memory cues (vs control cues) may reflect a triggered memory reinstatement and subsequent stabilization of the memory. This idea is further supported by the published behavioural findings of the current study, which showed reduced forgetting for the cued (vs. non-cued) items (Cairney et al., 2017). Taken together, our findings suggest that theta and spindle oscillations represent successful triggered memory reactivation which, in turn, strengthens memories.

We also observed a later decrease in spindle/beta power for memory cues compared to control cues. This was a surprising finding which, to our knowledge, has not been reported before. This may partly be because of the specific comparison of memory cues to control cues (where previous studies have used other comparisons) and partly because of our sample size (N = 51) possibly providing sufficient statistical power to detect this effect. Beta desynchronization has been linked to successful learning and retrieval during wakefulness and thought to reflect information representation (Griffiths et al., 2016; Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021; Hanslmayr et al., 2012; Hanslmayr et al., 2011). While it is unclear whether such findings extend to sleep, it may be that beta decreases for memory cues (vs control cues) support the information processing of the stimulus. It should be noted, however, that these effects are usually observed when comparing subsequently remembered items to forgotten items, whereas here, we compare memory cues with control cues. It is therefore unclear how the present findings map onto the literature on beta desynchrony during wakefulness. An alternative interpretation is that this decrease in spindle/beta power is driven by a spindle refractory period following the memory cue. Recent work suggests that the likelihood of spindles occurring is separated by 3-6 s: when presenting memory cues within this period rather than after, this led to poorer memory performance suggesting that these gaps between reactivation are necessary for memory consolidation (Antony et al., 2018). Based on this, Antony et al. (2019) proposed a framework where spindles initially support memory reinstatement, and the function of subsequent spindle

refractory periods is to protect memory reprocessing from interference. In the present data, the decrease in spindle/beta power observed ~2 s after memory cues may therefore support the reprocessing of the recently reactivated memory.

Intriguingly, our findings demonstrated that the evoked spindle response was amplified for verbal relative to non-verbal memory cues after taking the control cues into account. Based on the idea that spindles facilitate memory stabilization (Schreiner & Rasch, 2017), the present data suggest that verbal memory cues may more effectively trigger memory stabilization than non-verbal memory cues. However, in the published behavioural data (Cairney et al., 2017), they observed no differences in memory performance for items cued with verbal and non-verbal stimuli. Considering that a large proportion of the participants did not forget any pairings between pre-sleep and post-sleep, these measures might not have been sufficiently sensitive to detect any differences, in particular, if the behavioural effect size is small (which was the case for the EEG data). Thus, verbal memory cues may evoke stabilization of reactivated memories to a greater extent than non-verbal memory cues, possibly due to an increased access to meaning elicited by linguistic compared to non-linguistic stimuli (Gaskell & Mirkovic, 2016). Importantly, we observed power increases for the verbal memory cues compared to verbal control cues, whilst this effect was not present for the non-verbal memory and control cues. Furthermore, the largest cluster was found in the right hemisphere, whereas left hemisphere is often linked to language processing (Vigneau et al., 2011). This suggests that our findings do not merely reflect linguistic processing on its own, but rather a stronger memory retrieval process elicited by cues with linguistic information. Considering that spindles are found to mediate the information content of the reactivated memory trace (Cairney, Guttesen, et al., 2018), verbal memory cues may elicit a stronger reinstatement than non-verbal memory cues. Further work is needed to address whether there is evidence of reinstatement (possibly using a decoding approach similar to Cairney, Guttesen, et al., 2018) and furthermore, to test whether memory strengthening is demonstrated in behaviour, potentially, by reducing the amount of training prior to sleep to avoid ceiling effects.

We found no significant differences in evoked EEG responses for verbal memory cues that were matched or mismatched relative to learning (in terms of the speaker's voice). This could mean that the acoustic matching does not play a role in the effectiveness of memory reactivation. However, this is at odds with the published behavioural findings. When the speaker of the verbal cues was matched between learning and sleep, Cairney et al. (2017) observed low forgetting rates for the cued pairings but not the non-cued pairings. Interestingly, when the speaker was mismatched, they observed low forgetting rates for both cued and non-cued verbal pairings. They suggested that these results could reflect a generalized reactivation of all memories when cueing occurs through mismatched stimuli, whereas matched cues might evoke more specific representations. Considering that we did not observe any differences when comparing the two groups, it appears that this generalized compared to specific reactivation is not reflected in the neural response. However, recent evidence showed that memory cues evoked increases in delta/theta (0.5-8 Hz) and spindle (11-16 Hz) activity irrespective of whether they were previously associated with one or multiple items, but that the level of increase was modulated by the amount of items associated with the cue (Schechtman et al., 2021). From this perspective, the oscillatory response to cues reactivating one memory (matched) and cues reactivating multiple memories from the learning experience (mismatched) might only be observed as a more fine-grained gradual increases in power rather than distinct differences when directly comparing the conditions. If matched and mismatched speaker cues evoke these subtle differences, a between-subjects comparison of 28 and 23 participants may be insufficiently sensitive to capture this. If future studies were to address this in a within-subjects design, they might predict incremental increases in memory-related oscillations (e.g. theta and spindle power) for memory cues that are non-identical to learning as these might reactivate multiple memories compared to the identical memory cues reactivating individual memories.

It is important to note that in the present study, two types of control stimuli were repeatedly played. By repeatedly presenting the same control stimuli in the present study, this might have resulted in habituation effects. Indeed, we observed reduced evoked potentials for the control cues compared to

the memory cues. In a previous study, various unheard control stimuli were presented where they observed no difference in the ERP (Cairney, Guttesen, et al., 2018). Thus, the findings from the present comparisons between memory cues and control cues should be considered with caution. Ideally, future research comparing neural signatures of memory cues with control cues would ensure that the control cues are optimal for comparison, by matching the two types of stimuli in characteristics (e.g. linguistic and auditory characteristics) and their frequency of repetition.

The timing of evoked neural response varies across studies. In the present study, we observed an increase in spindle power at ~1 s after cue onset which replicates previous findings (Göldi et al., 2019; Groch et al., 2017; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). In contrast, Cairney, Guttesen, et al. (2018) found that TMR cueing prompted an increase in fast spindle power approximately 2 s after memory cue onset when compared to control stimuli. Furthermore, evidence suggests that reactivation patterns reoccur autonomously every second (Schreiner et al., 2018), possibly driven by up-states of slow oscillations (< 1 Hz, Göldi et al., 2019; Schreiner et al., 2021). This leaves the question of whether the timing of the neural response, i.e. whether the increase in spindle power occurs 1 or 2 seconds after the memory cue, plays a role in the memory stabilization. Interestingly, the memory benefits of TMR driving these later spindle responses were not apparent immediately after the nap, but emerged the next day, suggesting that additional overnight memory processing was needed to stabilize the reactivated memory trace (Cairney, Guttesen, et al., 2018). In contrast, the present study observed behavioural benefits after overnight TMR (Cairney et al., 2017). Furthermore, the observed earlier timings of spindle responses are similar to the findings of multiple other overnight studies observing immediate benefits of TMR (Göldi et al., 2019; Groch et al., 2017; Lehmann et al., 2016; Schreiner, Lehmann, et al., 2015), suggesting that these earlier power increases sufficiently reinstate and stabilize the memory trace without the need for further memory processing. More work is needed to determine whether the reinstatement occurs in the first or second SO up-state after cue onset may determine the stage of the memory stabilization process, whether it is fully complete or 'tagged' for synaptic changes in subsequent sleep.

In conclusion, we found that memory cues evoke increases in theta and spindle power, which have been linked to memory reinstatement and stabilization during sleep. Furthermore, it seems that verbal memory cues evoke a stronger spindle response than non-verbal memory cues. We did not observe any differences when comparing evoked responses to memory cues that were acoustically matched or mismatched to those presented at learning. By considering the previously published behavioural data and the present EEG findings in combination, we have gained a better understanding of the neural pathways by which memory cues support memory reactivation. These findings are the first to demonstrate increased spindle activity evoked by verbal memory cues when compared to non-verbal cues, suggesting that verbal cueing may be more effective than non-verbal cueing at reactivating memories in the sleeping brain.

Chapter 3:

Sleep loss disrupts the neural signature of successful learning

Anna á V. Guttesen[1], M. Gareth Gaskell[1,2], Emily V. Madden[1], Gabrielle Appleby[1], Zachariah R. Cross[3], Scott A. Cairney[1,2]

[1] Department of Psychology, University of York, York, UK

[2] York Biomedical Research Institute, University of York, York, UK

[3] Cognitive Neuroscience Laboratory – Australian Research Centre for Interactive and Virtual Environments, University of South Australia, Adelaide, Australia

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3.1 Abstract

Sleep supports memory consolidation as well as next-day learning. The influential *Active Systems* account of offline consolidation suggests that sleep-associated memory processing paves the way for new learning, but empirical evidence in support of this idea is scarce. Using a within-subjects (N = 30), crossover design, we assessed behavioural and electrophysiological indices of episodic encoding after a night of sleep or total sleep deprivation in healthy adults (aged 18-25 years), and investigated whether behavioural performance was predicted by the overnight consolidation of episodic associations formed the previous day. Sleep supported memory consolidation and next-day learning, as compared to sleep deprivation. However, the magnitude of this sleep-associated consolidation benefit did not significantly predict the ability to form novel memories after sleep. Interestingly, sleep deprivation prompted a qualitative change in the neural signature of encoding: whereas 12-20 Hz beta desynchronization – an established marker of successful encoding – was observed after sleep, sleep deprivation disrupted beta desynchrony during successful learning. Taken together, these findings suggest that effective learning depends on sleep, but not necessarily sleep-associated consolidation.

Keywords

Learning; Memory; Consolidation; Beta Desynchronization; Sleep Deprivation

3.2 Introduction

How do we remember events from days gone by? It is now firmly established that sleep facilitates memory consolidation; the process by which weak and initially labile memory traces become strong and enduring representations (Ashton & Cairney, 2021; Ashton et al., 2020; Cairney, Lindsay, et al., 2018; Durrant et al., 2016; Gais et al., 2006; Gaskell et al., 2018; Payne et al., 2012; Talamini et al., 2008). Whereas sleep was originally thought to provide only passive protection to memory consolidation (i.e. by shielding memories from the interference posed by wakeful experience), recent work suggests that newly formed memories are actively strengthened during sleep (Cairney, Guttesen, et al., 2018; Rasch et al., 2007; Schönauer et al., 2017; Schreiner et al., 2021; Wang et al., 2019).

The influential *Active Systems* account of sleep-associated consolidation posits that the reactivation of hippocampus-dependent memories during slow-wave sleep (SWS) facilitates their migration to neocortex for long-term storage (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). Supporting this view, functional neuroimaging studies have shown that overnight consolidation supports a shift in the memory retrieval network from hippocampus to neocortex (Takashima et al., 2009), with time spent in SWS predicting the reduction in hippocampal retrieval dependency (Cairney et al., 2015; Takashima et al., 2006). Along the same lines, other work has shown that post-learning sleep (as compared to sleep deprivation) promotes functional coupling between activity in the hippocampus and prefrontal cortex when retrieval is assessed 48 h later (Gais et al., 2007). Taken together, these findings suggest that hippocampal-to-neocortical information transfer emerges during the first nights after learning, although the consolidation process presumably takes many weeks or even months to complete (Dudai, 2004; Dudai et al., 2015).

While the benefits of sleep for memory consolidation are well known, recent work has indicated that sleep also supports next-day learning of hippocampus-dependent memories. When a night of sleep deprivation precedes a novel learning opportunity, declarative memory recall is severely impaired, even after recovery sleep (Alberca-Reina et al., 2014; Cousins et al., 2018; Kaida et al., 2015; Tempesta

et al., 2016), suggesting that an absence of sleep disrupts memory encoding in hippocampus. Indeed, as compared to a normal night of sleep, sleep deprivation weakens hippocampal responses during successful learning (i.e. for memories that are correctly recalled in a later retrieval test, after recovery sleep), leading to an overall decline in recall performance (Yoo et al., 2007). Correspondingly, daytime naps not only facilitate learning (Mander et al., 2011), but also restore hippocampal encoding capabilities, as compared to an equivalent period of wakefulness (Ong et al., 2020).

The interplay of various brain rhythms has been identified as a key mechanism that regulates communication between hippocampus and neocortex during sleep-associated memory processing. Slow oscillations (< 1 Hz EEG activity) have been causally linked to overnight memory retention (Leminen et al., 2017; Marshall et al., 2006; Ngo et al., 2013; Ong et al., 2016; Papalambros et al., 2017; Perl et al., 2016) and are thought to play a central role in the reactivation and reorganisation of hippocampus-dependent memories (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). Delta waves (1-4 Hz), by contrast, have been implicated in forgetting via processes of synaptic renormalization (Genzel et al., 2014) and are thought to interact with slow oscillations to regulate the balance between memory consolidation and weakening (Kim et al., 2019).

Intriguingly, neural oscillations implicated in overnight memory processing have also been linked to new learning in hippocampus, suggesting that these processes rely on overlapping mechanisms. For example, selectively suppressing slow-wave activity SWA (0.5-4 Hz) via an acoustic perturbation approach impairs declarative memory encoding and reduces encoding-related activity in hippocampus (Van Der Werf et al., 2009). Reciprocally, enhancing SWA though electrical stimulation improves encoding of hippocampus-dependent memories but not non-hippocampal procedural skills (Antonenko et al., 2013). Augmenting slow oscillations via auditory stimulation leads to similar effects, with the magnitude of the slow oscillation enhancement predicting both hippocampal activation and behavioural performance at encoding (Ong et al., 2018). To what extent memory processes mediated

by sleeping brain rhythms contribute to next-day learning capabilities has yet to be directly examined in empirical research.

In this pre-registered study (osf.io/78dja), we tested the hypothesis that the extent to which individuals consolidate new memories during sleep predicts their ability to encode novel information the following day, and that SWA (0.5-4 Hz) contributes to this relationship. In a within-subjects, crossover design, healthy young adults were trained on a visuospatial memory task before a night of either EEG-monitored sleep or total sleep deprivation, and were tested the following morning. Afterwards, participants were trained on a novel paired-associates task, but were not tested until 48 h later (allowing for recovery sleep in the sleep deprivation condition). Retrieval performance on the visuospatial memory and paired-associates tests thus provided independent metrics of overnight consolidation and next-day learning, respectively.

We chose these particular memory tasks because they are both reliant on hippocampus (Eichenbaum, 2004; Konkel & Cohen, 2009) and the Active Systems framework is primarily concerned with the overnight consolidation of hippocampus-dependent memories (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). Moreover, previous work has consistently shown that the consolidation of both visuospatial and paired-associate memories is bolstered by overnight sleep (Ashton & Cairney, 2021; Ashton et al., 2020; Cairney, Lindsay, et al., 2018). We reasoned that employing two conceptually different tasks was optimal as this would ensure that any potential relationship between overnight consolidation and next-day learning would not be influenced by retroactive or proactive interference between the tasks, considering that participants were tested on one task immediately before learning on the other and that the follow-up tests were closely spaced in time.

By comparing overnight sleep and sleep deprivation, we could also investigate how protracted wakefulness affects the neural correlates of learning. Specifically, EEG recordings were acquired during paired-associates learning to test the hypothesis that sleep deprivation disrupts theta (4-8 Hz)

and gamma (> 40 Hz) synchronisation, which support item binding in episodic memory (Henin, Shankar, et al., 2019; Köster et al., 2018; Osipova et al., 2006; Summerfield & Mangels, 2005). Furthermore, in an exploratory analysis, we investigated the effect of sleep deprivation on 12-20 Hz beta desynchronization; an established marker of successful learning (Griffiths et al., 2016; Hanslmayr et al., 2014; Hanslmayr et al., 2009; Hanslmayr et al., 2012; Hanslmayr et al., 2011). Understanding how sleep disturbances impair learning and memory is increasingly important in modern society, where many people fail to regularly obtain an adequate amount of sleep (Becker et al., 2018; Bonnet & Arand, 1995; Stranges et al., 2012).

3.3 Materials and Methods

3.3.1 Participants

Fifty-nine participants (32 females, mean ± SD age = 20.10 ± 1.80) were recruited on a voluntary basis and completed a preliminary session (see below). After the preliminary session, ten participants were excluded for not meeting the performance criterion and one participant was excluded for not meeting the study requirement of being a native English speaker. Among those individuals who met the performance criterion of the preliminary session, eighteen participants withdrew due to being unable to commit to the main study schedule. Our final sample size was N = 30 participants (17 females, mean ± SD age, 20.10 ± 1.65), each of whom completed both the sleep and sleep deprivation conditions (order counterbalanced, see Figure 3.1a). Following standard procedures in our laboratory (Ashton et al., 2019; Harrington, Ashton, Ngo, et al., 2021; Harrington, Ashton, Sankarasubramanian, et al., 2021; Strachan et al., 2020), participants were asked to refrain from caffeine and alcohol for 24 h and 48 h, respectively, before each study session. Participants reported no history of sleep or psychiatric disorders. Written informed consent was obtained from all participants in line with the requirements of Research Ethics Committee of the Department of Psychology at the University of York. Participants received £100 compensation upon completion of the study.

Statistical power was calculated prior to data collection using an effect size of d = 0.56 from Ashton et al. (2020). This effect size was derived from a paired-samples t-test comparing forgetting after a night of sleep or total sleep deprivation. Based on this effect size, our pre-registered sample of N = 30 participants provided 83.7% power (alpha = .05, two-tailed).

3.3.2 Tasks and Stimuli

Visuospatial task (see Figure 3.1b)

One-hundred images of neutral scenes were taken from the International Affective Picture System (Lang et al., 1997) and the Nencki Affective Picture System (Marchewka et al., 2014). These were divided into two sets of 50 images for use in the sleep and sleep deprivation conditions (assignment of image set to condition was counterbalanced). The visuospatial task was divided into three phases:

1. Training I: Passive viewing

Each of the 50 images was presented in a randomly selected location on a grid background (exposure time = 3 s, interstimulus interval [ISI] = 1 s). Participants were instructed to try and memorise the image locations for a later test. Image presentation order was randomised.

2. Training II: Active viewing

Each image appeared in the centre of the grid and participants moved it to the location that they believed it had appeared at passive viewing. The image then reappeared in its correct location to serve as feedback. This continued until all images had been placed < 4.8 cm (< 150 pixels) from their correct location on two consecutive rounds of active viewing (images for which this criterion was met were dropped from subsequent active viewing rounds). Image presentation order was randomised.

3. Test

The test phase followed the same procedures as one round of active viewing with the exception that no feedback was provided. Three tests were completed (immediate, delayed and follow-up).

Paired-associates task (see Figure 3.1c)

Two hundred images of natural and manmade objects on a white background were taken from Konkle et al. (2010) and online resources. These were divided into two sets of 100 objects (50 natural and 50 manmade) for use in the sleep and sleep deprivation conditions (assignment of object set to condition was counterbalanced). Three hundred adjectives (150 adjectives per condition, assignment counterbalanced) were taken from Cairney, Guttesen, et al. (2018). Within each condition, 100 adjectives were randomly selected as targets and the remaining 50 as foils.

1. Adjective familiarisation

Each of the 100 target adjectives was presented for 3 s. Participants were instructed to rate how often they would use each adjective in conversation on a scale of 1 to 9 (1 = never, 5 = sometimes and 9 = often) within an additional 4 s (ISI with fixation crosshair = 1.5 s ± 100ms). Adjective presentation order was randomised.

2. Image familiarisation

Each of the 100 images (50 natural and 50 manmade objects) was presented for 3 s. Participants were instructed to imagine themselves interacting with each object and then categorise it as being natural or manmade within an additional 4 s (ISI with fixation crosshair = 1.5 s ± 100ms). Image presentation order was randomised.

3. Learning

On each trial, participants were presented with an adjective and image from each of the prior familiarisation phases for 4.5 s and instructed to memorise the adjective-image pairing for a future

test. To facilitate learning, participants were asked to create a story or mental image in their mind that involved the adjective and image interacting for the full duration of the trial, and then to rate this association as realistic or bizarre within an additional 4 s. A longer ISI of 5 s (± 100ms) was used to facilitate the analysis of EEG data acquired during adjective-image learning (this comprised a 2 s progression bar followed by 3 s of fixation). Adjective-image pairing order was randomised.

4. Test

Each of 150 adjectives (100 from learning and 50 unseen foils) was presented for 3 s. Participants were first instructed to indicate whether the adjective was old or new within an additional 10 s. Feedback on accuracy (correct/incorrect) was then provided for 1 s. For correct old responses, participants were presented with four images (all of which had been seen at learning) and asked to indicate which image was paired with the adjective within 10 s. Participants then rated how confident they were in their response on a scale of 1 (not confident) to 4 (very confident) within 10 s. For incorrect old responses or new responses, participants moved immediately onto the next trial (ISI with fixation crosshair = 1.5 s ± 100 ms). Adjective presentation order was randomised.

Psychomotor vigilance task (PVT)

The PVT was obtained from Khitrov et al. (2014), bhsai.org/downloads/pc-pvt). Participants were instructed to respond when a digital counter appeared on the screen (ISI = 2-10 s). Participants received feedback on their response times and the task lasted for 3 min.

3.3.3 Procedure

Preliminary session

Participants completed a preliminary memory assessment before entering the main study. They learned 180 semantically related word pairs (e.g. *Horizon* – *Sun*) and were immediately tested with a

cued recall procedure. Participants scoring between 50% and 95% were invited back for the main experiment. This ensured that participants were unlikely to perform at floor or ceiling in the visuospatial and paired-associates tests of the main study.

Session one: evening

Participants arrived between 8:30 PM and 10 PM. In the sleep condition (earlier arrivals), participants were immediately wired-up for overnight EEG monitoring. Participants began the study by completing the Stanford Sleepiness Scale (Hoddes et al., 1973), PVT and then the training and immediate test phases of the visuospatial task.

Overnight interval

In the sleep condition, participants went to bed at ~11 PM and were woken up in the morning at ~7 AM (thus achieving ~8 h of EEG-monitored sleep). In the sleep deprivation condition, participants remained awake across the entire night under the supervision of a researcher. During the sleep deprivation period, participants were provided with refreshments and were permitted to play games, watch movies or complete coursework. Because our sample was mostly made up of university students and a significant number of daytime study hours would be lost as a result of overnight sleep deprivation, we chose to allow participants to complete coursework in order to facilitate recruitment. Importantly, all of the permitted activities were deemed suitable because they were not conceptually linked to the materials that participants had learned the previous evening (i.e. object-location associations) or would learn the following morning (i.e. adjective-image pairings).

Session two: morning

Participants in the sleep deprivation condition were wired-up for EEG monitoring (this was not necessary in the sleep condition as electrodes had already been attached the previous night, however,

impedance checks were conducted again in the morning). Participants then completed another round of the Stanford Sleepiness Scale and PVT, and another (delayed) visuospatial test. Afterwards, participants carried out the familiarisation phases of the paired-associates task, before completing the paired-associates learning phase with EEG monitoring. Participants were not given any explicit instruction on what to do (e.g. when to go to sleep) during the 48-h interval that preceded session three.

Session three: follow-up

Participants returned 48 h after session two (thereby allowing for recovery sleep in the sleep deprivation condition) and completed a final round of the Stanford Sleepiness Scale and the PVT. They then carried out the paired-associates test and a final (follow-up) visuospatial test.

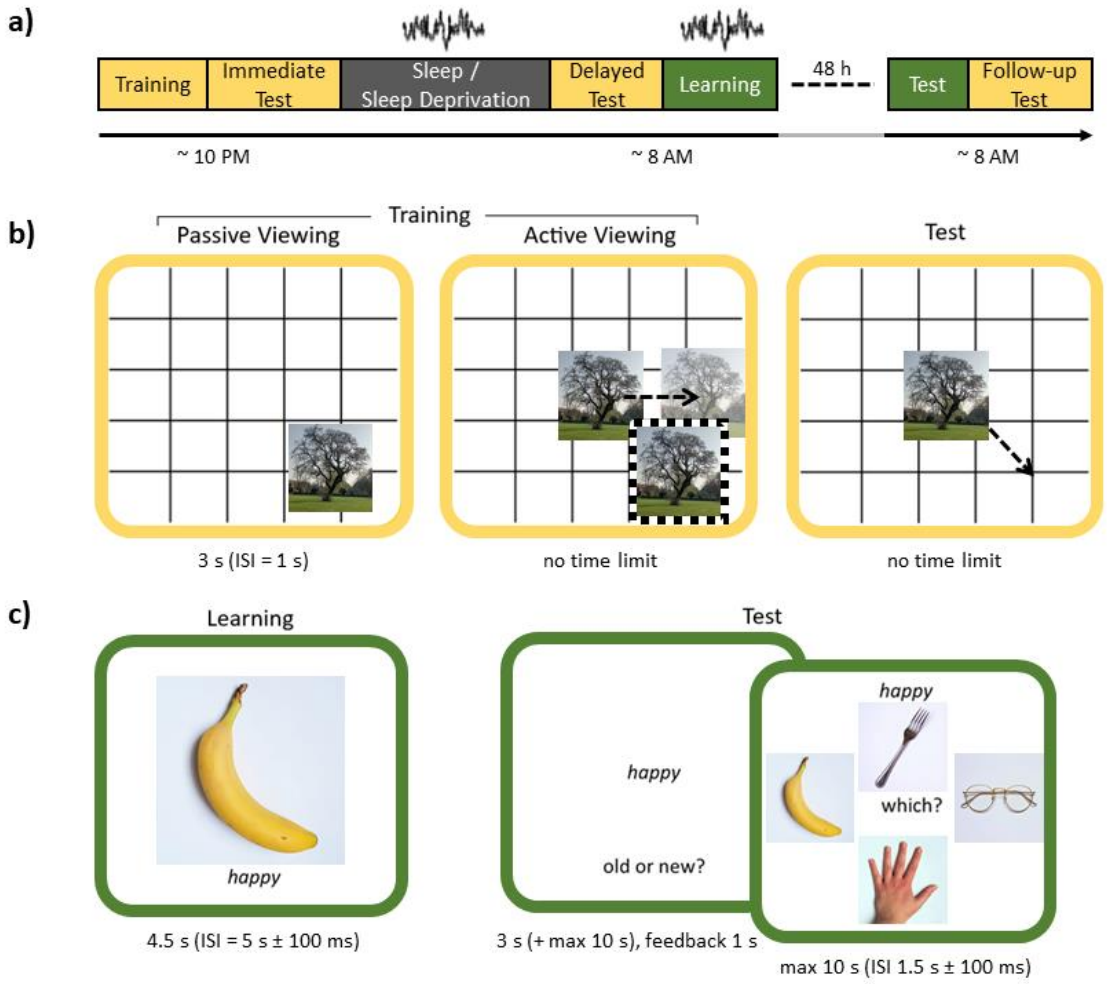

Figure 3.1. Experimental procedures and tasks.

a) Study timeline. The colours represent the tasks: visuospatial task in yellow (see b) and paired-associates task in green (see c). Participants arrived in the evening to complete the visuospatial task (training and immediate test). After overnight sleep or sleep deprivation, participants were tested again (delayed test) and then completed the learning phase of the paired-associates task. Participants returned 48 h later (after recovery sleep) to complete the paired-associates test and a follow-up visuospatial memory test. EEG recordings were acquired during sleep and paired-associates learning. The study was a within-subjects comparison of sleep and sleep deprivation (condition order counterbalanced across participants separated by at least a week and different stimulus sets were used for each condition). ISI = Interstimulus interval.

b) Visuospatial memory task. Participants completed one round of passive viewing, during which they viewed the location of each image on a grid. Next, in the active viewing phase, participants moved each image to the location that they thought it had appeared during passive viewing and received feedback on its correct location (dashed frame). Active viewing continued until participants had met the performance criterion for all images (< 4.8cm from correct location, mean ± SD number of rounds to meet criterion: Sleep: 8.77 ± 2.39, Sleep Deprivation: 9.07 ± 2.89). The test phases followed the same procedures as one round of active viewing, but no feedback was provided. Each test trial provided an accuracy score in cm, which described how far the image was placed from its correct location.

c) Paired-associates task. Participants completed one round of learning, during which they encoded adjective-image pairings. At test, a word was presented in isolation and participants first indicated whether it was 'old' (i.e. they recognised the word from learning) or 'new' (i.e. they did not recognise the word from learning). For correctly recognised (old) words, participants then indicated which of the four presented images was associated with that word at learning. For words identified as new, or for previously unseen words that were incorrectly identified as old, participants moved immediately onto the next trial.

3.3.4 Equipment

Experimental tasks

All tasks were executed on a Windows PC and participant responses were recorded with a keyboard or mouse. The visuospatial task was implemented in Presentation version 14.1 (Neurobehavioural Systems, Inc.) and the paired-associates task was implemented in Psychtoolbox 3.0.13 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) and MATLAB 2019a (The MathWorks, Inc.).

EEG

EEG recordings were administered with two Embla N7000 systems and one Embla NDx system with REMLogic 3.4 software. The Embla NDx was acquired when upgrading our sleep laboratory from a two- to three-bedroom facility (the N7000 was no longer available for purchase). For all but three participants, the same EEG system was used in the sleep and sleep deprivation conditions. Gold-plated electrodes were attached to the scalp according to the international 10-20 system at frontal (F3 and F4), central (C3 and C4), parietal (P3 and P4) and occipital (O1 and O2) locations. Left and right electrooculography electrodes were attached, as were electromyography electrodes at the mentalis and submentalis bilaterally, and a ground electrode was attached to the forehead. An additional reference electrode was placed at Cz for the NDx system (used for online recording only). We ensured that all electrodes had a connection impedance of < 5 kΩ immediately before any EEG data was collected (i.e. for participants in the sleep condition, impedances were checked before sleep and again in the morning before the learning task). Any electrodes that fell above this threshold were replaced and re-checked. All online signals were digitally sampled at 200 Hz (N7000) or 256 Hz (NDx, down-sampled to 200 Hz during preprocessing).

Actigraphy

Participants wore wristwatch actigraphy devices (Actiwatch 2, Philips Respironics, USA). throughout the study so that we could monitor their sleep when they were outside of the laboratory.

3.3.5 Data analyses

Behaviour

Behavioural data were analysed using R Studio (v.1.4.1717, RStudio Team, 2021). Memory consolidation was indexed by the change in visuospatial memory accuracy between the immediate and delayed test. For each participant and test, we computed an error score for each image by calculating the distance (cm) between the recalled location (image centre) and the location that the image had appeared at passive viewing. We derived a retention index (RI) by subtracting the error score at the delayed test from the error score at the immediate test for each image, and then averaging across images. A follow-up RI was calculated between the immediate and follow-up tests using the same method. To ease understanding (e.g. higher RI = better retention), we swapped the order of the RI subtraction to that which was pre-registered. This change yields statistically identical results aside from the sign change. As pre-registered, one participant was removed from analyses that included $RI^{SleepBenefit}$ scores (see below) because their RI at the delayed test in the sleep deprivation condition was > 3 SD from the mean.

Next-day learning was assessed by the learning index (LI), which equated to the percentage of correctly recognised images on the paired-associates test. Between-condition differences in RI and LI were analysed using paired-samples t-tests with a significance threshold of $p < .05$. We report the "classical" Cohen's d as our effect size estimate because it is unaffected by experimental design and thus facilitates comparisons across different studies (R function: cohensD, R package: lsr, Navarro, 2015).

One of our primary aims was to investigate the relationship between sleep-associated consolidation and next-day learning, and how SWA contributes to this relationship. To do this, we first quantified the benefit of sleep (vs sleep deprivation) on the RI and LI. We subtracted (for each participant) the RI in the sleep deprivation condition from the RI in the sleep condition to derive a $RI^{SleepBenefit}$. Similarly, we subtracted (for each participant) the LI in the sleep deprivation condition from the LI in the sleep condition to obtain a $LI^{SleepBenefit}$. Positive scores on the $RI^{SleepBenefit}$ and $LI^{SleepBenefit}$ therefore indicate a sleep-associated improvement in performance. $RI^{SleepBenefit}$ and SWA (see below) were entered as predictors of $LI^{SleepBenefit}$ in a forced-entry multiple regression analysis. A Bayesian multiple regression analysis (R package: BayesFactor, Morey & Rouder, 2018) was used to test for evidence of the null (i.e. no relationship between sleep-associated consolidation [$RI^{SleepBenefit}$], SWA and next-day learning [$LI^{SleepBenefit}$]). Exploratory correlations were computed using Pearson's R.

EEG (Sleep)

Preprocessing. Sleep EEG data were partitioned into 30 s epochs and scored in RemLogic 3.4 according to standardised criteria (Iber, 2007). Epochs scored as sleep stage N2 or slow-wave sleep (SWS) were exported to MATLAB 2019a using the FieldTrip toolbox (Oostenveld et al., 2011, v.10/04/18) for further analysis. Data were re-referenced to linked mastoids (average of M1 and M2), artifacts were identified and removed using FieldTrip's Databrowser (mean ± SD artifacts rejected, 3.5 ± 2.85), noisy channels were removed (four channels across four participants) and two entire datasets were excluded due to excessive noise. The remaining data were band-pass filtered between 0.3 and 30 Hz using Butterworth low-pass and high-pass filters.

Power spectral analysis. Due to significant noise in the occipital channels (as a result of electrodes detaching during the night in several participants), we only included frontal (F3 and F4), central (C3 and C4) and parietal (P3 and P4) channels in our spectral analysis of the sleep EEG data. Using functions from the FieldTrip toolbox, artifact-free N2 and SWS epochs were applied to a Fast Fourier

Transformation with a 10.24 s Hanning window and 50% overlap. EEG Power in the SWA (0.5-4 Hz) and fast spindle (12.1-16 Hz) bands was determined by averaging across the corresponding frequency bins and across channels.

EEG (Learning)

Preprocessing. All eight EEG channels (F3, F4, C3, C4, P3, P4, O1 and O2) were included in our analysis of learning. Data were re-referenced to linked mastoids (average of M1 and M2), high-pass filtered (0.5 Hz), notch filtered (49-51 Hz), and segmented into trials (-3 s to 4.5 s around stimulus onset). Trials for which participants did not provide a response were removed from the analysis (mean ± SD excluded trials, sleep: 0.1 ± 0.45, sleep deprivation: 5.11 ± 7.93, Priest et al. 2001). From scalp electrodes, eye-blinks and cardiac components were identified and removed using an independent components analysis, and noisy channels were interpolated via a weighted-average of their nearest neighbours (fourteen channels across six participants and two conditions). Trials were visually inspected and data from two participants were removed due to excessive noise in multiple channels.

Time-frequency analyses. Time-frequency representations (TFRs) were calculated separately for lower (4-30 Hz) and higher frequencies (30-60 Hz). Our pre-registered upper bound was 120 Hz, but because our sampling rate was 200 Hz the upper bound was above the Nyquist frequency and had to be lowered. For lower frequencies, data were convolved with a 5-cycle Hanning taper in 0.5 Hz frequency steps and 5 ms time steps using an adaptive window-length (i.e. where window length decreases with increasing frequency, e.g. 1.25 s at 4 Hz and 1 s at 5 Hz, to retain 5 cycles). For higher frequencies, data were convolved with tapers of Slepian sequence (3 tapers), also in steps of 0.5 Hz and 5 ms with an adaptive window-length. For this latter analysis, frequency smoothing was set to 0.4 of the frequency of interest (e.g. 20 Hz smoothing at 50 Hz). Artifact rejection was achieved via a data-driven approach, applied separately to the analyses of lower and higher frequencies: power values that exceeded the 85th percentile across all time/frequency points and trials were removed from each

participant's dataset. TFRs were converted into percent power change relative to a -400 to -200 ms pre-stimulus baseline window. This window was chosen to mitigate baseline contamination by post-stimulus activity while preserving proximity to stimulus onset (note that our post-stimulus time-window of interest started at 0.3 s, see below). Trials were divided into subsequently remembered and forgotten adjective-image pairings (based on the test phase 48 h later). Because our 49-51 Hz notch filter overlapped with our gamma frequency range, we re-ran our higher frequency analysis (30-60 Hz) without a notch filter and the results in the gamma frequency range (40-60 Hz) were unchanged.

Statistics. TFR analyses were performed as dependent samples analyses and corrected for multiple comparisons using FieldTrip's nonparametric cluster-based permutation method (1000 randomisations). Clusters were defined by channel * time whilst averaging across the frequency bands of interest (theta [4-8 Hz], alpha [8-12 Hz], beta [12-20 Hz] and gamma [40-60 Hz], cluster threshold $p < .05$). Pre-registered analyses in theta and gamma bands were one-tailed, whereas exploratory analyses were two-tailed. To reduce interference from early visual evoked responses, the time window of interest was set from 0.3-2 s (Friedman & Johnson, 2000; Osipova et al., 2006). A factorial approach was used to assess the impacts of sleep deprivation (vs sleep) on the neural correlates of encoding: we calculated the grand average TFR difference for subsequently remembered > forgotten adjective-image pairings within each condition (sleep and sleep deprivation), and then entered these contrasts into the cluster-based permutation analysis ($Sleep^{remembered>forgotten}$ > $Sleep\ Deprivation^{remembered>forgotten}$). To reflect the rationale of the cluster-based permutation test, we report effect sizes as Cohen's d_z based on the average of the largest cluster (i.e. averaging across all channels and time points that contributed at any point to the largest cluster, (Meyer et al., 2021).

3.4 Results

3.4.1 Sleep benefits memory consolidation

To assess overnight consolidation, we computed a retention index (RI) from the immediate and delayed visuospatial memory tests (higher RI = better overnight retention, see Materials and Methods). As expected, the RI was significantly higher after sleep than sleep deprivation ($t(28) = 3.78$, $p < .001$, $d = 0.71$, see Figure 3.2a). To ensure that our findings were not driven by between-condition differences in fatigue at the delayed test, we also assessed memory retention between the immediate and follow-up test (which took place 48 h after the delayed test, thereby allowing for recovery sleep). As expected, the RI was still significantly higher in the sleep (vs sleep deprivation) condition ($t(28) = 2.18$, $p = .038$, $d = 0.44$, see Figure 3.2b), suggesting that sleep had facilitated overnight consolidation. There was no significant between-condition difference in visuospatial accuracy at the immediate test (mean ± SEM, sleep: 2.44 ± 0.10, sleep deprivation: 2.57 ± 0.10, $t(28) = -0.98$, $p = .337$, $d = 0.19$, $BF_{01} = 3.28$), and no difference in the benefit of sleep on retention ($RI^{SleepBenefit}$ [i.e. sleep condition RI – sleep deprivation condition RI], see below) between participants who completed the sleep condition before or after the sleep deprivation condition ($t(27) = 0.22$, $p = .828$, $d = 0.08$, $BF_{01} = 2.81$), suggesting that the order of the conditions did not drive these effects.

Although response times on the PVT were slower in the morning after sleep deprivation (mean ± SEM, 399.00ms ± 17.63) than sleep (289.15 ± 4.34, $p < .001$), there was no significant relationship between $RI^{SleepBenefit}$ and $PVT^{SleepBenefit}$ (i.e. [mean RT after sleep – mean RT after sleep deprivation], $R^2 = -.15$, $p = .440$, $BF_{01} = 1.92$). Similarly, as indicated by the Stanford Sleepiness Scale (SSS), participants felt less alert after sleep deprivation (mean ± SEM, 5.37 ± 0.15) than sleep (2.27 ± 0.16). However, there was no significant correlation between $RI^{SleepBenefit}$ and $SSS^{SleepBenefit}$ (i.e. [mean rating after sleep – mean rating after sleep deprivation], $R^2 < -.01$, $p = .991$, $BF_{01} = 2.46$) with anecdotal evidence for the null. Extended analysis of the PVT and Stanford Sleepiness Scale data is available in the Supplementary Material.

3.4.2 Sleep improves next-day learning

To assess encoding performance after sleep or sleep deprivation, we calculated a learning index (LI), which equated to the percentage of correctly recognised images on the paired-associates test (this took place 48 h after encoding, following recovery sleep). As expected, encoding performance was significantly higher after sleep than sleep deprivation ($t(29) = 12.19$, $p < .001$, $d = 2.17$, see Figure 3.2c), suggesting that sleep had benefited next-day learning. There was no significant difference in the benefit of sleep on new learning ($LI^{SleepBenefit}$ [i.e. sleep condition LI – sleep deprivation condition LI], see below) between participants who completed the sleep condition before or after the sleep deprivation condition ($t(28) = 0.37$, $p = .712$, $d = 0.14$, $BF_{01} = 2.75$).

There was no significant relationship between $LI^{SleepBenefit}$ and $PVT^{SleepBenefit}$ ($R^2 = -.30$, $p = .113$), although the evidence for the null remained inconclusive ($BF_{01} = 0.86$). Similarly, there was no significant correlation between $LI^{SleepBenefit}$ and $SSS^{SleepBenefit}$ (i.e. [mean rating after sleep – mean rating after sleep deprivation], $R^2 = -.35$, $p = .056$) with inconclusive evidence for the null ($BF_{01} = 0.53$).

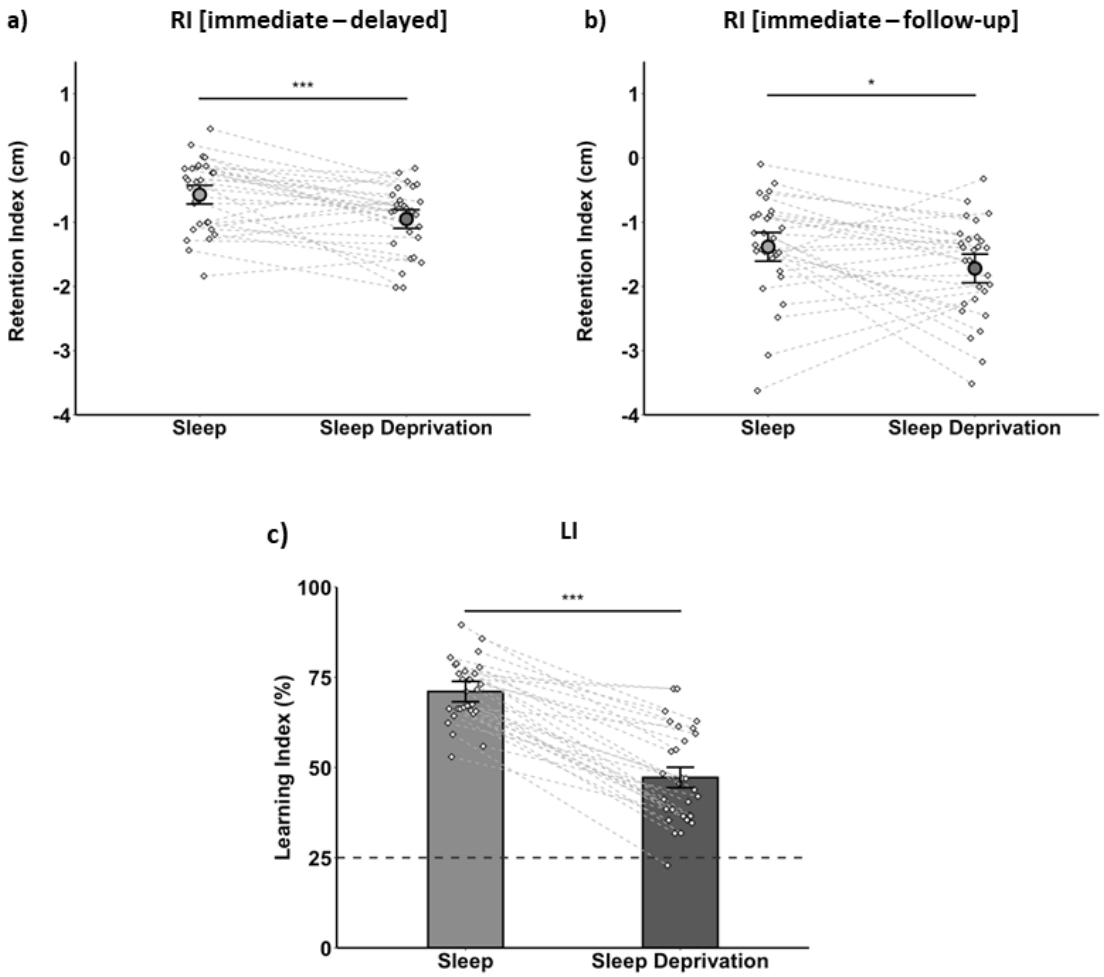

Figure 3.2. Behaviour.

a) Retention index (RI) between the immediate and delayed test, and **b)** between the immediate and follow-up test (i.e. 48 h after the delayed test, following recovery sleep). A higher RI indicates better retention. **c)** Learning index (LI, tested 48 h after sleep or sleep deprivation). Higher scores indicate better learning and the dashed line represents chance performance (25%). All figures show condition means (± SEM). Diamonds and connecting lines represent individual participants. *** $p < .001$, * $p < .05$.

3.4.3 No relationship between sleep-associated consolidation, slow-wave activity and next-day learning

Next, we tested the hypothesis that overnight consolidation predicts next-day learning, and that slow-wave activity (SWA) contributes to this relationship. Because our aim was to target the relationship between sleep-associated memory processing and next-day learning, it was necessary to first quantify the positive impact of sleep (vs sleep deprivation) on the RI and LI. We therefore subtracted both the RI and LI between the sleep and sleep deprivation conditions (on a participant-by-participant basis), such that positive scores on the resultant $RI^{SleepBenefit}$ and $LI^{SleepBenefit}$ metrics indicated a sleep-associated improvement in performance. SWA was defined as EEG power within the 0.5-4 Hz frequency band during sleep stages N2 and slow-wave sleep (SWS, collapsed across all EEG channels). In a multiple regression model, we entered $RI^{SleepBenefit}$ and SWA as predictors and $LI^{SleepBenefit}$ as the outcome variable. Contrary to expectations, sleep-associated consolidation ($RI^{SleepBenefit}$) and SWA did not significantly account for next-day learning ($LI^{SleepBenefit}$, $F(2,24) = 1.51$, $R^2 = 0.11$, $p = .242$, see Figure 3.3). No significant relationship was observed between $RI^{SleepBenefit}$ and $LI^{SleepBenefit}$ independently of SWA ($B = 3.30$, $t(24) = 0.86$, $p = .399$), nor between SWA and $LI^{SleepBenefit}$ independently of $RI^{SleepBenefit}$ ($B = -0.51$, $t(24) = -1.65$, $p = .111$). $RI^{SleepBenefit}$ did not significantly correlate with SWA ($R^2 = 0.21$, $p = .298$). A follow-up Bayesian analysis revealed anecdotal evidence in support of the null (i.e. that sleep-associated consolidation and SWA did not account for next-day learning, $BF_{01} = 2.04$).

In a subsidiary analysis, we repeated this multiple regression but only entered data from the sleep condition into our model (i.e. the $RI^{SleepBenefit}$ and $LI^{SleepBenefit}$ were replaced with the RI and LI from the sleep condition alone). Our findings mirrored those of the foregoing analysis: sleep-associated consolidation (RI) and SWA did not significantly account for next-day learning (LI, $F(2,25) = 1.83$, $p = .181$, $R^2 = 0.13$, $BF_{01} = 1.68$). There was also no significant relationship between RI and LI independently of SWA ($B = 4.46$, $t(25) = 1.67$, $p = .107$), nor between SWA and LI independently of RI ($B = -0.25$, $t(25) = -1.16$, $p = .256$), and no significant correlation was observed between RI and SWA ($R^2 = 0.28$, $p = .143$).

We also explored whether RI in the sleep condition was correlated with other sleep parameters previously implicated in declarative memory consolidation: time (min) in SWS (Backhaus et al., 2006; Scullin, 2013) and fast spindle power (12.1-16 Hz, (Cox et al., 2012; Tamminen et al., 2010). However, no significant relationships emerged (all $p > .368$). Sleep data is available in Table 3.1.

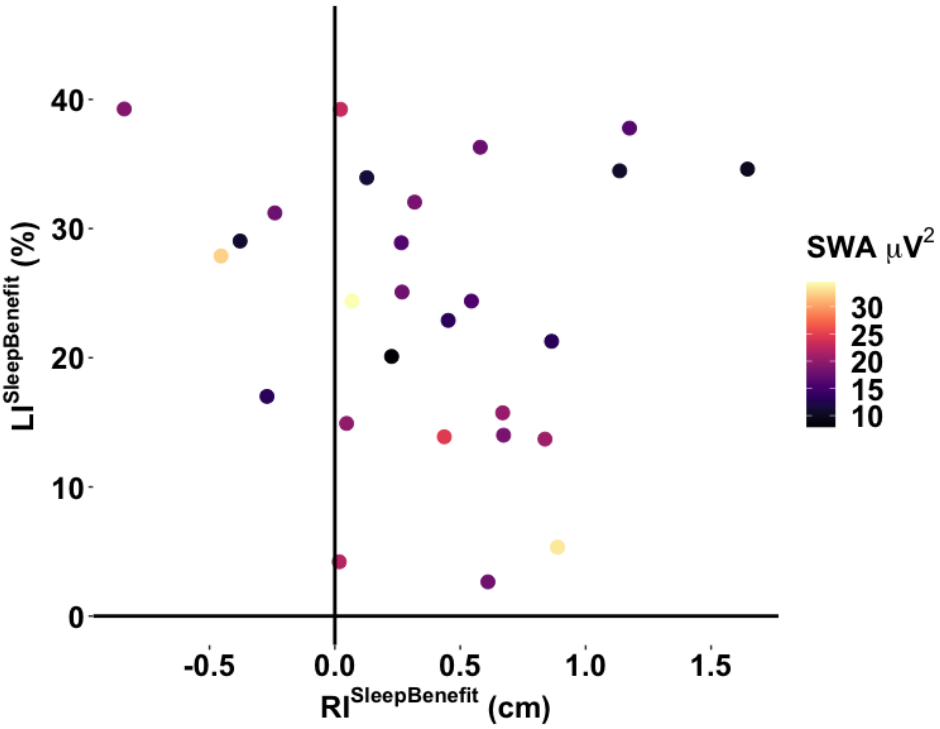

Figure 3.3. Relationship between sleep-associated consolidation, SWA and next-day learning. Sleep-associated consolidation ($RI^{SleepBenefit}$) and SWA had no significant impact on next-day learning ($LI^{SleepBenefit}$).

Table 3.1: Sleep data. Parameters include total sleep time (TST), time spent in each stage of sleep (N1, N2, slow-wave sleep [SWS] and rapid eye movement sleep [REM]) and power in the slow-wave activity (SWA, 0.5-4 Hz) and fast spindle (12.1-16 Hz) bands within N2 and SWS. Data are shown as mean (± SEM).

TST (min)	N1 (min)	N2 (min)	SWS (min)	REM (min)	SWA (μV^2)	Spindle (μV^2)
454.86 (± 4.18)	48.45 (± 5.58)	200.63 (± 6.30)	122.96 (± 5.89)	82.82 (± 4.21)	18.16 (± 1.30)	0.24 (± 0.02)

3.4.4 Sleep deprivation disrupts beta desynchronization during successful learning

Finally, we tested the hypothesis that sleep deprivation disrupts theta and gamma synchronisation at learning. However, no significant differences were observed in the theta (4-8 Hz) or gamma (40-60 Hz) bands when comparing time-frequency representations between subsequently remembered and forgotten adjective-image pairings or between the sleep and sleep deprivation conditions, and there was no significant interaction between these contrasts (all $p > .05$).

In an exploratory analysis, we investigated the effect of sleep deprivation on beta desynchronization; an established marker of successful learning (Griffiths et al., 2016; Hanslmayr et al., 2014; Hanslmayr et al., 2009; Hanslmayr et al., 2012; Hanslmayr et al., 2011). Consistent with these previous findings, an overall reduction in beta power was observed during encoding of subsequently remembered (vs forgotten) adjective-image pairings when combining the sleep and sleep deprivation conditions (corresponding to two clusters in the left hemisphere beginning at ~1.5-1.7 s ($p = .044$, $d = -.66$) and ~1.75-1.9 s ($p = .038$, $d = -.49$) after stimulus onset (see Figure 3.4a).

Interestingly, changes in beta power accompanying successful learning were significantly different in the sleep and sleep deprivation conditions (interaction, corresponding to a cluster in the left hemisphere at ~0.5-0.7 s, p = .014, d = -.33, see Figures 3.4b and 3.4d). Whereas encoding of subsequently remembered (vs forgotten) adjective-image pairings was associated with a downregulation of beta power after sleep (p = .005), an apparent upregulation of beta power emerged from the same contrast after sleep deprivation (p = .019, see Figure 3.4c, although this latter post-hoc test did not survive Bonferroni correction, alpha = .0125). Moreover, beta power was significantly reduced during encoding of subsequently remembered pairings in the sleep (vs sleep deprivation) condition (p = .001), but no such difference was observed during encoding of subsequently forgotten pairings (p = .928).

To explore whether this significant interaction was driven by increased fatigue in the sleep deprivation (vs sleep) condition, we correlated (for each participant) average beta power for the contrast $Sleep^{remembered>forgotten}$ > $Sleep\ Deprivation^{remembered>forgotten}$ (within the significant group-level cluster) with $SSS^{SleepBenefit}$ and $PVT^{SleepBenefit}$. No significant relationships were observed (SSS: R^2 = -0.20, p = .311, BF_{01} = 1.58, PVT: R^2 = .18, p = .371, BF_{01} = 1.73), suggesting that the foregoing findings did not arise from between-condition differences in fatigue.

An overall reduction in beta power was also observed for the sleep (vs sleep deprivation) condition when combining subsequently remembered and forgotten adjective-image pairings, corresponding to two clusters in the left (~1-1.5 s, p = .014, d = -0.63) and right hemisphere (~1.3-1.7 s, p = .038, d = -0.47).

Given the previously reported links between alpha (8-12 Hz) desynchronization and successful learning (Griffiths et al., 2016; Weisz et al., 2020), we also explored activity in this frequency band (same contrasts as above), but no significant effects were observed (all p > .05).

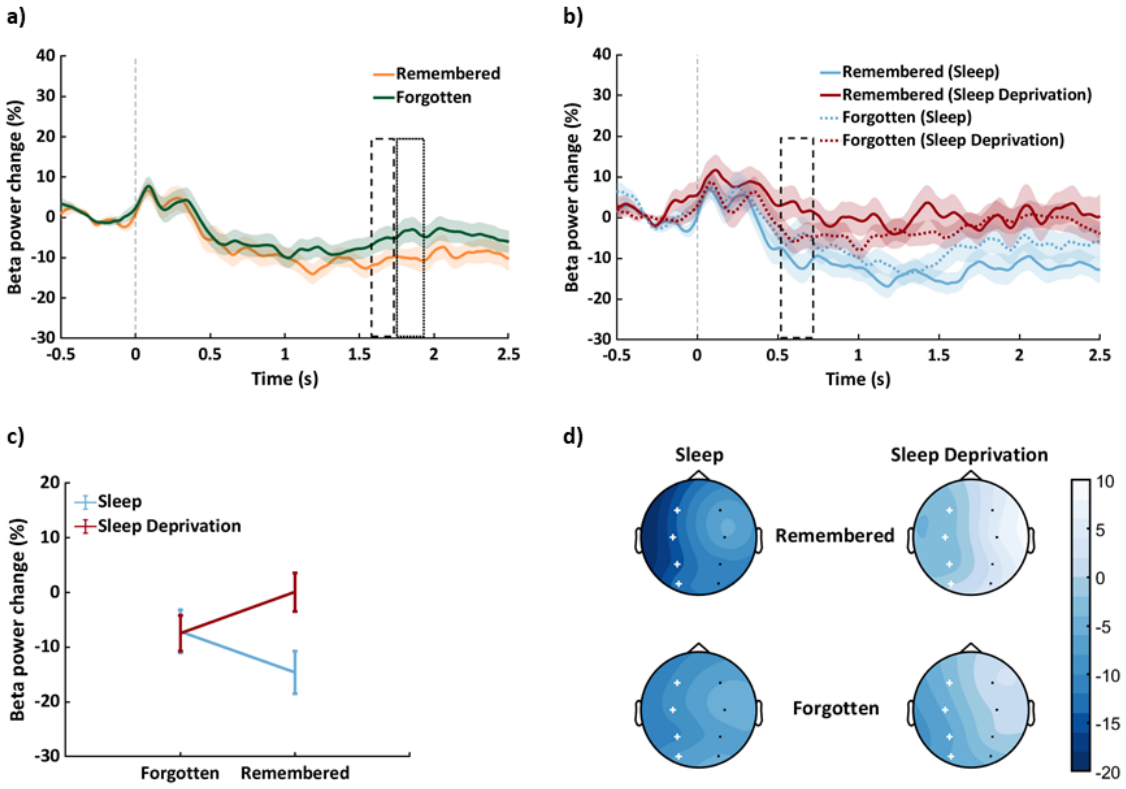

Figure 3.4. Changes in beta power during successful learning after sleep and sleep deprivation. **a)** Grand average change in beta power from baseline (12-20 Hz, all channels) for subsequently remembered and forgotten adjective-image pairings. Dashed and dotted boxes approximate the time windows contributing to the significant clusters and shaded areas represent SEM. **b)** The same contrast as in panel a, but presented separately for the sleep and sleep deprivation conditions. **c)** Corresponds to the significant cluster (interaction) in panel b, averaged across time (error bars represent SEM). Whereas encoding of subsequently remembered (vs forgotten) adjective-image pairings was associated with reduced beta power after sleep, no significant difference in beta power emerged from the same contrast after sleep deprivation. **d)** Topographical representations of the change in beta power for subsequently remembered and forgotten adjective-image pairings in the sleep and sleep deprivation conditions, averaged across the time-window of interest (0.3-2 s). Crosses represent the channels of the cluster that corresponds to the significant interaction. The vertical bar represents the change in beta power from baseline (%).

3.4.5 Actigraphy

Hours slept during the 48-h interval between the delayed and follow-up tests (as estimated via wristwatch actigraphy) were applied to a 2 (Condition: Sleep/Sleep Deprivation) * 2 (Night: One/Two) repeated measures ANOVA (R function: anova_test, R package: rstatix). Note that two participants were not included in this analysis due to technical problems with the actigraphy device. There was a main effect of Night ($F(1,27) = 62.47$, $p < .001$, $\eta_p^2 = .70$), indicating that all participants slept for longer on night one than night two. A significant Condition * Night interaction ($F(1,27) = 14.21$, $p < .001$, $\eta_p^2 = .35$) also emerged, with Bonferroni-corrected post-hoc tests indicating that sleep duration was longer in the sleep deprivation (vs sleep) condition on night one (mean ± SEM hours sleep, sleep deprivation: 9.03 ± 0.45, sleep: 7.52 ± 0.24, $p = .006$) but shorter on night two (sleep deprivation: 5.33 ± 0.23, sleep: 6.00 ± 0.25, $p = .036$). There was no main effect of Condition ($F(1,27) = 3.07$, $p = .091$, $\eta_p^2 = .10$).

It is possible that the longer duration of sleep on the first night after learning in the sleep deprivation (vs sleep) condition augmented the consolidation of newly learned adjective-image pairings, potentially mitigating the initial impact of sleep loss on encoding. To test this possibility, we correlated the between-condition difference in sleep duration on the first night after learning (sleep deprivation condition – sleep condition) with the $LI^{SleepBenefit}$. However, no significant relationship emerged ($R^2 = -0.06$, $p = .756$, $BF_{01} = 2.33$).

3.5 Discussion

Sleep provides a benefit over wake for retaining memories and also for learning new ones (Alberca-Reina et al., 2014; Ashton & Cairney, 2021; Ashton et al., 2020; Cairney, Lindsay, et al., 2018; Cousins et al., 2018; Durrant et al., 2016; Gais et al., 2006; Gaskell et al., 2018; Kaida et al., 2015; Payne et al., 2012; Talamini et al., 2008; Tempesta et al., 2016; Yoo et al., 2007). Some suggest that these benefits can be explained by an active role of slow-wave sleep (SWS) and associated neural oscillations in

shifting the memory retrieval network from hippocampus to neocortex, and thus restoring hippocampal capacity for new learning (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). In the current study, we tested the hypothesis that the extent to which individuals consolidate new memories during sleep predicts their ability to encode new information the following day, and that slow-wave activity (SWA) contributes to this relationship. Although we observed a benefit of sleep (relative to sleep deprivation) on our measures of overnight consolidation and next-day learning, we found no evidence of a relationship between the two measures, nor with SWA.

Given the importance of sleep for new learning, we further sought to understand how sleep deprivation affects the neural correlates of successful encoding. Interestingly, whereas learning of subsequently remembered (vs forgotten) associations was associated with a downregulation of 12-20 Hz beta power after sleep (as reported in previous work, (Benjamin James Griffiths et al., 2019; Hanslmayr et al., 2014; Hanslmayr et al., 2009; Hanslmayr et al., 2012; Hanslmayr et al., 2011), no significant difference in beta power emerged after sleep deprivation. These findings suggest that an absence of sleep disrupts the neural operations underpinning memory encoding, leading to suboptimal performance.

3.5.1 Sleep benefits overnight consolidation and next-day learning

Previous work has shown that sleep supports memory consolidation (Ashton & Cairney, 2021; Ashton et al., 2020; Cairney, Lindsay, et al., 2018; Durrant et al., 2016; Gais et al., 2006; Gaskell et al., 2018; Payne et al., 2012; Talamini et al., 2008) and subsequent learning (Cousins et al., 2018; Kaida et al., 2015; McDermott et al., 2003; Tempesta et al., 2016; Yoo et al., 2007). In keeping with these studies, we found that memory retention and next-day learning benefited from overnight sleep relative to sleep deprivation.

Although this was a pre-registered investigation of sleep's role in learning and memory, and was motivated by prior work on the same topic (Gais et al., 2006; Yoo et al., 2007), it is important to

consider the extent to which our findings can disentangle the memory effects of sleep from the disruptive influences of sleep deprivation. Extended periods of wakefulness give rise to various cognitive impairments (Krause et al., 2017), meaning that poorer performance in the sleep deprivation (vs sleep) condition could reflect the indirect consequences of sleep loss, rather than a direct absence of sleep (indeed, participants in the current study were slower to respond on the PVT and reported being less alert on the Stanford Sleepiness Scale after sleep deprivation than sleep). Focusing first on our assessment of overnight consolidation, generalised cognitive impairments arising from sleep deprivation could have impaired retrieval performance, creating the impression of a sleep-associated improvement in retention. While this is a reasonable concern in view of the sleep-memory effects observed at our delayed test (which followed immediately after the overnight interval), it does not explain why the retention advantage in the sleep condition was still present 48 h later (once sleep deprived individuals had had ample opportunity for recovery sleep). Moreover, we observed no significant relationship between the benefits of sleep (vs sleep deprivation) on memory retention and between-conditions differences in Stanford Sleepiness Scale scores or PVT response times, suggesting that our findings were not driven by the general cognitive impairments that accompany sleep deprivation. It is therefore reasonable to conclude that our data reflect a positive impact of sleep on memory retention. To what extent this memory benefit of sleep can be explained by an absence of wakeful interference (such as that experienced in the sleep deprivation condition) or an active sleep-dependent consolidation mechanism, however, cannot be inferred from our data.

Turning to our analysis of next-day learning, although the assessment phase also took place 48 h after encoding, the initial learning phase occurred immediately after sleep or sleep deprivation. We therefore cannot rule out the possibility that the apparent improvement in encoding performance after sleep was influenced by generalised cognitive impairments following sleep deprivation. Importantly, however, we think that our EEG data provide reasonable evidence that an absence of sleep does in itself disrupt new learning. Specifically, if our effects were driven by non-specific cognitive deficits following sleep deprivation, one would expect to have observed only generalised

differences in EEG activity between the sleep and sleep deprivation conditions (i.e. only a main effect of condition, across all encoding trials). By contrast, a significant interaction showed that beta desynchronization disrupted by the sleep deprivation (vs sleep) condition, specifically on trials for which adjective-image pairings were subsequently remembered. This impact of sleep on beta desynchronization during successful learning was not predicted by between-condition differences in Stanford Sleepiness Scale scores or PVT response times, and no between-condition difference in beta power emerged for pairings that were subsequently forgotten (see Figures 4b and 4c). Because beta desynchronization is an established neural marker of semantic processing during successful learning (Griffiths et al., 2016; Hanslmayr et al., 2014; Hanslmayr et al., 2011), these findings may suggest that the neural mechanisms of encoding are indeed disrupted by an absence of sleep. Further support for this view is available below, where we outline how the brain may engage in compensatory learning strategies when semantic processing pathways are compromised by sleep deprivation (see *Sleep loss disrupts effective learning*).

Because our retention index was based on tests for the same items at the immediate, delayed and follow-up sessions, it is possible that our data were influenced by retrieval practice effects (i.e. memories that undergo retrieval practice are typically better remembered than those that do not, (Carpenter et al., 2008; Roediger & Karpicke, 2006). That is, the retention advantage observed after sleep (vs sleep deprivation) at the delayed test might have been maintained at the follow-up test as a result of retrieval practice. However, given that memories strengthened through retrieval gain little benefit from sleep-associated consolidation (Antony et al., 2017; Antony & Paller, 2018; Bäuml et al., 2014), then, under a retrieval practice hypothesis, the immediate test should have nullified any later impact of sleep on retention. While it may still be argued that a between-condition difference in retention at the delayed test was driven by non-specific impairments following sleep deprivation, this would not explain why the memory advantage in the sleep condition was still present 48 h later (once recovery sleep had taken place). We therefore think that retrieval practice effects cannot provide a reasonable explanation of our findings.

Given that recovery sleep after sleep deprivation is characterised by a homeostatic increase in SWS (Borbély, 1982; Borbély et al., 2016), one might have expected the overnight consolidation of newly learned adjective-image pairings to be amplified in the sleep deprivation (vs sleep) condition, potentially tempering the initial impact of sleep loss on encoding. Although we did not record sleep EEG during the time that participants were away from the laboratory (and thus have no insight into homeostatic increases in SWS after sleep deprivation), we did monitor sleep behaviour with wristwatch actigraphy. Participants slept for longer during the first night after learning in the sleep deprivation (vs sleep) condition, but this between-condition difference in sleep duration was not significantly correlated with the magnitude of sleep's benefit for learning. This suggests that longer recovery sleep in the sleep deprivation condition did not meaningfully influence the impact of sleep loss on new learning.

It is worth noting, though, that an enhanced consolidation of newly learned adjective-image pairings in the sleep deprivation (vs sleep) condition (due to longer or deeper recovery sleep) could have obscured a relationship between sleep-associated memory retention and next-day learning in our multiple regression analysis. However, the same null effects were observed when our analysis was restricted to data from the sleep condition alone, rather than subtractions between the sleep and sleep deprivation conditions (as was done in our primary analysis). Hence, no relationship between overnight consolidation and next-day learning was observed when the influence of sleep deprivation (and the putative enhancement of sleep-associated consolidation during recovery sleep) was removed from our data.

3.5.2 No link between sleep-associated consolidation and next-day learning

If memory consolidation during SWS supports a shift in the memory retrieval network from hippocampus to neocortex, then sleep-associated consolidation of hippocampus-dependent memories should predict next-day learning of new, hippocampally-mediated associations, and SWA should facilitate this relationship. However, we observed no such effects in our data, suggesting that

new learning in hippocampus may not be contingent on hippocampal memory processing during the preceding night of sleep.

An alternative interpretation of these null effects is that our experimental paradigm could not provide an adequate test of our hypothesis. Although we reasoned that the use of two conceptually different hippocampus-dependent tasks would prevent our findings from being influenced by retroactive or proactive interference, qualitative differences between these tasks might have negated our ability to detect a relationship between sleep-associated memory consolidation and next-day learning. This is nevertheless a speculative suggestion that can be addressed in future research (e.g. by using a paired-associates task to assess both overnight memory retention and subsequent encoding).

Although our study was motivated by the assumptions of the Active Systems framework (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009), it is important to also consider our findings in the context of homeostatic synaptic downscaling, which is regarded as another fundamental mechanism through which sleep supports learning and memory (Tononi & Cirelli, 2014, 2016). From this perspective, sleep is the price the brain pays for waking plasticity, in order to avoid an accumulation of synaptic upscaling. Because synaptic renormalization should mainly occur during sleep (when neural circuits can undergo a broad and systematic synaptic downscaling), a night of sleep deprivation would prevent the restoration of cellular homeostasis and impair next-day learning. A number of theoretical accounts of sleep-associated memory processing have made progress in reconciling the key tenets of the Active Systems and Synaptic Homeostasis frameworks, suggesting that these processes work in concert to support global plasticity and local downscaling, respectively, and in doing so prepare the hippocampus for future encoding (Genzel et al., 2014; Klinzing et al., 2019; Lewis & Durrant, 2011). Interestingly, whereas global memory replay and consolidation have been linked to slow (< 1 Hz) oscillations, downscaling and forgetting are associated with delta waves (1-4 Hz) in local networks (Genzel et al., 2014; Kim et al., 2019). How interactions between global slow oscillations and local delta waves regulate overnight memory processing is therefore pertinent to

further understanding of the relationship between sleep-associated consolidation and next-day learning.

3.5.3 Sleep loss disrupts effective learning

Successful learning is associated with left-lateralised beta desynchronization ~0.5-1.5s after stimulus onset (Griffiths et al., 2016; Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021; Hanslmayr et al., 2014; Hanslmayr et al., 2009; Hanslmayr et al., 2012; Hanslmayr et al., 2011). Consistent with these prior studies, we observed a decrease in beta power ~0.3-2 s after stimulus onset during the encoding of subsequently remembered (vs forgotten) associations, and this was most pronounced in the left hemisphere. Beta desynchronization is thought to reflect semantic processing during successful memory formation (Fellner et al., 2013; Hanslmayr et al., 2011); as beta power decreases, the depth of semantic processing increases (Hanslmayr et al., 2009). More broadly, neocortical alpha/beta oscillations have been linked to the processing of incoming information during episodic encoding (Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021). For our learning task, participants were instructed to form vivid mental images or stories that linked the adjective and image of each pairing. The observed downregulation of beta power during successful learning might thus reflect an engagement of information processing operations, possibly involving semantic representations, allowing these novel associations to be bound together into one coherent episode and committed to memory.

Importantly, however, the change in beta power that accompanied successful learning differed according to whether participants had slept or remained awake across the overnight interval. Whereas encoding of subsequently remembered (vs forgotten) adjective-image pairings was associated with beta desynchronization after sleep, no significant difference in beta power emerged from the same contrast after sleep deprivation. Hence, a protracted lack of sleep appeared to disrupt semantic processing operations when participants were successfully forming new memories. This interpretation is in line with previous behavioural findings where sleep deprived individuals have had difficulty in

encoding semantically incongruent stimulus pairs (Alberca-Reina et al., 2014). The sleep deprived brain might thus rely on alternative processing routes when committing new information to memory. Indeed, prior studies have shown that sleep deprivation leads to compensatory neural responses during learning (Chee & Choo, 2004; Drummond et al., 2004) and recognition (Sterpenich et al., 2007).

What might be the nature of this alternative route to learning after sleep deprivation? It is interesting to note that we observed an upregulation of beta activity during successful (vs unsuccessful) learning in the sleep deprivation condition (although this difference did not survive a Bonferroni correction for multiple comparisons). Increases in beta power have been linked to working memory and active rehearsal (Deiber et al., 2007; Hwang et al., 2005; Onton et al., 2005; Tallon-Baudry et al., 2001), suggesting that sleep-deprived individuals may engage in more surface-based rehearsal strategies due to semantic processing pathways being compromised by an absence of sleep.

It is important to note that the foregoing findings on beta desynchronization arose from an exploratory analysis that was not pre-registered, and should therefore be treated with caution until such time that they are replicated in confirmatory research.

3.5.4 Conclusions

We investigated whether memory consolidation in sleep predicts next-day learning and whether SWA contributes to this relationship. Furthermore, we investigated how the neural correlates of successful learning are affected by sleep deprivation. Although sleep improved both memory retention and next-day learning, we found no evidence of a relationship between these measures, nor with SWA. Whereas beta desynchronization – an established marker of semantic processing during successful learning – was present during the encoding of subsequently remembered (vs forgotten) associations after sleep, no such difference in beta power was observed after sleep deprivation. An extended lack of sleep might therefore disrupt our ability to draw upon semantic knowledge when encoding novel associations, necessitating the use of more surface-based and ultimately suboptimal routes to learning.

Chapter 4:

Learning is linked to prior daytime forgetting but not overnight memory consolidation

Anna á V. Guttesen[1], Marcus O. Harrington[1], M. Gareth Gaskell[1,2], & Scott A. Cairney[1,2]

[1] Department of Psychology, University of York, UK

[2] York Biomedical Research Institute, University of York, UK

Note for examiners

A.áV.G. collected the data for Experiment 1 and M.O.H. collected the data for Experiment 2. A.áV.G. wrote the scripts for all of the analyses and figures.

The preregistration for Experiment 1 is available on the Open Science Framework:

https://osf.io/khwzm

The preregistration for Experiment 2 is available on the Open Science Framework:

https://osf.io/jywvz

4.1 Abstract

Sleep supports memory consolidation and next-day learning. The *Active Systems* model of memory consolidation posits that sleep drives the redistribution of newly acquired memory representations from hippocampus to neocortex for long-term storage. Accordingly, overnight consolidation may pave the way for efficient next-day learning by preparing the hippocampus for the acquisition of new information. Here, we tested this hypothesis across two preregistered experiments. In both experiments, participants learned a set of word pairs and their ability to recall the word pairs was assessed before and after a 12 h delay containing overnight sleep (Sleep group) or daytime wakefulness (Wake group). Participants then learned, and were immediately tested on, a new set of word pairs. As expected, word pair retention was better after sleep as compared to wakefulness, demonstrating a benefit of sleep for memory consolidation. Critically, however, sleep did not benefit subsequent word pair learning, and there was no evidence of a relationship between overnight memory consolidation and next-day learning. Unexpectedly, there was a significant relationship between daytime forgetting and subsequent learning. In sum, our data indicate that overnight consolidation does not modulate next-day learning, and instead suggests that daytime forgetting may be a prerequisite of efficient encoding.

4.2 Introduction

How do we form new memories without overwriting existing ones? This dilemma between stability and plasticity was addressed by the Standard Model of Systems Consolidation (Marr et al., 1971; McClelland et al., 1995; Squire et al., 1984). According to this framework, declarative memories (i.e. memories for facts and events that can be consciously brought to mind) are initially encoded concurrently in both hippocampal and disparate cortical networks. Over time, the memory traces are repeatedly reinstated and cortico-cortical connections are gradually established and strengthened. Through this consolidation process, memory traces integrate with pre-existing cortical representations, allowing the neocortex to retrieve the memories independently of the hippocampus.

It has long been known that sleep benefits memory retention. It was initially believed that by preventing the brain from acquiring new information, sleep passively protected recent memories from interference that would otherwise occur during wakefulness (Jenkins & Dallenbach, 1924). From this passive perspective, any superior recall demonstrated by those that had slept immediately after learning compared to those that had been awake was not a result of sleep-associated consolidation, but rather reflected the negative effects of interference during wakefulness. More recent accounts have suggested that sleep benefits memory by reducing contextual interference (Yonelinas et al., 2019). However, others have suggested that sleep actively contributes to the memory consolidation process (Ellenbogen, Payne, et al., 2006). In one study, participants encoded a list of word pairs that competed with pairs they had learned 12 h earlier. Participants who slept during the 12 h interval exhibited better recall of the original pairs as compared to participants who remained awake during the interval. Critically, the benefit of sleep was sizeably smaller in a separate condition where participants did not learn competing information, elegantly demonstrating that sleep strengthens memories such that they become resistant to subsequent associative interference (Ellenbogen, Hulbert, et al., 2006). In other studies, researchers have manipulated the temporal proximity between learning and sleep. By measuring retention across a 24 h delay which includes both wakefulness and sleep, researchers have repeatedly found that participants retain more information across the delay

when learning is immediately followed by a night of sleep, compared to when learning is immediately followed by a day of wakefulness (Backhaus et al., 2008; Gais et al., 2006; Payne et al., 2012; Talamini et al., 2008). This suggests that sleeping immediately after learning helps stabilize memories, diminishing the deleterious consequences of subsequent wakefulness.

Declarative memory consolidation is thought to be driven primarily by slow-wave sleep (SWS): a stage of non-rapid eye movement (NREM) sleep characterised by the occurrence of slow oscillations (SOs; <1 Hz) and sleep spindles (~12-16 Hz). Additional evidence supporting the notion that the role of sleep in consolidation is active rather than passive comes from correlational studies that have found associations between memory consolidation and these oscillatory signatures of SWS (Cairney, Guttesen, et al., 2018; Schabus et al., 2004; Schreiner et al., 2021; Scullin, 2013). Other studies have facilitated memory consolidation by directly manipulating slow oscillations and their temporal coupling with spindles (Marshall et al., 2006; Ngo et al., 2013; Ngo et al., 2015), demonstrating a causal relationship between memory consolidation and SWS oscillations.

Addressing the critical role of sleep in memory consolidation and building on the ideas of the Standard Model, researchers proposed an updated account of memory consolidation known as the Active Systems Model (Born & Wilhelm, 2012; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). According to this model, SWS oscillations drive the stabilization of memories by means of reactivation and reorganisation. Similar to the Standard Model, sleep-associated consolidation helps shift retrieval dependency away from hippocampus so that memory traces become fully dependent on neocortex. Using behavioural and neuroimaging techniques, Takashima et al. (2009) tested the idea that memories become less dependent on hippocampus with consolidation. Consistent with the Active Systems Model, the authors found that a 24 h delay featuring a night of sleep led to a decrease in hippocampal activity and a concomitant increase in neocortical connectivity during declarative memory retrieval. Similarly, Gais et al. (2007) found that sleeping after learning (as compared to sleep deprivation) promoted functional coupling between activity in the hippocampus and neocortex,

supporting the idea of hippocampal-to-neocortical transfer. Other studies have also found a link between slow-wave sleep and hippocampal disengagement during retrieval suggesting a shift in dependency away from the hippocampus (Cairney et al., 2015; Takashima et al., 2006). Together, these findings support the notion that sleep plays an active role in hippocampal-to-neocortical systems consolidation.

One indirect and less studied assumption of the Active Systems model is that declarative memory consolidation during sleep 'refreshes' hippocampal encoding capacity (Walker, 2009). Providing some initial support for this idea, several studies have found that learning is better after sleep than sleep deprivation (Alberca-Reina et al., 2014; Cousins et al., 2018; Guttesen et al., 2022; Kaida et al., 2015; Tempesta et al., 2016; Van Der Werf et al., 2009). Sleep deprivation has also been shown to lead to reduced hippocampal activation during encoding (Yoo et al., 2007). Thus, it seems that sleep deprivation disrupts memory processing that relies on the hippocampal system, including encoding of declarative memories. Conversely, as compared to wakefulness, daytime napping has been shown to improve subsequent learning (Mander et al., 2011) and restore hippocampal engagement during encoding (Ong et al., 2020). Furthermore, slow oscillations and sleep spindles have been found to be associated with the subsequent encoding of declarative memories (Antonenko et al., 2013; Lustenberger et al., 2012; Mander et al., 2011; Ong et al., 2018). From an Active Systems perspective, these components of slow-wave sleep facilitate the hippocampal-to-neocortical reorganisation of memory traces, restoring the capacity for new learning in hippocampus.

In summary, there is evidence that sleep is associated with memory consolidation and subsequent memory formation. However, little is known about whether sleep-associated consolidation and learning are directly associated. If memory consolidation during sleep benefits next-day learning, one would expect to see a link between the two processes. However, there is very little empirical work addressing the relationship between overnight consolidation and next-day learning. Guttesen et al. (2022) provided some preliminary evidence that learning is linked to sleep but not necessarily sleep-

associated consolidation. The authors measured the consolidation of visuospatial memories over a night of sleep or sleep deprivation in addition to measuring learning performance of image-word pairs the following day. They found no evidence of a relationship between these two measures, however, the Bayes Factor evidence for the null was merely anecdotal (Guttesen et al., 2022). Thus, the role of consolidation for subsequent learning remains poorly understood and further studies are needed to address this link.

In the study by Guttesen et al. (2022), the tasks measuring consolidation and learning may have been too distinct from one another, possibly masking any relationship between the indices of consolidation and learning. In the present study, we therefore ran two preregistered experiments to test the hypothesis that overnight consolidation is linked to next-day learning using the same task to measure both indices. In Experiment 1, participants learned word pairs, and we measured memory retention across a 12 h delay containing either overnight sleep (Sleep group) or daytime wakefulness (Wake group). To follow up Guttesen et al. (2022), an additional measure of visuospatial retention was implemented. This provided two indices of consolidation. After the delay, participants encoded novel word pairs and we tested their memory for these pairs immediately afterwards. Performance in this recall test provided an index of participants' ability to learn new information after the sleep/wake delay. By examining the relationship between forgetting across the delay and recollection of information encoded after the delay, we were able to study whether memory consolidation could predict subsequent learning. We included two separate tasks as indices of consolidation to test whether any relationship between overnight consolidation and subsequent learning is restricted to memories of the same type, or whether it generalizes to situations where the consolidated and to-be-learned materials are both declarative but qualitatively different.

Our first hypothesis was that overnight sleep would benefit consolidation as well as subsequent learning, as compared to daytime wakefulness. Our second hypothesis was that the index of consolidation from our word pair task would correlate with the index of word pair learning for the

Sleep group but not the Wake group. Based on the findings of a previous study (Guttesen et al., 2022), however, we predicted that there would be no relationship between the image location consolidation index and the word pair learning index, suggesting that learning is not linked to consolidation when the learned materials are distinct.

Experiment 1

4.3 Method

4.3.1 Participants

One-hundred-and-eighty-nine participants were recruited online via Prolific (https://prolific.co/) and randomly assigned to a Sleep or Wake group. As indicated by self-report, all participants were native English speakers who resided in the United Kingdom. All participants were instructed to abstain from alcohol and caffeine for the duration of the study. Participants in the Wake group were instructed to refrain from napping during the delay. Informed consent was obtained from all participants in line with the requirements of the Research Ethics Committee of the Department of Psychology, University of York.

Because we assessed memory consolidation across a 12 h delay, participants were required to complete two separate sessions. As preregistered, 74 participants were excluded from all analyses because they: failed to return for the second session (n = 26), did not meet the performance thresholds in our behavioural tasks (see below; n = 45), napped in the Wake group (n = 1), or fell outside the desired age range of 18-30 years (n = 2).

After exclusions, our final sample consisted of 115 participants (Table 4.1). Our sample size was calculated using an effect size observed in published data (Ashton & Cairney, 2021). The effect of interest (*d* = .570) was derived from a t-test comparing the forgetting of semantically-related word pairs across a 12 h delay containing either overnight sleep or daytime wake. Based on an alpha level of .05 (two-tailed) and power of .85, the minimum required sample size was estimated at n = 114 (n = 57 per group).

Table 4.1. Participant demographics in Experiment 1.

	Sleep Group	Wake Group
N (Male/Female)	57 (15/42)	58 (14/44)
Age (Years)	24.05 (± 3.32)	24.24 (± 3.40)
Typical Sleep Duration (Hours)	7.52 (± 1.07)	7.63 (± 1.14)
Morning/Evening Type		
Definitely morning type (N)	3	10
Rather morning type (N)	20	13
Rather evening type (N)	22	20
Definitely evening type (N)	12	15
Mean ± SD	2.75 (± 0.85)	2.69 (± 1.05)
Sleep Duration Before Study (Hours)		
Pre-Delay session	7.52 (± 1.05)	7.26 (± 1.11)
Post-Delay session	7.25 (± 1.16)	N/A

Age, sleep parameters, and morning/evening preference were based on self-report. Morning/evening preference was assessed using a single forced-choice question: "One hears about "morning" and "evening" types of people. Which one of these types do you consider yourself to be?" A mean score of 2.5 would indicate no morning/evening preference across our sample, whereas higher scores reflect an evening preference. Data are shown as means (± SEM) unless specified otherwise.

4.3.2 Materials

Twenty images of neutral scenes were acquired from the Nencki Affective Picture System (Marchewka et al., 2014) for use in a visuospatial memory task.

Ninety semantically-related word pairs were acquired from the University of South Florida Word Association Norms (Nelson et al., 1998) for use in a paired-associates learning task. Word pairs were divided into three equal lists of 30 for use in three separate recall tests. The lists were counterbalanced across recall tests and did not differ significantly with regards to semantic relatedness, cue length, or target length (all pairwise $p > .05$).

4.3.3 Procedure

The experimental procedure is illustrated in Figure 4.1A. All participants completed two experimental sessions (Pre-Delay and Post-Delay), which were separated by a 12 h delay spanning either a night of sleep (Sleep group) or a day of wakefulness (Wake group). Participants completed the study online using a desktop or laptop computer. The first session lasted ~35 min and the second ~20 min.

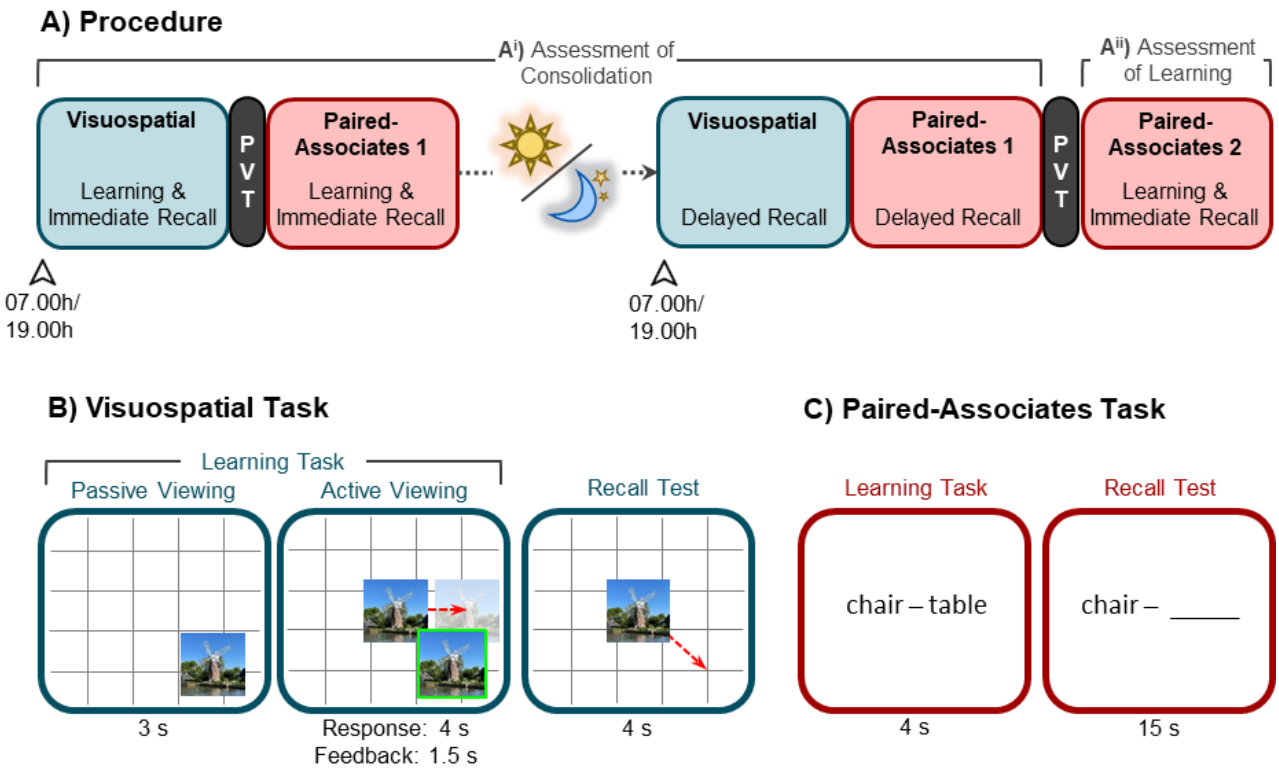

Figure 4.1. Procedures and tasks in Experiment 1. *(A^{i})* Participants learned and were tested on the locations of 20 images. They also learned 60 word pairs (A-B^{1-60}) and were tested on half of those pairs (A-B^{1-30}). After a 12 h delay of either overnight sleep (Sleep group) or daytime wakefulness (Wake group), participants were tested again on the locations of the 20 images, and were also tested on the remaining word pairs (A-B^{31-60}). *(A^{ii})* Participants learned 30 new word pairs (C-D^{1-30}), before having their memory tested for all of these new pairs. Alertness was assessed prior to each word pair learning phase in a Psychomotor Vigilance Task (PVT), where participants were required to respond to the presentation of a red cross as quickly as possible. *(B)* During the visuospatial learning task, participants completed one round of Passive Viewing, during which they viewed the location of each image on a grid (3 s). Next, in the Active Viewing phase, participants moved each image to the location that they believed it had appeared during Passive Viewing (4 s) and received feedback on its correct location (green frame; 1.5 s). Active Viewing continued until participants had met the performance criterion for all images. The test phases followed the same procedures as one round of Active Viewing, but no feedback was provided. Each test trial provided an accuracy score in normalized units, which described how far the image was placed from its correct location. *(C)* During the paired-associates learning task participants viewed word pairs (4 s). During recall tests, participants saw the first word of each pair (cue) and were required to type the corresponding second word (target; 15 s).

Assessment of consolidation

During the Pre-Delay session, participants completed two learning tasks: a visuospatial task (Figure 4.1B) and a paired-associates task (Figure 4.1C). Immediately after each respective learning task, participants completed an immediate recall test that assessed their memory for the information that they had just learned. At the beginning of the Post-Delay session, participants completed delayed recall tests that assessed their memory for the information they learned during the Pre-Delay session. These elements of the experiment were designed to assess memory consolidation (Figure 4.1A[i]). All experimental tasks were created using Pavlovia (https://pavlovia.org/).

Visuospatial learning task

The visuospatial learning task consisted of two phases: Passive Viewing and Active Viewing. In the Passive Viewing phase, each of 20 images were presented at a random location on a grid background for 3 s, followed by a 0.5 s inter-stimulus interval (ISI). Participants were instructed to memorize the image locations for a later test. In the Active Viewing phase, each of the 20 images appeared in the centre of the grid, and participants were required to move the image to the location that they believed it had appeared during the Passive Viewing phase within 4 seconds (0.5 s ISI). The image then reappeared within a green frame in its correct location for 1.5 s (to serve as feedback). This continued until all images had been placed within a success zone around the centre of the correct image location on two consecutive rounds of Active Viewing (images for which this criterion was met were dropped from subsequent Active Viewing rounds) or they had completed 10 rounds of Active Viewing. The size of the success zone square was based on Guttesen et al.'s (2022) laboratory study with a success zone of 300x300 pixels. For use across various screen resolutions, we converted this value to normalised units of .4167 NU^2.

Visuospatial recall tests

Each visuospatial test phase (immediate and delayed) followed the same procedures as one round of Active Viewing, with the exception that no feedback on the correct location of images was provided.

Paired-associates learning task

In the paired-associates learning task, participants viewed each of 60 semantically related word pairs (e.g. *chair–table*), which have been shown to be sensitive to sleep-related changes in previous studies (Ashton & Cairney, 2021; Ngo et al., 2013). On each trial, a randomly selected word pair was presented in the centre of the screen for 4 s, followed by a 1 s ISI. Participants were informed that their memory for the word pairs would be tested. To help participants remember the word pairs, they were instructed to think of a mental image or story in their mind that links the words together.

To check whether participants were paying attention, twelve attention check trials were randomly intermixed within the word pair trials. On each attention check, a pair of randomly generated four-digit numbers (e.g. *8121–3482*) appeared in the centre of the screen and participants were instructed to press the Space Bar within 5 s. As preregistered, individuals who failed more than two attention check trials were not invited back for the Post-Delay session (n = 26).

Paired-associates recall tests

During the immediate paired-associates recall test, participants' memory was assessed for half of the word pairs that were shown in the learning task (only the first 30 that were encoded). On each trial, the first word (cue) of a randomly selected pair was presented in the centre of the screen. Participants were instructed to type the corresponding second word (target) within 15 s, and then press the Return key to submit their response. As preregistered, participants who completed the study but achieved < 20% correct were excluded from all analyses (n = 7).

When participants were unable to recall the target word, they were instructed to type in the cue word. For example, if "*chair*–" appeared on the screen, and the participant was unable to recall the target word (i.e. *table*), they would simply type and submit the word "*chair*". This instruction was designed to prevent participants from providing low-quality responses to complete the task more quickly (i.e., it would take as long to type the target word as it would the cue word). As preregistered, participants who submitted either a blank response or a nonsense word on > 20% of trials were not invited back for the Post-Delay session (n = 5, not including those already excluded for failing too many attention checks).

The delayed recall test was identical to the immediate recall test, except that it contained the other half of the word pairs from the learning task (i.e. the latter half that did not feature in the immediate recall test). Participants were not required to perform above a certain threshold in the delayed recall test.

Assessment of learning

In the Post-Delay session, after the delayed recall test, participants completed a second paired-associates learning task and a corresponding second immediate recall test. These elements of the experiment were designed to assess learning after the sleep/wake delay (Figure 4.1A[ii]). The second paired-associates learning task was identical to the first, except it contained half as many word pairs (n = 30) and attention check trials (n = 6). As preregistered, participants were excluded if they failed > 1 attention check (n = 1). Because we were interested in the learning of new information after the sleep/wake delay, the word pairs that were shown in the second learning task were entirely novel: they did not feature in the first learning task. The second immediate recall test was identical to the other paired-associates recall tests, except it contained all the word pairs from the second paired-associates learning task. As before, participants were excluded if they achieved < 20% correct (n = 4) or submitted either a blank response or a nonsense word on > 20% of trials (n = 2).

Alertness

Subjective sleepiness was assessed at the beginning of each session using the Stanford Sleepiness Scale (Hoddes et al., 1973). Vigilance was assessed before each paired-associates learning task using a 3 min Psychomotor Vigilance Task (PVT). During the PVT, participants were shown a blank grey screen. At random intervals between 2 and 10 s, a red cross appeared in the centre of the screen, and participants were required to press the Space Bar as quickly as possible.

4.3.4 Data analysis

Unless stated otherwise, all data were analysed in RStudio (v.1.4.1717, RStudio Team, 2021).

Consolidation

Visuospatial

To assess the consolidation of visuospatial memories across the sleep/wake delay, we first calculated how precisely participants recalled the location of each image, separately for each recall test. Specifically, we computed an error score that reflects the distance between the correct image location and the participant's recalled location. Next, for each image, we calculated the difference in error score between the two recall tests [*immediate recall test – delayed recall test*]. Finally, we calculated the average of the differences to create an overall Visuospatial Retention Index for each participant. Higher scores thus reflect better retention. To ease understanding (e.g. higher RI = better retention), we swapped the order of Retention Index subtraction to that which was pre-registered. This change yields statistically identical results aside from the sign change.

Paired-associates

We also assessed the consolidation of paired-associates across the sleep/wake delay. We began by calculating the percentage of correctly recalled word pairs, separately for each recall test. Responses were considered correct if they were identical to the target word, were a plural or singular of the target word, or if they were identical barring a clear and obvious spelling or typographical error. To quantify retention across the sleep/wake delay, we calculated a Paired-Associates Retention Index: the difference in recall performance between the first immediate recall test and the delayed recall test [*delayed recall test – immediate recall test 1*]. Higher scores thus reflect better retention. Similar to above, we swapped the order of Retention Index subtraction to that which was preregistered.

To investigate the effect of sleep (vs. wakefulness) on consolidation, we conducted independent t-tests (Sleep Group vs Wake Group) on the Visuospatial Retention Index and Paired-Associates Retention Index.

Learning

To assess new learning, we calculated the percentage of correctly recalled word pairs in the second immediate paired-associates recall test. This measure is referred to hereafter as the Learning Index. To investigate the effect of sleep (vs. wakefulness) on learning, we conducted an independent t-test (Sleep group vs Wake group) on the Learning Index.

Parallel to the t-tests used to investigate consolidation and new learning, we also analysed these results using a Bayesian approach, primarily because it can quantify evidence in favour of the null hypothesis. Specifically, we computed Bayes Factors (BF) comparing the independent samples (R package: BayesFactor, function: ttestBF; Morey & Rouder, 2018) using the default prior of √(2)/2 (Ly et al., 2016) as we expected a medium effect size. Our interpretation of the BF follow the standard

recommendations (Jarosz & Wiley, 2014; Jeffreys, 1961). Specifically, a BF between 1 and 3 imply anecdotal evidence, 3–10 substantial evidence, and 10–30 strong evidence.

Relationship between consolidation and subsequent learning

To assess the relationship between consolidation and subsequent learning, we examined the correlation between our retention indices (Visuospatial Retention Index, Paired-Associates Retention Index) and the Learning Index using skipped Pearson's correlation (MATLAB toolbox: Robust Correlation; Pernet et al., 2013), separately for the Sleep and Wake groups. Skipped correlations detect and ignore outliers by taking into account the overall structure of the data, providing accurate false positive control without loss of power. We compared the skipped correlations between groups using Zou's confidence intervals (R package: cocor; Zou, 2007). Skipped correlations were interpreted as significantly different if Zou's confidence interval did not contain zero (Zou, 2007). To complement the skipped correlations, we computed BF correlations (R package: BayesFactor, function: correlationBF; Morey & Rouder, 2018) with the default prior of 1/3, which was chosen because we were addressing a novel research question (Ly et al., 2016). The outliers detected and ignored in the skipped correlations were excluded from the BF correlations.

Alertness

To assess whether psychomotor vigilance differed between the Sleep and Wake groups in either experimental session, we first quantified the number of attention lapses (trials where the participant failed to respond within 500 ms; (Lim & Dinges, 2008) in each PVT task. Attention lapses were then applied to a 2 (Group: Sleep, Wake) x 2 (Session: Pre-Delay, Post-Delay) mixed ANOVA. Because of a violation of the normality assumption, we used robust ANOVA with 20% trimmed means (R package: walrus; Love & Mair, 2018; Mair & Wilcox, 2020).

We also assessed whether self-reported sleepiness differed between groups in either session by repeating the robust two-way mixed ANOVA with Stanford Sleepiness Scale scores as the dependent variable (these also violated the normality assumption). The ANOVA was followed up with post-hoc Bonferroni corrected Mann-Whitney U tests where appropriate.

4.4 Results

4.4.1 Baseline recall performance

There were no significant differences in performance between the Sleep and Wake groups during the Pre-Delay immediate recall tests (visuospatial task: $t(113) = 0.81$, $p = .418$, Table 4.2A; paired-associates task: $t(113) = 1.52$, $p = .132$; Table 4.2B).

Table 4.2. Recall performance in Experiment 1.

A	***Visuospatial Recall Performance***			
	Sleep Group		*Wake Group*	
	Immediate Recall	*Delayed Recall*	*Immediate Recall*	*Delayed Recall*
	0.38 (± 0.02)	0.49 (± 0.03)	0.35 (± 0.02)	0.55 (± 0.02)
B	***Paired-Associates Recall Performance***			
	Sleep Group		*Wake Group*	
	Immediate Recall	*Delayed Recall*	*Immediate Recall*	*Delayed Recall*
	61.52 (± 2.30)	33.33 (± 2.73)	56.44 (± 2.43)	19.25 (± 2.13)

(A) Error scores in the visuospatial task (normalized units), which quantify the distance between the correct image location and the participant's recalled location. Higher scores thus reflect poorer recall performance. (B) The percentage of correctly recalled target words in the paired-associates task. Data are shown as means (± SEM).

4.4.2 Sleep and memory consolidation

To test our hypothesis that overnight sleep would benefit memory consolidation relative to daytime wakefulness, we compared between groups the retention rates across the delay. As predicted, the Visuospatial Retention Index was significantly greater in the Sleep group than the Wake group ($t(113) = 2.54$, $p = .012$, $d = 0.47$, $BF_{10} = 3.47$; Figure 4.2A), as was the Paired-Associates Retention Index ($t(113) = 3.12$, $p = .002$, $d = 0.58$, $BF_{10} = 14.37$; Figure 4.2B). Together, these results suggest that sleep benefitted the consolidation of both the image locations and word pairs.

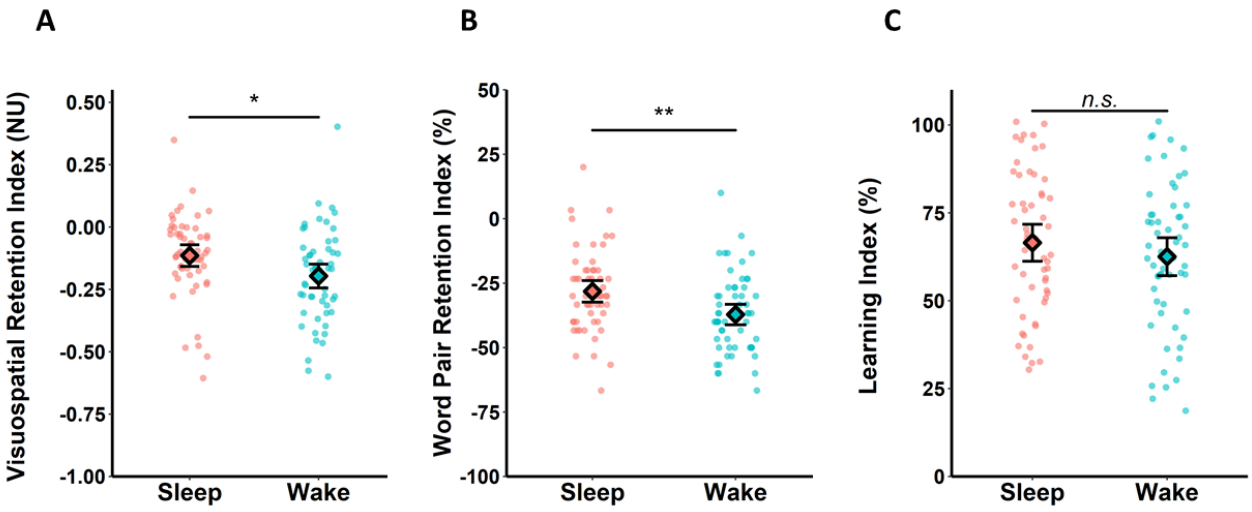

Figure 4.2. Rates of retention (Retention Indices) and new learning (Learning Index) by group in Experiment 1. Better retention occurred over sleep as compared to wakefulness (A) the visuospatial task and (B) the paired-associates task. Despite these effects of group on retention, there was (C) no between-group difference in subsequent learning performance. Data are shown as Mean ± SEM. Data points represent individual participants. (**) $p < .01$; (*) $p < .05$; (n.s.) non-significant.

4.4.3 Sleep and new learning

Next, we tested our hypothesis that new learning would be better after overnight sleep as compared to daytime wakefulness. Contrary to our prediction, the Learning Index did not differ significantly

between the Sleep and Wake groups (t(113) = 1.05, p = .295; Figure 4.2C). Importantly, corresponding Bayesian analysis demonstrated substantial support for the null hypothesis (BF_{01} = 3.07). To account for the contribution of working memory, the analysis was repeated whereby the final three encoded word pairs were excluded from the analysis, and the results were unchanged.

4.4.4 Relationship between consolidation and new learning

To test our hypothesis that overnight consolidation predicts next-day learning, we investigated the relationship between forgetting and next-day learning of word pairs in the Sleep group. Contrary to our prediction, there was no significant correlation between the Paired-Associates Retention Index and Learning Index (r-skipped = 0.17, [-0.03, 0.35] bootstrapped 95% CI; Figure 4.3A), with anecdotal support for the null hypothesis (BF_{01} = 1.68). There was also no significant correlation between the Visuospatial Retention Index and the Learning Index (r-skipped = 0.18, [-0.04, 0.39] bootstrapped 95% CI). Again, the evidence for the null was anecdotal (BF_{01} = 1.42). These results indicate that overnight consolidation does not facilitate next-day learning, regardless of whether the to-be-learned information is qualitatively identical to or different from the consolidated information.

We also tested the relationship between consolidation and new learning in the Wake group. Unexpectedly, there was a significant negative correlation between the Paired-Associates Retention Index and the Learning Index (r-skipped = -0.32, [-0.54, 0.11] bootstrapped 95% CI, BF_{10} = 4.51; Figure 4.3B). That is, the more word pairs that participants forgot across the delay, the better they were at learning new word pairs after the delay. The correlation differed significantly from the one observed in the Sleep group (Zou's 95% CI [0.12, 0.81]). As in the Sleep group, there was no significant correlation between the Visuospatial Retention Index and the Learning Index (r-skipped = -0.01, [-0.31, 0.35] bootstrapped 95% CI; Zou's 95% CI [-0.52, 0.20]), with substantial evidence for the null (BF_{01} = 3.36). These findings suggest that daytime forgetting may benefit future learning, but only when the to-be-learned information is qualitatively similar to the forgotten information.

These analyses were repeated without the final three encoded trials (for the Learning Index), and the results were unchanged.

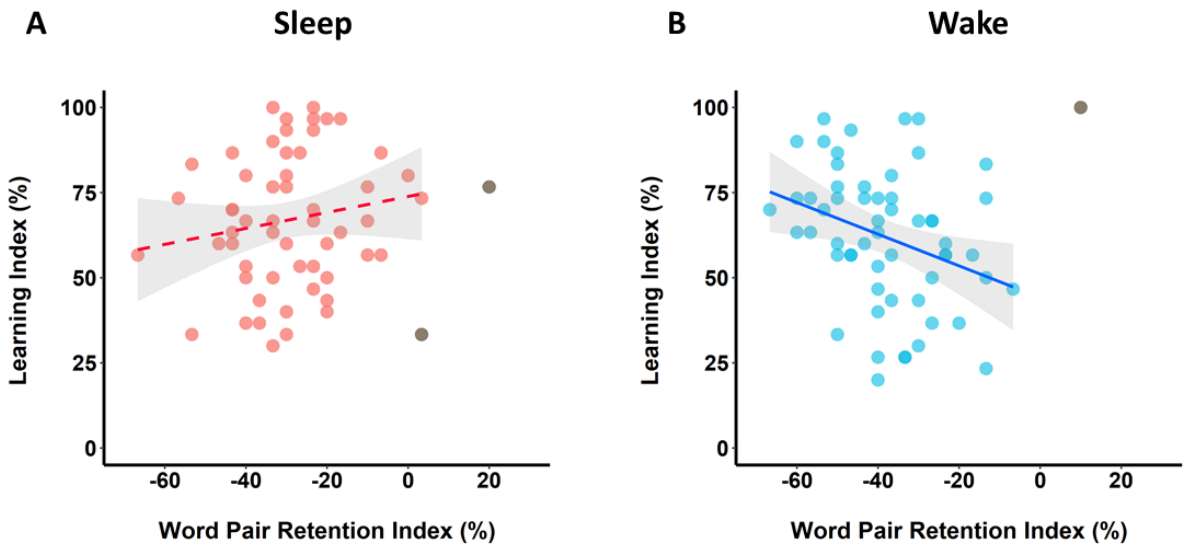

Figure 4.3. Relationship between retention (Paired-Associates Retention Index) and new learning (Learning Index) by group in Experiment 1. There was no significant correlation between retention and new learning of word pairs in the Sleep group (A). In the Wake group, however, there was a significant negative correlation, whereby lower word pair retention (i.e. more forgetting) across the delay was associated with better subsequent word pair learning (B). However, there was no relationship between visuospatial retention and subsequent word pair learning. Shaded areas represent 95% confidence intervals. Data points represent individual participants. Individuals who were identified as outliers by the skipped correlation analysis and thus did not contribute to the relationship (see Method) are shown as grey data points (n = 2 in A, n = 1 in B).

Alertness

Participants had more attention lapses during the PVT in the Post-Delay session as compared to the Pre-Delay session ($F(1,226) = 5.09$, $p = .026$; Table 4.3A). Importantly, however, performance did not differ significantly between the Sleep and Wake groups in either Session (main effect of Group: $F(1,226) = 0.36$, $p = .550$; Group x Session interaction: $F(1,226) = 0.24$, $p = .625$).

Regarding Stanford Sleepiness Scale (SSS) scores, there was a significant interaction between the factors Group (Sleep, Wake) and Session (Pre-Delay, Post-Delay; $F(1,226) = 32.50$, $p = .001$; Table 4.3B). Post-hoc tests showed that, in the Pre-Delay session, the Wake group reported feeling sleepier than the Sleep group ($W = 1198.50$, $p = .010$), whereas the opposite was true in the Post-Delay session ($W = 2341.00$, $p < .001$). There was also a significant main effect of Group ($F(1,226) = 8.90$, $p = .004$; Table 4.3B), whereby the Sleep group generally reported feeling sleepier than the Wake group. Overall, SSS scores were not affected by Session ($F(1,226) = 1.13$, $p = .291$).

We conducted exploratory analyses to investigate whether individual differences in subjective sleepiness could have influenced our key measures of consolidation and learning. Specifically, in both the Sleep and Wake groups we investigated whether the decay indices (Visuospatial Decay Index, Paired-Associates Decay Index) were associated with the change in SSS scores from the Pre-Delay to Post-Delay sessions, and whether the Learning Index was associated with SSS scores in the Post-Delay session. We used Spearman's rank correlation coefficient due to violation of the normality assumption. None of the results were statistically significant (all Bonferroni corrected $p > .05$), suggesting that subjective sleepiness did not influence task performance.

Table 4.3. Vigilance and Sleepiness in Experiment 1.

A	**Psychomotor Vigilance Task (PVT) Performance**			
	Sleep Group		Wake Group	
	Pre-Delay Session	Post-Delay Session	Pre-Delay Session	Post-Delay Session
	11.20 (± 2.43) 5.12_{tr}	11.49 (± 1.67) 8.69_{tr}	7.37 (± 1.17) 4.98_{tr}	11.41 (± 2.08) 7.28_{tr}
B	**Stanford Sleepiness Scale (SSS) Scores**			
	Sleep Group		Wake Group	
	Pre-Delay Session	Post-Delay Session	Pre-Delay Session	Post-Delay Session

2.97 (±0.09) 2.94_{tr}	3.61 (± 0.18) 3.51_{tr}	3.47 (± 0.14) 3.28_{tr}	2.72 (± 0.17) 2.44_{tr}

(A) The percentage of attention lapse trials in the psychomotor vigilance task (PVT). Attention lapses are trials where participants failed to respond within 500 ms. (B) Stanford Sleepiness Scale (SSS) scores, which quantify subjective sleepiness. Higher scores reflect greater sleepiness. Data are shown as means (± SEM) and 20% trimmed ($_{tr}$) means (used by robust ANOVA).

4.4.5 Interim summary of Experiment 1

To summarise, from Experiment 1, we found that memory retention for word pairs and image-locations was better after sleep than after daytime wakefulness. Unexpectedly, we found no evidence to suggest that sleep supports subsequent learning when compared to wake. Similar to previous work by Guttesen et al. (2022), we found no evidence of a relationship between memory retention of visuospatial memories and subsequent learning of word pairs. Contrary to our hypothesis, we found no relationship between sleep-associated memory consolidation and next-day learning. Instead, we found a surprising link between forgetting during daytime wakefulness and subsequent learning.

In this experiment, we measured memory consolidation using two separate tasks: a visuospatial task and a paired-associates task. While we did not find a relationship between sleep-associated consolidation and subsequent learning, it is plausible that using two tasks to assess memory consolidation could have created interference (Brophy et al., 2009), thereby obscuring the link between consolidation and subsequent learning.

Experiment 2

Experiment 2 (preregistration: https://osf.io/xf5zw) was identical to Experiment 1, except it did not feature the visuospatial tasks or the PVTs. Accordingly, the results of Experiment 2 are less likely to be affected by interference, offering a potentially cleaner insight into the relationship between overnight consolidation and next-day learning.

4.5 Method

4.5.1 Participants

One hundred and eighty-four participants were recruited online via Prolific (https://prolific.co/) and randomly assigned to a Sleep or Wake group. Fifty-eight participants were excluded from all analyses because either their demographic data was not recorded due to a technical fault (n = 1), they correctly recalled < 20% of the target words in one or both of the immediate recall tests (n = 10), they failed to return for the Post-Delay session (n = 23), they failed > 2 attention checks in the Pre-Delay learning task (n = 19), or they submitted a blank response or nonsense word on > 20% of trials in the Pre-Delay immediate recall test (n = 5, not including those already excluded for failing too many attention checks). This resulted in a final sample of 126 participants (Table 4.4).

Inclusion criteria and participant instructions were identical to Experiment 1. None of the participants from Experiment 1 participated in this experiment. Informed consent was obtained from all participants in line with the requirements of the University of York Department of Psychology Research Ethics Committee.

Table 4.4. Participant demographics in Experiment 2.

	Sleep Group	Wake Group
N (Male/Female)	59 (13/46)	67 (19/48)
Age (Years)	22.68 (± 3.39)	22.96 (± 3.71)
Typical Sleep Duration (Hours)	7.53 (± 0.96)	7.28 (± 1.33)
Morning/Evening Type		
Definitely morning type (N)	3	8
Rather morning type (N)	23	23
Rather evening type (N)	15	20
Definitely evening type (N)	18	16
Mean ± SD	2.81 (± 0.94)	2.66 (± 0.98)
Sleep Duration Before Study (Hours)		
Pre-Delay session	7.48 (± 1.34)	6.63 (± 1.23)
Post-Delay session	6.84 (± 1.21)	N/A

Age, sleep parameters, and morning/evening preference were based on self-report. Morning/evening preference was assessed using a single forced-choice question: "One hears about "morning" and "evening" types of people. Which one of these types do you consider yourself to be?" A mean score of 2.5 would indicate no morning/evening preference across our sample, whereas higher scores reflect an evening preference. Data are shown as means (± SEM) unless specified otherwise.

4.5.2 Materials

We used the same 90 semantically-related word pairs that were used in Experiment 1. The word pairs were divided up into the same three equal lists of 30 for use in three separate recall tests. The lists were counterbalanced across recall tests.

4.5.3 Procedure

We used the same procedure as Experiment 1 (Figure 4.1A), with the exception that the visuospatial tasks and the PVTs were omitted. All experimental tasks were created using Gorilla (https://gorilla.sc/). Each experimental session lasted ~15 min.

4.5.4 Data analysis

The statistical analysis was identical to Experiment 1. Although we did not preregister the use of Bayesian analyses or Zou's confidence intervals, these analyses were performed for consistency with Experiment 1.

4.6 Results

4.6.1 Baseline recall performance

Performance in the Pre-Delay immediate recall test did not differ significantly between the Sleep and Wake groups ($t(124) = 1.20$, $p = .233$; Table 4.5).

Table 4.5. Recall performance in Experiment 2.

Paired-Associates Recall Performance			
Sleep Group		Wake Group	
Immediate Recall	Delayed Recall	Immediate Recall	Delayed Recall
53.84 (± 2.40)	32.32 (± 2.36)	57.96 (± 2.43)	25.02 (± 2.10)

The percentage of correctly recalled target words in the paired-associates task. Data are shown as means (± SEM).

4.6.2 Sleep and memory consolidation

An analysis of the Paired-Associates Retention Index demonstrated that significantly better retention across the delay in the Sleep group as compared to the Wake group ($t(124) = 4.61$, $p < .001$, $d = 0.82$, $BF_{10} = 1747.21$; Figure 4.4A). This result replicates the findings of Experiment 1 and suggests that sleep benefitted memory consolidation.

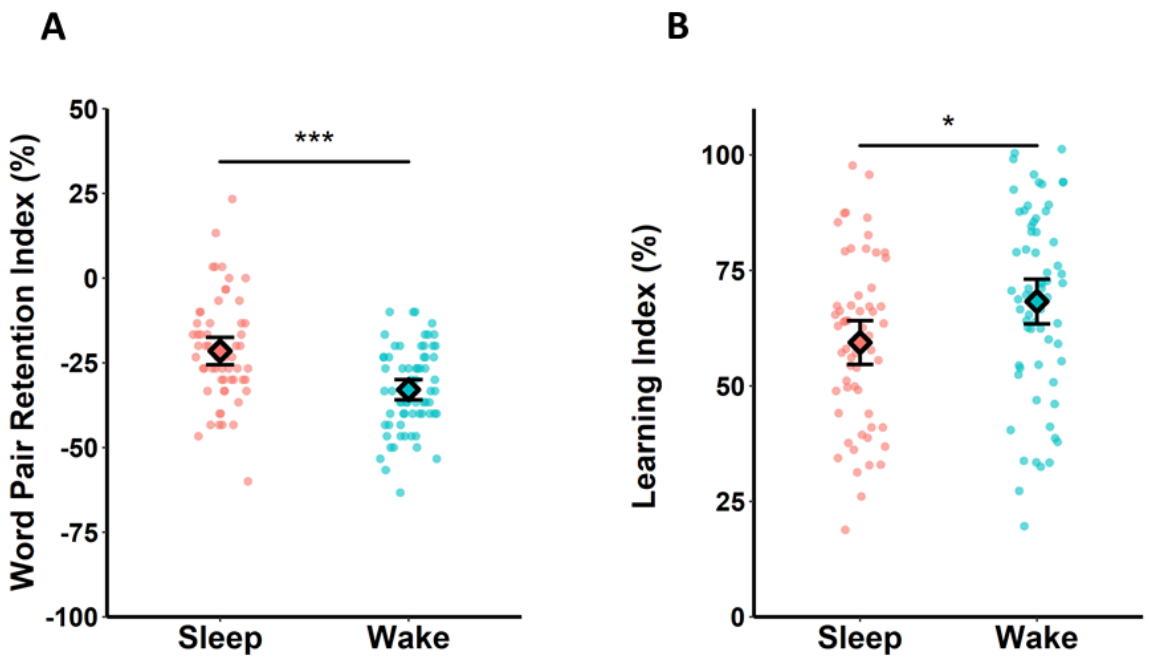

Figure 4.4. Rates of retention (Paired-Associates Retention Index) and new learning (Learning Index) by Group in Experiment 2. Better retention occurred over sleep as compared to wakefulness (A). New learning was better after wakefulness as compared to sleep (B). Data are shown as Mean ± SEM. Data points represent individual participants. (***) $p < .001$; (*) $p < .05$.

4.6.3 Sleep and new learning

We did not observe any benefit of sleep on new learning, as compared to an equal duration of daytime wakefulness. Surprisingly, in fact, the Learning Index was significantly greater in the Wake group relative to the Sleep group ($t(124) = 2.61$, $p = .010$, $d = 0.47$, $BF_{10} = 3.95$; Figure 4.4B), indicating that new learning was better after a day of wakefulness than a night of sleep. To account for the

contribution of working memory, the analysis was repeated whereby the final three encoded word pairs were excluded from the analysis, and the results were unchanged.

4.6.4 Relationship between consolidation and new learning

Of key interest was whether overnight consolidation was associated with next-day learning in the Sleep group. Consistent with Experiment 1, there was no significant relationship between the Paired-Associates Retention Index and Learning Index (r-skipped = -0.06, [-0.30, 0.18] bootstrapped 95% CI; Figure 4.5A) with substantial evidence for the null (BF_{01} = 3.11).

In Experiment 1, we observed an unexpected relationship between retention and subsequent learning in the Wake group, whereby forgetting seemingly facilitated the learning of new information. Intriguingly, in Experiment 2, we observed the same significant negative relationship between the Paired-Associates Retention Index and Learning Index (r-skipped = -0.29, [-0.48, -0.07] bootstrapped 95% CI; BF_{10} = 3.72; Figure 4.5B), offering further support for the idea that forgetting during wakefulness might facilitate effective subsequent encoding. The skipped correlations did not differ significantly between groups (Zou's 95% CI [-0.12, 0.56]).

These analyses were repeated without the final three encoded trials (for the Learning Index), and the results were unchanged.

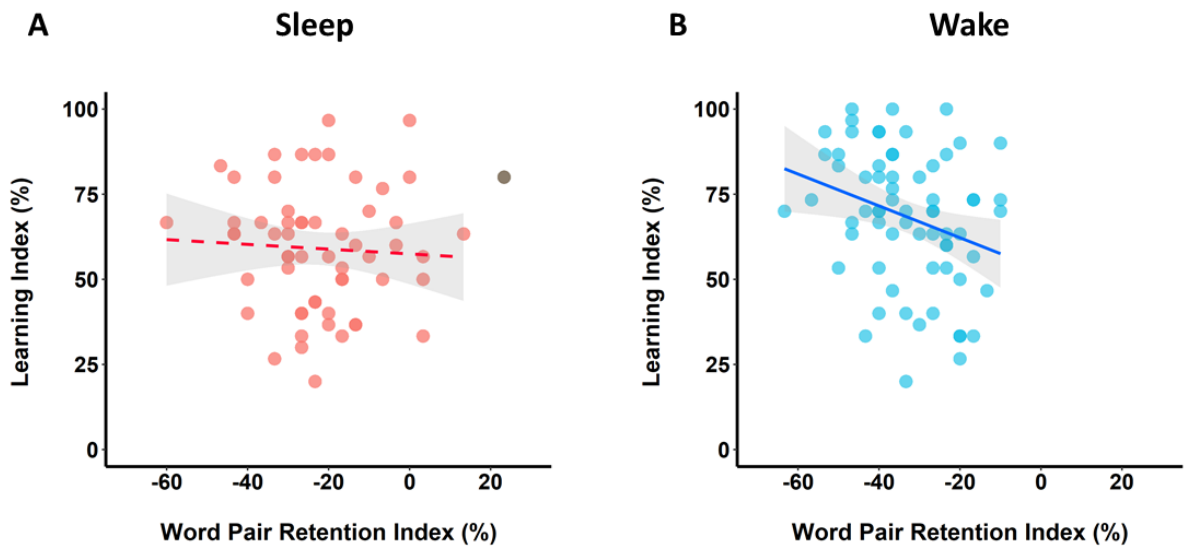

Figure 4.5. Relationship between retention (Paired-Associates Retention Index) and new learning (Learning Index) by group in Experiment 2. There was no evidence of a relationship between retention and new learning in the Sleep group (A). There was a significant negative correlation between retention and new learning in the Wake group, whereby more forgetting across the delay was associated with better subsequent learning (B). Shaded areas represent 95% confidence intervals. Data points represent individual participants. Individuals who were identified as outliers by the skipped correlation analysis and thus did not contribute to the relationship (see Method) are shown as grey data points (n = 1 in A, n = 0 in B).

4.6.5 Alertness

As in Experiment 1, our analysis of Stanford Sleepiness Scale (SSS) scores revealed a significant interaction between the factors Group (Sleep, Wake) and Session (Pre-Delay, Post-delay; $F(1,248) = 28.09$, $p < .001$; Table 4.6). Consistent with Experiment 1, Post-hoc tests showed that the Sleep group reported feeling more tired than the Wake group in the Post-Delay session ($W = 2997.50$, $p < .001$). Unlike Experiment 1, however, subjective sleepiness in the Pre-Delay session did not differ significantly between the Sleep and Wake groups ($W = 1631.50$, $p = .152$). There was also a significant main effect of Group, whereby the Sleep group generally felt sleepier than the Wake group ($F(1,248) = 12.80$, $p < .001$). The main effect of Session was not significant ($F(1,248) = 5.16$, $p = .982$).

We performed exploratory correlational analyses in the same way as in Experiment 1 to investigate the relationship between subjective sleepiness and our key measures of consolidation and new learning. In the Wake group, we observed a significant correlation between the Retention Index and the change in SSS scores from the Pre-Delay session to the Post-Delay session, whereby individuals who became sleepier across the delay surprisingly retained more word pairs ($r = .360$, Bonferroni corrected $p = .011$). No other significant relationships emerged (all Bonferroni corrected $p > .05$).

Table 4.6. Sleepiness in Experiment 2.

Stanford Sleepiness Scale (SSS) Scores			
Sleep Group		*Wake Group*	
Pre-Delay Session	*Post-Delay Session*	*Pre-Delay Session*	*Post-Delay Session*
2.70 (± 0.11) 2.68_{tr}	3.71 (± 0.19) 3.59_{tr}	3.18 (± 0.16) 2.98_{tr}	2.37 (± 0.18) 2.05_{tr}

Stanford Sleepiness Scale (SSS) scores, which quantify subjective sleepiness. Higher scores reflect greater sleepiness. Data are shown as means (± SEM) and 20% trimmed ($_{tr}$) means (used by robust ANOVA).

Integrated analyses of experiments 1 and 2

Because our individual experiments were powered to detect a benefit of sleep on memory retention, we may not have had sufficient statistical power to detect an association between consolidation and subsequent learning. To investigate the relationship between consolidation and new learning with greater statistical power, we combined the data from our two similar experiments. Here, we report these exploratory analyses, which were identical to those performed in the individual experiments.

4.7 Results

In our integrated analysis we again observed no significant correlation between the Paired-Associates Retention Index and Learning Index in the Sleep group (r-skipped = -0.03, [-0.19, 0.13] bootstrapped 95% CI; Figure 4.6A). There was substantial evidence in favour of the null hypothesis (BF_{01} = 4.46).

In the Wake group, there was a significant negative correlation between the Paired-Associates Retention Index and Learning Index (r-skipped = -0.26, [-0.41, -0.11] bootstrapped 95% CI; Figure 4.6B), with strong evidence for the alternative hypothesis (BF_{10} = 14.00). The skipped correlations did not differ significantly between groups (Zou's 95% CI [-0.02, 0.47]).

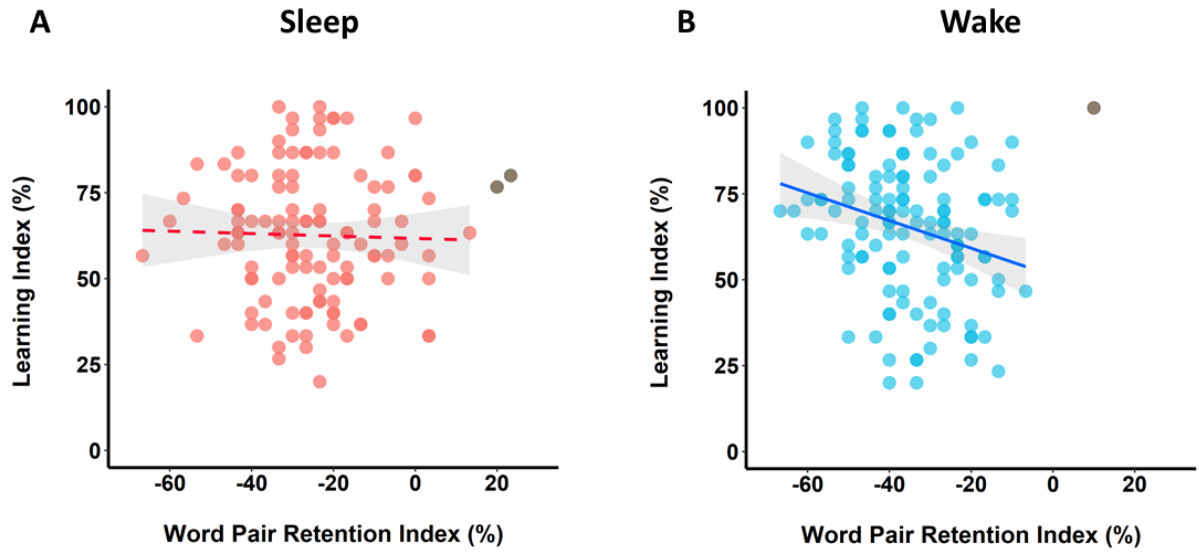

Figure 4.6. Relationship between retention (Paired-Associates Retention Index) and new learning (Learning Index) by group across both experiments. There was no significant correlation between retention and new learning in the Sleep group (A). However, in the Wake group, there was a significant negative correlation, whereby more forgetting across the delay was associated with better subsequent learning (B). Shaded areas represent 95% confidence intervals. Data points represent individual participants. Individuals who were identified as outliers by the skipped correlation analysis and thus did not contribute to the relationship (see Method) are shown as grey data points (n = 2 in A, n = 1 in B).

4.8 General Discussion

In this study, we investigated the relationship between overnight memory consolidation and next-day learning. Across two online experiments, we found that overnight sleep benefited the consolidation of visuospatial and word pair memories, as compared to daytime wakefulness. However, we found no evidence that overnight sleep (as compared to daytime wakefulness) facilitated subsequent word pair learning. Moreover, we observed no relationship between our measures of consolidation and subsequent learning in participants who slept. Surprisingly, we found that forgetting of word pairs during wakefulness predicted superior subsequent learning of new word pairs. Together, these findings oppose our hypothesis that overnight memory consolidation paves the way for efficient subsequent learning, and instead highlight the benefits of forgetting on new learning.

Memory retention was better after sleep than after daytime wakefulness. This finding is in keeping with previous lab-based studies showing improved memory retention across sleep relative to wakefulness (Cairney, Guttesen, et al., 2018; Cairney, Lindsay, et al., 2018; Gais et al., 2006; Guttesen et al., 2022; Jenkins & Dallenbach, 1924; Payne et al., 2012), and complements a recent series of online experiments confirming the benefits of sleep for declarative memory outside of the lab (Ashton & Cairney, 2021; Kroneisen & Kuepper-Tetzel, 2021). Retention benefits were observed for visuospatial memories (Experiment 1) as well as paired-associates memories (Experiments 1 and 2), suggesting that sleep benefits various forms of declarative memory (Schönauer, Pawlizki, et al., 2014). Interestingly, the effect size underlying the benefit of sleep (vs wakefulness) on the retention of paired-associates memories was markedly higher in Experiment 2 as compared to Experiment 1 (Experiment 2: $d = 0.82$; Experiment 1: $d = 0.58$). This observation likely reflects the absence of the visuospatial task in Experiment 2, which could have improved the retention of paired-associates by reducing proactive interference (Brophy et al., 2009) and/or alleviating the overall burden on memory load (Feld & Born, 2017; Feld et al., 2016; Kolibius et al., 2021).

Contrary to our predictions, we did not find that learning benefitted from prior sleep. This is a surprising result, considering that many other studies have observed a benefit of sleep on subsequent learning (Alberca-Reina et al., 2014; Antonenko et al., 2013; Cousins et al., 2018; Guttesen et al., 2022; Kaida et al., 2015; Mander et al., 2011; Ong et al., 2020; Tempesta et al., 2016; Van Der Werf et al., 2009; Yoo et al., 2007). This inconsistency between present and previous findings could be due to differences in study designs. We used a 12-12 design, whereby each session was separated by a 12 h interval consisting of either overnight sleep or daytime wakefulness. In contrast to this more naturalistic design, previous studies have imposed sleep/wake manipulations prior to learning that do not necessarily conform to the typical sleep/wake pattern. These manipulations were total or partial sleep deprivation, which impaired subsequent learning (Alberca-Reina et al., 2014; Cousins et al., 2018; Guttesen et al., 2022; Kaida et al., 2015; Tempesta et al., 2016; Van Der Werf et al., 2009; Yoo et al., 2007); daytime napping, which restored subsequent learning (Mander et al., 2011; Ong et al., 2020); and boosting slow oscillations via auditory and electrical stimulation, which enhanced subsequent learning (Antonenko et al., 2013; Ong et al., 2018). Thus, while sleep deprivation may disrupt learning, and napping or boosting sleeping brain rhythms may enhance learning, the benefit of sleep for subsequent learning may not be apparent after a typical night of sleep as compared to a single day of wakefulness.

Another explanation for why sleep did not seem to benefit subsequent learning relates to circadian factors pertaining to morning and evening testing. Specifically, the sleep groups completed the new learning task in the morning, whereas the wake groups completed the new learning task in the evening. Previous studies have shown that young adults tend to prefer learning in the afternoon or evening (May et al., 1993; Maylor & Badham, 2018). Moreover, our participants generally considered themselves to be more “evening types” than “morning types” (see Tables 4.1 and 4.4), and self-reported sleepiness scores indicated that participants felt more tired in the morning relative to the evening. These extraneous factors could have masked any learning benefits afforded by sleep. It should be noted, however, that we observed no correlation between Stanford Sleepiness Scale scores

in the Post-Delay session and the Learning Index in either study, so we find it unlikely that sleepiness had any major impact on our results.

One indirect assumption of the Active Systems model is that consolidation facilitates a shift in the memory retrieval network from hippocampus to neocortex, and thereby may restore hippocampal learning capacity (Walker, 2009). If sleep supports this process, greater overnight consolidation should predict superior next-day learning. However, we observed no relationship between overnight consolidation and next-day learning. Contrary to the present finding, a recent study indicated that promoting the consolidation of word pairs may *facilitate* the subsequent learning of new word pairs (Alizadeh Asfestani et al., 2018). Specifically, the authors found that administration of D-cycloserine – a drug that enhances sleep-related memory consolidation (Feld et al., 2013) – improved the subsequent learning of new word pairs following a 20 h delay, regardless of whether the participants slept or remained awake during the delay. Importantly, however, the authors did not examine how D-cycloserine impacted memory consolidation of specific materials and thus could not look at whether there was a relationship between the consolidation of word pairs and subsequent learning of new word-pairs.

One potential reason for the present null result is that a single night of sleep is insufficient to reduce retrieval dependency on the hippocampus, but rather that sleep initially increases hippocampal involvement, which then decreases over a longer period. Consistent with this view, previous work has shown that sleep increases hippocampal engagement during memory retrieval after a short delay (two days), which the authors interpret as evidence for an early consolidation process (Gais et al., 2007). Thus, if sleep initially increases hippocampal involvement during retrieval, this would not 'pave the way' for new hippocampus-dependent learning. However, other studies have found that a single night of sleep is sufficient to reduce hippocampal engagement during memory retrieval (Takashima et al., 2009; Takashima et al., 2006), indicating that it should have been possible to observe some evidence of a relationship between overnight consolidation and next-day learning with the present paradigm.

Additionally, it could be that without a benefit of sleep for learning, it may have been less likely to observe a relationship between individuals' indices of sleep-associated consolidation and next-day learning. Further work is required to better understand the time-course of sleep-associated systems consolidation.

Intriguingly, we observed a relationship between forgetting during wakefulness and subsequent learning, whereby greater forgetting was associated with superior subsequent learning. Earlier work has shown that the instruction to forget a prior-learned list of words can enhance the subsequent encoding of a new word list (Pastötter et al., 2012). To our knowledge, however, the present work is the first to show that undirected, unintentional forgetting is linked to new learning.

One interpretation of these results is based on the contextual binding account of episodic memory (Yonelinas et al., 2019). According to this view, forgetting during wakefulness is largely due to contextual interference, while sleep benefits memory retention by reducing contextual interference. Based on these assumptions, sleep would reduce forgetting between immediate and delayed recall as compared to wake due to reduced contextual interference. Furthermore, if sleep helps maintain the context in which the first items were learned, one might expect proactive interference of these items on subsequent encoding of new and similar items, in particular, when retrieval occurs shortly before new learning. Conversely, if wakefulness increases contextual interference between immediate and delayed recall, there would be less proactive interference of those items on subsequent encoding of similar items. We observed these patterns in the present experiments, whereby sleep reduced forgetting compared to wake, with some benefits of waking before learning compared to sleeping (Experiment 2), and, importantly, a relationship between forgetting during wakefulness and subsequent learning of similar materials (word-pairs). Thus, wakefulness (vs. sleep) may benefit subsequent learning through increased contextual interference, when retrieval of the (somewhat) overlapping information occurs shortly before learning.

An alternative explanation could be that the relationship between forgetting and new learning was driven by the fact that poor learners were less susceptible to forgetting than good learners simply because they had less information to forget. However, there was no evidence of floor effects in the delayed recall tests (see Tables 4.2 and 4.5), suggesting that our results were not distorted by poor learners having an inability to forget as many word pairs as good learners without scoring less than zero. Furthermore, if this were the case, one would expect a relationship between forgetting and learning in the sleep condition, which was not observed in the present experiments. It is clear that additional research is required to determine the cognitive mechanisms underlying the observed link between forgetting and subsequent learning. Such work could train participants to criterion in the pre-delay session to minimise the impact of individual differences in learning ability.

Interestingly, we found that post-delay learning was better in the wake group than the sleep group in Experiment 2. This surprising finding offers additional support the notion that forgetting benefits future learning. From the perspective that increased contextual interference explains forgetting during wakefulness, increased contextual interference during wakefulness may benefit new learning whilst reduced contextual interference during sleep may not. However, we did not find this result in Experiment 1. We speculate that the inclusion of the visuospatial task in Experiment 1 could have increased proactive interference between the visuospatial and paired associates tasks (Brophy et al., 2009) and/or increasing the overall burden on memory load (Feld & Born, 2017; Feld et al., 2016; Kolibius et al., 2021) compared to Experiment 2. This may, in turn, have reduced any differences in learning between conditions. Further work manipulating the number of tasks is needed to address this question.

It is important to note that the present study relied on correlational evidence to observe the relationship between retention and subsequent learning. As such, no causal inference about the role of consolidation or forgetting for subsequent learning could be made and would need to be addressed with future paradigms. Furthermore, a possible limitation of the present study is that we had no

objective measures of sleep or wakefulness. Thus, we had to rely on self-report data to gauge how well participants in the sleep group slept, and whether participants in the wake group stayed awake. In addition to rendering less control, conducting this study online meant that were unable to look at the neural mechanisms of consolidation and learning in sleep. The interplay between oscillations during slow-wave sleep is found to reflect key mechanisms that support the communication between hippocampus and neocortex during sleep-associated consolidation (Ngo et al., 2013; Schreiner et al., 2021; Staresina et al., 2015) as well as forgetting through synaptic renormalization (Genzel et al., 2014; Kim et al., 2019; Tononi & Cirelli, 2006, 2014). To investigate how sleep-associated consolidation may support next-day learning, future studies could address how oscillations of slow-wave sleep may regulate the balance between memory consolidation and forgetting. Furthermore, the data were collected during the COVID-19 lockdown. Studies investigating sleep patterns and well-being during lockdown have found evidence of increased sleep loss and anxiety in some individuals (Carrigan et al., 2020; Falkingham et al., 2022; Owens et al., 2022). If participants in our experiments experienced sleep loss, this may have influenced the effects of sleep on consolidation and learning. While online studies may render less control than studies conducted in the laboratory, they do provide better opportunities for larger sample sizes and potentially wider representation (e.g. not only including undergraduate university students).

To summarise, we found that overnight sleep benefits declarative memory consolidation as compared to daytime wakefulness. Contrary to our expectations, we did not observe that sleeping benefitted subsequent learning compared to staying awake. Furthermore, we observed no relationship between sleep-associated consolidation and next-day learning. By contrast, we found that forgetting during wakefulness was linked to subsequent learning. Together, these findings suggest that consolidation during sleep does not facilitate next-day learning, but that forgetting during wakefulness may instead support subsequent learning.

Chapter 5:

General Discussion

The overarching aim of this thesis was to further our understanding of how sleep supports the consolidation and subsequent learning of hippocampus-dependent memories. The Active Systems account of sleep-associated memory consolidation postulates that during sleep, recently formed hippocampus-dependent memories are reactivated and gradually reorganised within neocortical networks. Thus, sleep supports consolidation by driving a shift in the memory retrieval network from hippocampus to neocortex. This shift may thereby restore new hippocampus-dependent learning. With a basis in these theoretical assumptions, the research in this thesis firstly aimed to investigate how sleep supports consolidation through memory reactivation processes, by exploring the neural underpinnings of sleep-associated consolidation elicited by verbal and non-verbal memory cues (Chapter 2). Secondly, based on the idea that memory reorganisation may support subsequent learning, a novel question emerges of whether consolidation during sleep is linked to new learning. Three experiments investigated the role of sleep for consolidation and next-day learning, and whether there is a relationship between the two (Chapters 3 and 4). Finally, to better understand the consequences of sleep loss on memory formation, the neural signatures of learning were investigated (Chapter 3). Together, these chapters have provided insights into the ways in which sleep supports declarative memory consolidation through reactivation and how sleep may – and may not – support subsequent learning. This discussion will begin by summarising the key findings from each chapter, before considering their broader implications for how sleep supports consolidation and next-day learning.

5.1 Summary of findings

5.1.1 Chapter 2

To better understand the neurocognitive mechanisms underpinning memory reactivation and consolidation during sleep, Chapter 2 explored the neural oscillations evoked by verbal and non-verbal memory cues using a paradigm known as targeted memory reactivation (TMR). During sleep, fifty-one participants were presented with auditory cues previously linked to words (memory cues) as well as

unheard cues (control cues). Half of the cues consisted of verbal stimuli whilst the other half consisted of non-verbal stimuli. For a subset of the participants, the speaker of the verbal cues was mismatched between learning and TMR during sleep. Compared to control cues, memory cues elicited increases in theta and spindle power – two neural markers which have consistently been linked to memory reinstatement and memory stabilization (Cairney, Guttesen, et al., 2018; Göldi et al., 2019; Groch et al., 2017; Laventure et al., 2018; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015). A subsequent decrease in beta power was also observed, possibly reflecting a refractory period following reactivation, whereby sleep protects further reinstatements. Interestingly, verbal memory cues evoked a stronger increase in spindle power relative to non-verbal memory cues and control cues, suggesting that verbal memory cueing may be more effective at reactivating memories in sleep. Furthermore, when the speaker of the verbal cues was mismatched between learning during wake and TMR during sleep, there were no apparent oscillatory differences evoked by these cues.

These findings were discussed alongside the published behavioural findings (Cairney et al., 2017) showing lower forgetting rates for cued items (compared to non-cued items). Considering the present cue-induced oscillatory response in combination with their behavioural results, these findings suggest that cueing during sleep facilitates reinstatement and stabilization of memories. Furthermore, Cairney et al. (2017) found no retention differences between memories cued by verbal and non-verbal memory stimuli. From the presently observed oscillatory response, however, it appears that verbal cues may more effectively reinstate memories than non-verbal cues. Given this discrepancy between the behavioural and EEG results, more studies are needed to address whether verbal memory cues improve memory retention beyond that of non-verbal cues by using behavioural tests that are sufficiently sensitive to small changes in retention rates. Interestingly, Cairney et al. (2017) found that when the speaker of the verbal cues was mismatched between learning and TMR, both cued and non-cued items showed lower forgetting rates compared with non-verbal cues, suggesting that memory cues that do not acoustically match stimuli during learning may reactivate multiple memories from the learning experience, whilst those that match, only reactivate the unique memories. However, a

direct contrast between the two types of cues did not reveal any oscillatory differences, suggesting that further work more sensitive to gradual power changes is needed. Together, these findings provide insights into the neural pathways in which memories are reactivated and consolidated during sleep.

5.1.2 Chapter 3

Chapter 3 investigated whether sleep-associated consolidation is linked to next-day learning. Furthermore, considering that slow-wave activity (SWA) has been associated with both consolidation and subsequent learning, the contribution of SWA to the relationship between consolidation and next-day learning was examined. In a within-subjects design (N = 30), participants completed a memory task (visuospatial) in the evening and then either slept (with EEG monitoring) or stayed awake overnight. The following morning, they were tested again and subsequently completed a learning phase of new materials (word-image paired-associates) with EEG monitoring. Two days later, after recovery sleep, they returned to complete a memory test of the new paired-associates items. By measuring retention of visuospatial memories across the night and memory performance on paired associates the following morning, these provided indices of consolidation and subsequent learning, respectively. The results showed that sleep (vs. sleep deprivation) was linked to benefits in consolidation and subsequent learning, however, there was no significant relationship between the two measures, nor did slow-wave activity (SWA, 0.5-4 Hz) in the sleep condition contribute to this relationship. Furthermore, exploratory analyses revealed no apparent associations between memory retention and sleep parameters (SWA, spindles and SWS) which have previously been linked to consolidation (Backhaus et al., 2006; Cox et al., 2012; Scullin, 2013; Tamminen et al., 2010). Thus, the hypothesis of a relationship between sleep-associated consolidation and next-day learning was not supported.

This study furthermore addressed a second research question of whether sleep loss disrupts the neural underpinnings of learning. From the EEG measured during paired-associates learning, oscillatory signatures of learning were differentially affected after sleep compared to after sleep

deprivation. Although no effects were observed in the pre-registered theta (4-8 Hz) and gamma bands (40-60 Hz), sleep loss seemingly disrupted beta (12-20 Hz) desynchrony – a neural marker of successful learning. More specifically, while subsequently remembered associations (vs. forgotten) were associated with a decrease in beta power after sleep, no significant differences emerged after sleep deprivation, suggesting that sleep loss disrupts a neural signature of successful learning. Taken together, these findings point to an important function of sleep for learning, however, this function may not be linked to overnight consolidation.

5.1.3 Chapter 4

The two experiments in Chapter 4 had a similar rationale to Chapter 3, in that they investigated the relationship between sleep-associated consolidation and next-day learning. In contrast to the within-subjects laboratory-based sleep deprivation paradigm in Chapter 3, Chapter 4 was based online and compared two separate groups with delays of either overnight sleep or daytime wakefulness. Whereas the retention index in Chapter 3 was based on a visuospatial task and the learning index on a paired-associates task, the retention and learning indices in Chapter 4 were both based on the same paired-associates task, but with different word pair stimuli. The rationale for using similar tasks in Chapter 4 was to explore whether a relationship between consolidation and subsequent learning became clearer under conditions where the measures overlap more directly. To follow up on Chapter 3, the visuospatial task was also included as an additional measure of consolidation in Experiment 1, but not included in Experiment 2.

Confirming our hypothesis, memory retention for word pairs was better after sleep than wakefulness across both experiments, showing a particularly large effect size in Experiment 2 where participants only completed paired-associates tasks. Similar to Chapter 3, memory retention for visuospatial memories was also better after sleep than wakefulness in Experiment 1. Thus, sleeping (vs. waking) after learning benefitted memory retention of word pairs as well as image-location pairs. In contrast to Chapter 3, however, sleep did not appear to benefit subsequent learning of word pairs in either

experiment. Instead, the learning performance was higher after daytime wakefulness in Experiment 2. Once again, there was no relationship between overnight consolidation and next-day learning, irrespective of the measure of retention, with substantial evidence for the null. Unexpectedly, across both experiments, there was a relationship between word pair forgetting during wake and new word pair learning, whilst no such link was observed for visuospatial forgetting and word pair learning. Taken together with the findings from Chapter 3, Chapter 4 demonstrates that the magnitude of sleep-associated consolidation is not linked to subsequent memory formation. Instead, this Chapter shows that the magnitude of forgetting during wakefulness may support future memory formation, in particular, when the materials are similar.

5.2 An active role of sleep for consolidation

A central tenet of the Active Systems account is that sleep supports the reactivation of newly formed memories. Cardinal oscillations of slow-wave sleep, slow oscillations (SOs), spindles and ripples support the repeated reactivations, thereby stabilizing and redistributing the memory traces. This thesis investigated the ways in which sleep supports consolidation and subsequent learning. In this section, I will firstly consider what the findings from the thesis contribute to our knowledge about the role of sleep in memory consolidation and next-day learning, in the context of the Active Systems account. The section will conclude with a consideration of alternative perspectives on sleep's role in consolidation.

5.2.1 Sleep (vs. wake) benefitted retention

Sleep is thought to strengthen memories. In line with this, three experiments in this thesis showed that sleeping after learning showed higher retention rates as compared to overnight (Chapter 3) or daytime wakefulness (Chapter 4). This is consistent with several studies finding that memory retention after sleep is superior to that after overnight (Ashton et al., 2020; Gais et al., 2006; Maquet et al., 2003; Sterpenich et al., 2007) or daytime wakefulness (Ashton & Cairney, 2021; Ashton et al., 2020; Backhaus et al., 2008; Gais et al., 2006; Kroneisen & Kuepper-Tetzel, 2021; Payne et al., 2012; Talamini

et al., 2008). Chapters 3 and 4 found this sleep benefit for both visuospatial memories and word pair memories, suggesting that sleep supports various forms of declarative memory. This is in line with a previous study suggesting that sleep benefits all types of declarative memories (Schönauer, Pawlizki, et al., 2014).

Researchers have argued that memories that undergo retrieval practice gain little benefit from sleep-associated consolidation (Antony et al., 2017; Antony & Paller, 2018; Bäuml et al., 2014). However, the benefits of sleep on retention observed in this thesis emerged irrespective of the testing approach: In the visuospatial task, participants were trained to criterion and then tested on accuracy (i.e. distance from correct location) of all items at the immediate and delayed test (and follow-up test in Chapter 3). In the paired-associates task in Chapter 4, only one round of training was required and participants were tested on half of the items at immediate test and the rest at delayed test. Testing participants only once on each item in Chapter 4 addressed this potential issue of retrieval practice effects in Chapter 3. Furthermore, if retrieval practice was an issue, the repeated testing in the visuospatial task would have nullified any impact of sleep on retention, whilst this would not have been an issue for the paired-associates task as they were only tested once per word pair. Considering that all approaches showed these sleep-associated benefits, retrieval practice effects are unlikely to explain the findings.

While conducting a study within a laboratory has the benefits of carefully controlling external variables, this type of environment can sometimes seem relatively artificial. In the present thesis, the benefits of sleep for memory retention were apparent within both a laboratory setting and an online setting, where participants completed the tasks in the comfort of their own homes. These findings complement a series of recent studies showing sleep-memory effects outside the lab (Ashton & Cairney, 2021; Kroneisen & Kuepper-Tetzel, 2021). Furthermore, these effects emerged when using a within-subjects design (Chapter 3) as well as between-subjects design (Chapter 4). Considering the different designs (i.e. within- or between-subjects) and settings (i.e. laboratory or online) of the

present experiments and the various approaches of previous experiments (Ashton & Cairney, 2021; Ashton et al., 2020; Backhaus et al., 2008; Gais et al., 2006; Kroneisen & Kuepper-Tetzel, 2021; Payne et al., 2012; Talamini et al., 2008), these replications suggest that the effects of superior memory retention after sleeping compared to staying awake are relatively robust to different experimental designs.

While retention was better in the sleep conditions compared to the wake conditions, these findings did not reflect memory improvements across the delay, but rather less forgetting. Therefore, it is difficult to disentangle the active contribution of sleep from that of interference during wakefulness in Chapter 3. Indeed, Jenkins and Dallenbach (1924) suggested that lower forgetting rates during sleep were attributable to the passive protection from interference. By manipulating the timing between learning and sleep whilst keeping the hours of sleep and wake consistent across conditions, researchers have found that sleeping immediately after learning improves memory retention compared to sleeping ~12 hours after learning (Backhaus et al., 2008; Gais et al., 2006; Payne et al., 2012; Talamini et al., 2008). Thus, the present findings suggest that sleep seemingly provides the optimal circumstances for memory stabilization. Whether that process is merely passive (Yonelinas et al., 2019) or whether it actively facilitates consolidation (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009), is unclear without measures of how sleep parameters actively contribute to consolidation and these will therefore be considered in the following section.

5.2.2 The relationship between sleep parameters and memory retention

When sleeping after learning, slow oscillations are thought to drive memory reactivations along with spindle-ripple events, and in this manner transfer the memory trace from short-term to long-term stores (Diekelmann & Born, 2010; Klinzing et al., 2019; Rasch & Born, 2013; Walker, 2009). However, Chapter 3 found no evidence for a relationship between visuospatial retention and SWA power, time spent in SWS nor with spindle power. This conflicts with previous work demonstrating links between declarative memory retention and sleep parameters such as time spent in NREM sleep (N2 or SWS),

SWA and spindle activity (Alger et al., 2012; Backhaus et al., 2006; Cox et al., 2012; Diekelmann et al., 2012; Gais et al., 2002; Schabus et al., 2004; Scullin, 2013; Wagner et al., 2007). However, some of these previous studies consist of small sample sizes and therefore may suffer from low statistical power. Addressing this issue, a high-powered study (N = 929) showed no evidence of a relationship between picture memory retention and sleep parameters including time spent in SWS, SWA power and spindle density, suggesting that previous studies may have overestimated the association between sleep stages and declarative memory performance (Ackermann et al., 2015). Similarly, others have failed to find such correlations on an intra-individual basis, whereby no apparent links were observed for within-participant differences in memory retention and time in SWS or SWA power (Cordi & Rasch, 2021). Thus, the findings from Chapter 3 are in line with these studies. In addition to the problems arising from low statistical power, recent attention has been drawn to the issues with the long list of possible sleep parameter candidates supporting consolidation, for example, the frequency range of interest (SO, SWA, spindle), the type of EEG parameter (absolute relative, amplitude, density etc.) the sleep stage of interest, etc. (Nemeth et al., 2021). These issues might contribute to the inconsistent findings observed in the literature.

With recent advances in non-invasive stimulation techniques, researchers have been able to rely on causal inference by enhancing SOs (Leminen et al., 2017; Marshall et al., 2006; Massimini et al., 2007; Ngo et al., 2013; Ong et al., 2016; Papalambros et al., 2017; Perl et al., 2016; Prehn-Kristensen et al., 2020). In particular, SO-spindle coupling has received more attention as a key contributor to memory consolidation process and has been reported in several studies (Bar et al., 2020; Helfrich et al., 2018; Latchoumane et al., 2017; Maingret et al., 2016; Mikutta et al., 2019; Mölle et al., 2011; Ngo et al., 2013; Ong et al., 2016; Papalambros et al., 2017). However, some studies have not been able to replicate these findings (Bueno-Lopez et al., 2019; Henin, Borges, et al., 2019; Paßmann et al., 2016; Sahlem et al., 2015), suggesting that there might be specific conditions under which the benefits of SO enhancement facilitate retention. While this thesis does not provide any data from such manipulations, SO stimulation techniques offer promising future avenues for the sleep and memory

field by providing some insight into how oscillations during sleep help mediate the reactivation and redistribution of memories.

5.2.3 Oscillations of memory reactivation during sleep

A key assumption of the Active Systems model is that memory reactivations mediated by sleep oscillations represent a mechanism of overnight memory consolidation. In this thesis, EEG data from a targeted memory reactivation (TMR) paradigm provided insights into how sleep actively facilitates memory consolidation. Chapter 2 showed that memory cues (vs. control cues) evoked increases in theta and spindle power. These findings complement a number of previous studies using various types of stimuli and analysis approaches which also show that memory cues elicit an initial increase in theta power accompanied by an increase in spindle power (Cairney, Guttesen, et al., 2018; Göldi et al., 2019; Groch et al., 2017; Laventure et al., 2018; Lehmann et al., 2016; Schechtman et al., 2021; Schreiner, Lehmann, et al., 2015), suggesting that theta and spindle power might robustly reflect memory reactivation during sleep.

According to a working model, theta and spindle oscillations have complementary roles in memory reactivation during sleep (Schreiner & Rasch, 2017). Theta oscillations are thought to support the reinstatement of the memory representation, whilst subsequent spindle activity enables undisturbed reprocessing of the memory, which facilitates memory strengthening and stabilization. Evidence shows that patterns of theta activity occurring during wakeful retrieval reoccur during TMR in sleep, supporting the view that theta reflects memory reinstatement (Schreiner et al., 2018). Furthermore, blocking theta and subsequent spindle power immediately after TMR also blocks the memory benefits of TMR at a later test (Schreiner, Lehmann, et al., 2015). In Chapter 2, the observed increases in theta power followed by increases in spindle power for the memory cues may therefore reflect an initial memory reinstatement event, which is followed by a spindle-mediated stabilization of the memory. Taken together with the previously published behavioural data showing reduced forgetting for the cued (vs. non-cued) items (Cairney et al., 2017), these findings suggest that theta and spindle

oscillations represent successfully triggered memory reactivation which, in turn, strengthens memories.

Chapter 2 was the first study to show an amplified spindle response to verbal memory cues relative to that of non-verbal memory cues (after taking control cues into account). Thus, verbal memory cues appear to be more effective at eliciting spindle-mediated reactivation processes than non-verbal memory cues, possibly due to the enhanced access to meaning with the linguistic stimuli. While forgetting rates in the previous behavioural data (Cairney et al., 2017) were not significantly different between the cued verbal and non-verbal items, further work with increased sensitivity to forgetting rates is needed to establish whether these increases in spindle response leads to amplified behavioural benefits of TMR. These findings suggest that spoken words elicit stronger memory reactivation processes than do environmental sounds. If spoken words are indeed a more efficient reminder during sleep, this information could also be useful for optimising memory reactivation paradigms.

Chapter 3 also showed that when the speaker of the verbal cues was mismatched between learning and TMR, there were no apparent differences in the oscillatory response. While this could point to similar pathways of reactivation evoked by matched and mismatched reminders, this interpretation is at odds with the published behavioural results: When the speaker of the verbal cues was matched between learning and sleep, Cairney et al. (2017) observed low forgetting rates for the cued pairings but not the non-cued pairings. However, when the speaker was mismatched, they observed low forgetting rates for both cued and non-cued verbal pairings. These data might reflect a generalized reactivation of all memories from the learning session when cueing occurs through mismatched stimuli, whereas matched cues might evoke more specific representations. Previous evidence suggests that the level of delta/theta and spindle power increase is modulated by the amount of items associated with the cue (Schechtman et al., 2021). Thus, further work is needed to explore whether there is a gradual increase from reactivation of specific memories (matched) relative to reactivation

of groups of related memories (mismatched). Overall, instead of only considering behavioural or oscillatory findings on their own, a combined evaluation of the data provides a clearer understanding of how memories are reactivated and stabilized in sleep.

It is important to note that the response to control cues showed evidence of habituation effects. Memory cues evoked a larger ERP than did control cues, and this difference was particularly evident for the verbal memory cues and control cues. It is likely that this decrease in evoked response was a result of repeated control cues (i.e. the verbal cue 'surface' or the non-verbal sound of a guitar strum). Previous work has shown that repeatedly presenting similar auditory stimuli can result in reduced neural response (Polich, 1989). In Chapter 2, the comparison between memory cues and control cues was computed to observe the links between memory reactivation and oscillatory power. With reduced neural response to control cues, however, the difference between memory cues and control cues might become larger than had the control cues consisted of various spoken words and environmental sounds, similar to the memory cues. Thus, it is important that future studies address any confounds of repeated stimulation by presenting different control cues, like some previous work has done (Cairney, Guttesen, et al., 2018), and for better control, these cues should match the memory cues in characteristics such as linguistic and auditory features.

Recent evidence suggests that memories are endogenously reactivated and clocked by SO-spindle complexes (Schreiner et al., 2021). Considering the role of spindles for memory stabilization and redistribution, the findings from Chapter 2 are in line with the Active Systems account whereby increases in spindle power mediate the gradual shift of the reactivated memory trace from hippocampal short-term stores to neocortical long-term stores. There is, however, currently no evidence that memory reactivation in sleep facilitates a change in the memory retrieval network. This could be achieved by measuring endogenous reactivation patterns and SO-spindle coupling (similar to the previously mentioned study by Schreiner et al., 2021) and subsequently, using fMRI, measure neural activity during retrieval of memories formed before sleep (remote) and after sleep (recent). If

the hippocampal and neocortical retrieval network shows changes for the remote memories, which have been reactivated during sleep, as compared to the recent ones which have not, this would show evidence of reorganisation. Importantly, this would make it possible to observe the relationship between the degree of memory reorganisation, reactivation patterns in sleep and associated SO-spindle events. In this manner, it would be possible to more directly test the central tenets of the Active Systems account, namely, reactivation and reorganisation of memory traces.

5.2.4 Memory reorganisation – not a mechanism for future learning?

One potential consequence of an overnight shift in the memory retrieval network from hippocampus to neocortex is that it could 'refresh' learning capacities in hippocampus (Walker, 2009). If it is the case that sleep-associated consolidation paves the way for subsequent learning, one might expect a relationship between the two. There is evidence that the sleep oscillations found to support consolidation overlap with those reported to contribute to subsequent learning, suggesting that the underlying mechanisms might be shared, for example, enhancing SOs during sleep has been linked to memory retention (Ngo et al., 2013) as well as subsequent learning performance (Ong et al., 2018). Chapters 3 and 4 addressed this novel question by implementing measures of overnight consolidation and subsequent learning. In contrast to this hypothesis, there was no evidence of a relationship between memory retention and next-day learning performance. This was the case across three experiments: one laboratory experiment and two online experiments, regardless of which measure of consolidation was implemented, visuospatial or word pair memory retention. Instead, an exploratory analysis of word pair retention and word pair learning across both online experiments showed substantial evidence for the null. These data suggest that overnight consolidation is not linked to subsequent learning.

A remaining question concerns whether one night of consolidation is sufficient to observe such a relationship, considering that the evidence on the timescale of systems consolidation is somewhat conflicting. On one hand, studies have shown reduced hippocampal involvement during retrieval after

a nap (Himmer et al., 2019; Takashima et al., 2006) and after 24 h including a period of sleep (Cairney et al., 2015; Takashima et al., 2009). Furthermore, some of these studies have found a relationship between SWS duration and hippocampal disengagement during retrieval (Cairney et al., 2015; Takashima et al., 2006). On the other hand, studies have found an initial increase in hippocampal involvement during retrieval after 48 h (Gais et al., 2007) and 72 h (Sterpenich et al., 2007) in those participants that slept after encoding compared to those that were sleep deprived. Gais et al. (2007) referred to this initial hippocampal engagement in the well-rested participants as an early consolidation process as this was accompanied by increased hippocampal-neocortical connectivity which became stronger over a few months. Furthermore, it has been suggested that the consolidation process takes weeks or even months to complete (Dudai, 2004; Dudai et al., 2015). Thus, the timescale of when memories become less dependent on hippocampus is unclear. Based on the findings suggesting that sleep promotes an initial hippocampal involvement during retrieval (Gais et al., 2007), it might be the case that the disengagement of hippocampus may not be linear in nature. Considering the data from this thesis, it might be that one night of sleep-associated consolidation is not sufficient to restore new hippocampal encoding capacities, and thus, no relationship would be observable from the present paradigm.

Alternatively, it may be the case that there is a fundamental difference between these previous studies, which is driving the different timings of when hippocampus becomes less involved during retrieval. These previous studies showing an increase in hippocampal involvement during retrieval were based on comparisons between sleep and sleep deprivation (Gais et al., 2007; Sterpenich et al., 2007), whilst the studies observing hippocampal disengagement compared sleep to daytime wakefulness (Takashima et al., 2009; Takashima et al., 2006). Considering the detrimental effects of sleep loss on cognition (Walker, 2008), the system-level consolidation process might be differentially affected compared to that from a typical day awake. For example, sleep deprivation has shown to induce fragmented memory loss beyond that of daytime wakefulness (Ashton et al., 2020). If a typical night of sleep is sufficient to reduce hippocampal involvement, the present data might show a link

between overnight consolidation and subsequent learning. However, Chapters 3 and 4 reported no such relationship. Thus, there might instead be alternative models that better explain the absence of a relationship between consolidation and learning.

5.2.5 Alternative theories of sleep-dependent consolidation

Episodic memories that were initially dependent on the hippocampus might continue to depend on it. The Multiple Trace Theory postulates that the hippocampus is needed for storing and retrieving recent as well as remote episodic memories rich in contextual detail, whereas the neocortex supports retrieval of decontextualized (semantic) memories (Moscovitch et al., 2006; Nadel & Moscovitch, 1997; Nadel et al., 2000). Building upon this account, Yonelinas et al. (2019) proposed a contextual binding account whereby sleep benefits memory by reducing interference. In contrast to the Active Systems view that sleep supports the reactivation and stabilization of memories, this model suggests that replay in wake or sleep merely reflects context-related residual activity which diminishes with changes in spatial and temporal context. Considering the findings from Chapters 3 and 4, the memory retention benefits of sleeping rather than staying awake between the sessions could be equally well explained by the Contextual Binding model as the Active Systems model, where reduced contextual interference during sleep reduces forgetting rates. Considering that no correlations between sleep physiology and consolidation were observed in Chapter 3, this could further speak in favour of sleep minimizing contextual interference. However, the difficulty reconciling the thesis findings with a passive role of sleep arise when considering the memory reactivation findings from Chapter 2, whereby memory cues evoked spindle responses, hinting at an active role of sleep for reactivating memories. More convincingly, previous evidence has found that the extent of spindle response to memory cues is associated with memory retention and that memories could be decoded from the same timing as spindle power increases were observed (Cairney, Guttesen, et al., 2018). Furthermore, others have found that evidence of reactivation along with SO-spindle coupling predicts memory

retention (Schreiner et al., 2021). Taken together, these findings suggest that sleep actively supports consolidation rather than passively protects memories from interference.

An alternative theory for the benefits of sleep for memory is the Synaptic Homeostasis Hypothesis (Tononi & Cirelli, 2012, 2014). This theory proposes that sleep is essential for brain plasticity. During waking, synapses require more energy to form connections. If synaptic strength continues to increase, this will lead to saturated neural signalling, which impairs learning and memory due to the saturation of upregulated synapses. During the subsequent period of sleep, SWA downscales the potentiated synapses to a baseline level, preparing them for new learning (Bushey et al., 2011; de Vivo et al., 2017; Gilestro et al., 2009; Huber et al., 2013; Liu et al., 2010; Spano et al., 2019; Vyazovskiy et al., 2008). In addition, by improving signal-to-noise ratio, synaptic homeostasis indirectly benefits retention and learning by renormalizing the synapses back to baseline level, thereby preventing saturated neural signalling where meaningful signal is separated from unwanted interference. Behaviourally, this would mean that memory performance would be worse after wake than sleep due to the saturated neural signalling, which was the case for findings in Chapters 3 and 4. However, there was no apparent relationship between retention and SWA in Chapter 3. Considering that SWA is found to downscale synapses and thereby benefit retention, the findings do no fully align with the model assumptions.

Newer integrative models may be in a better position to explain the results from this thesis. Slow-waves (0.5-4 Hz) are a central oscillatory signature of both the Active Systems model and the Synaptic Homeostasis model, making it difficult to tease these theories apart. Importantly, however, the models are not mutually exclusive. Indeed, recent work has attempted to reconcile the key tenets of these theories into one unified framework where sleep is involved in synapse potentiation as well as renormalisation (Genzel et al., 2014; Ngo & Born, 2019). According to this model by Genzel et al. (2014), global slow oscillations and concomitant memory reactivations facilitate the systems consolidation of memory traces between hippocampal and neocortical stores, whilst local delta activity supports the downscaling of weak synapses and thereby improves the signal-to-noise ratio,

improving learning capacity. Kim et al. (2019) empirically addressed the question of whether SWA supports two functions that are difficult to disentangle. They therefore separated SOs (> 1 Hz, global, high amplitude) from delta waves (1-4 Hz, local, low amplitude) and found that global SOs and nested spindles facilitate consolidation, while local delta-waves support forgetting. The complementary nature of these oscillations could hint at two separate processes, one involved in reactivating and redistributing memories for stability, and the other downscaling and renormalizing the previously potentiated synapses. In Chapter 3, there was no observable link between SWA (0.5-4 Hz) and indices of consolidation and learning. Considering the limited spatial resolution and the coarse measure of SWA, the present data could not differentiate between global SOs and local delta waves and their differential contribution to consolidation and forgetting. In light of the evidence indicating no relationship between sleep-associated consolidation and next-day learning (Chapters 3 and 4), this raises the question: *if SOs and delta support consolidation and forgetting, respectively, which processes contribute to new learning?* An important next step would be to dissociate these global SOs and concomitant spindles with local delta waves, to address the question of whether consolidation and subsequent learning are supported by separable mechanisms. For example, it may be that consolidation and subsequent learning are not linked because consolidation relies on global SO-spindle events, whilst renewed encoding capacity relies on the forgetting linked to downscaling of previously saturated neural signalling. One possible approach to dissociate global from local oscillations would be to use techniques with good spatial resolution such as magnetoencephalography (MEG), in order to better capture local delta-related processes.

5.3 The role of sleep for subsequent learning

5.3.1 Does new learning depend on sleep?

In this thesis, sleeping prior to learning did not always benefit learning performance. While Chapter 3 observed a benefit of sleeping the night prior to learning compared to staying awake, Chapter 4 observed no such benefits across two experiments when comparing groups that had slept the night

before learning to those that had stayed awake during the day. Looking to previous literature may help explain such discrepancies. Similar to Chapter 3, previous studies have observed a benefit of overnight sleep (vs. sleep deprivation) on next-day declarative learning (Alberca-Reina et al., 2014; Kaida et al., 2015; Poh & Chee, 2017; Tempesta et al., 2016; Yoo et al., 2007). Similar findings have been observed with partial sleep deprivation (Cousins et al., 2018) and perturbed sleep (by disrupting SWA (Van Der Werf et al., 2009). Conversely, daytime napping (vs daytime wakefulness) has shown to improve subsequent hippocampus-dependent learning (Mander et al., 2011; Ong et al., 2020) with similar observations using techniques to enhance SOs with auditory (Ong et al., 2018) and electrical stimulation (Antonenko et al., 2013). A commonality among these previous study designs is that they implemented sleep manipulations not necessarily reflecting a typical sleep/wake pattern (i.e. sleep deprivation, daytime napping and SO stimulation/disruption). In contrast to these previous studies, Chapter 4 made use of participants' natural sleep/wake cycles whereby the sessions were separated by a 12 h interval consisting of either overnight sleep or daytime wakefulness, thus, participants went about their daily sleep/wake routine as usual. With this manipulation, sleep did not appear to benefit subsequent learning. Taken together, it appears that sleep deprivation may disrupt learning and furthermore napping or boosting sleep rhythms may enhance learning. However, the benefit of sleep for learning may not be apparent after a typical night of sleep as compared to a single day of wakefulness and, therefore, sleep may not benefit new learning under all conditions.

As with all experiments taking place in the morning and evening, it is important to consider that circadian rhythms may have contributed to the absence of a sleep effect for subsequent learning in Chapter 4. The participants in the sleep condition completed the learning task in the morning, whilst the participants in the wake condition completed this task in the evening. Previous studies have shown that young adults tend to prefer learning in the afternoon or evening (May et al., 1993; Maylor & Badham, 2018). In line with this, the participants tended to rate themselves as more "evening types" than "morning types". Furthermore, self-reported sleepiness scores indicated that participants felt more tired in the morning relative to the evening. That said, there was no apparent correlation

between their self-reported sleepiness and memory performance on the learning task. Furthermore, there was no apparent difference in baseline memory performance between the conditions (which took place in the morning and evening), and previous work using this type of morning-evening design have similarly found no differences at baseline (Ashton & Cairney, 2021). Nevertheless, further research is needed to disentangle circadian effects from the effects of sleeping overnight compared to staying awake during the day prior to learning.

5.3.2 Wakeful forgetting and new learning

Another novel and surprising question that originated from this thesis was whether forgetting during wakefulness predicts future learning. Chapter 4 observed a correlation between daytime forgetting of word pairs and subsequent learning of new word pairs, whereas this was not observed for the sleep group and no such links were observed between visuospatial retention and word pair learning after sleep or wakefulness. A recent model suggests that sleep reduces contextual interference as compared to wakefulness, which in turn, benefits memories learnt before sleep (Yonelinas et al., 2019). If contextual interference is increased during wakefulness, one would expect increased forgetting across the delay of wake compared to sleep. Furthermore, if the materials learned before the delay overlapped with the to-be-learned materials, they might lead to proactive interference of subsequent learning, in particular, with reduced contextual interference during sleep. Conversely, increased contextual interference during wakefulness might benefit new learning of similar materials. This interpretation is supported by the present data, showing reduced forgetting after sleep (compared to after wake), as well as a link between word pair forgetting during wakefulness and subsequent word pair learning. Considering that participants retrieved previously learned word pairs just before learning new ones, this effect may also have been more apparent than if retrieval and new learning were separated further in time (or allowing for some contextual interference) – a possible future manipulation to test this interpretation. This perspective that increased contextual interference during wake may benefit future learning of similar materials is also consistent with the higher learning

indices observed after wake compared to after sleep in Experiment 2 of Chapter 4. However, considering that this was not observed in Experiment 1, further data is needed to confirm such effects.

It is important to note that these were correlational findings, thus no claims can be made about the directionality of forgetting and learning. With these correlational findings, it is also possible that the relationship between forgetting during wakefulness and learning was driven by the fact that poor learners forgot less simply because they had less information to forget. For example, a participant who got 70% of the word pairs correct on the immediate test would have more word pairs to forget after the delay than someone scoring 25% on the immediate test. However, there was no evidence of floor effects in the tests after the delay, indicating that the relationship was not merely reflecting that poor learners could not forget as much as good learners as they could not score below zero. Evidently, these are initial findings that will need to be confirmed under different conditions where it is possible to minimise the impact of individual differences in learning ability, for instance, by training participants to criterion prior to the immediate test.

5.3.3 Sleep loss and oscillatory signatures of learning

While many studies have observed the negative impact of sleep deprivation on hippocampus-dependent learning (Alberca-Reina et al., 2014; Kaida et al., 2015; Poh & Chee, 2017; Tempesta et al., 2016; Yoo et al., 2007), Chapter 3 found that sleep loss disrupted beta desynchrony during learning – a neurocognitive marker of successful memory formation. More specifically, there was a decrease in beta power during learning of subsequently remembered (vs. forgotten) word-image pairs after sleep, whereas this decrease in beta power was not observed after sleep deprivation. Previously, alpha (8-12 Hz) and beta (12-20 Hz) decreases have robustly been associated with subsequently remembered items (Fellner et al., 2019; Griffiths et al., 2016; Griffiths, Martín-Buro, Staresina, Hanslmayr, et al., 2021; Hanslmayr et al., 2014; Klimesch et al., 1996). In particular, beta desynchrony is thought to reflect semantic processing (Fellner et al., 2013; Hanslmayr et al., 2009; Hanslmayr et al., 2011) and, more broadly, information processing (Griffiths, Martín-Buro, Staresina, & Hanslmayr, 2021).

Considering that the left hemisphere has been linked to semantic processing (Gabrieli et al., 1998; Jackson, 2021) and the oscillatory response observed in Chapter 3 was largest in channels on the left hemisphere, these results may indicate that sleep loss disrupts semantic processing of word and image pairs. This interpretation is in line with previous behavioural findings where sleep deprived individuals have had difficulty in encoding semantically incongruent stimulus pairs (Alberca-Reina et al., 2014). It may be the case that the sleep deprived brain relies on alternative processing routes when committing new information to memory. Indeed, prior studies have shown that sleep deprivation leads to compensatory neural responses during learning (Chee & Choo, 2004; Drummond et al., 2004) and recognition (Sterpenich et al., 2007). Furthermore, there was a slight upregulation of beta activity during learning of later remembered (vs. later forgotten) pairs (although this difference did not survive a Bonferroni correction for multiple comparisons). This compensatory response during learning may reflect a more surface-based rehearsal strategy, which has previously been linked to increases in beta power (Deiber et al., 2007; Hwang et al., 2005; Onton et al., 2005; Tallon-Baudry et al., 2001), rather than the deep semantic processing pathways which are compromised by an absence of sleep. Given the exploratory nature of these findings, this would, of course, need to be tested with confirmatory research.

In Chapter 3, participants were significantly less vigilant and reported feeling sleepier on the morning after sleep deprivation than after sleep. Although no links were observed between these measures and beta desynchrony, future studies would firstly need to address whether the differences in beta desynchrony between conditions are driven by the detrimental impact of extended wakefulness (Walker, 2008) or whether sleep might benefit these processes. With daytime napping paradigms it is possible to investigate the role of sleep compared to daytime wakefulness whilst controlling for time-of-day effects.

Furthermore, future work could get a finer grained account of how the neurocognitive mechanisms of learning are affected by sleep. Extending work by Griffiths and colleagues (2021), it would be

possible to experimentally disentangle information processing from item-binding during learning after sleep in order to unveil how sleep interacts with neurocognitive processes of memory formation. For example, using MEG, a better spatial resolution would provide insight into how sleep affects hippocampal theta/gamma synchrony during item binding along with neocortical alpha/beta desynchrony during sequence perception. Considering previous findings suggesting that hippocampal learning is restored after a nap (Mander et al., 2011; Ong et al., 2020), researchers might predict that after a daytime nap compared to wake, there would be a reduction in neocortical alpha/beta power during sequence perception whilst there would be an increase in hippocampal theta/gamma coupling during item-binding.

5.4 Concluding remarks

This thesis addressed questions of how sleep supports consolidation and subsequent learning of hippocampus-dependent memories. Across all experimental chapters, there was evidence that sleep supports memory consolidation with EEG evidence from a TMR protocol (Chapter 2) and behavioural evidence from comparing memory retention across intervals of sleep and wake (Chapters 3 and 4). More specifically, Chapter 2 showed that memory cues trigger oscillatory signatures of memory reinstatement and stabilization, and furthermore that verbal cues may more effectively trigger memory reactivation than non-verbal cues. Chapters 3 and 4 observed benefits on memory retention when participants slept after learning compared to when they stayed awake. The benefits of sleeping after learning could reflect an active role of sleep, however, without apparent relationships with sleep physiology, further data is needed to address sleep's contribution to these retention benefits. Sleep loss disrupted beta desynchrony – a neural signature of successful learning (Chapter 3), a finding which underlines the detrimental effects of sleep deprivation for learning processes. Behaviourally, sleeping before learning benefitted learning performance as compared to staying awake overnight (Chapter 3). In contrast, sleeping prior to learning showed no behavioural advantages when compared to daytime wakefulness (Chapter 4). Furthermore, there was no apparent relationship between overnight consolidation and next-day learning (Chapters 3 and 4). Instead, there was a link between daytime

forgetting and subsequent learning of similar materials (Chapter 4), which raises questions about which processes during sleep and wake might contribute to subsequent learning. This thesis provides novel insights into how the sleeping brain processes verbal and non-verbal memory cues, how sleep-associated consolidation may not be linked to subsequent learning and has highlighted the detrimental effects of sleep loss on neural signatures of learning.

Appendices

Supplementary Material to Chapter 3

Psychomotor Vigilance Task

A 2 (Condition: Sleep/Sleep Deprivation) x 3 (Session: Immediate/Delayed/Follow-up) repeated measures ANOVA with Greenhouse-Geisser correction showed that participants were significantly slower at responding in the sleep deprivation condition ($F(1,28) = 20.71$, $p < .001$, $\eta_p^2 = 0.43$) and that response times varied significantly across sessions ($F(1.11,30.95) = 30.10$, $p < .001$, $\eta_p^2 = 0.52$, see Table A.1). There was also a Condition * Session interaction ($F(1.15,32.12) = 28.84$, $p < .001$, $\eta_p^2 = 0.51$), which was driven by slower responses in the morning after sleep deprivation as compared to sleep (Delayed Session: $p < .001$, Bonferroni corrected). Please note that one participant was removed from this analysis because their data from the follow-up session of the sleep deprivation condition was missing.

Table A.1. Mean (± SEM) response times (ms) on the Psychomotor Vigilance Task at each session per condition. Note that one datapoint was missing for the follow-up session in the sleep deprivation condition.

Condition	Immediate Session	Delayed Session	Follow-up Session
Sleep	283.93 (± 5.05)	289.15 (± 4.34)	283.69 (± 6.11)
Sleep Deprivation	278.03 (± 4.92)	399.00 (± 17.63)	287.46 (± 5.06)

Stanford Sleepiness Scale

A 2 (Condition: Sleep/Sleep Deprivation) x 3 (Session: Immediate/Delayed/Follow-up) repeated measures ANOVA showed that participants rated themselves as feeling less alert in the sleep deprivation condition ($F(1,29) = 72.95$, $p < .001$, $\eta_p^2 = 0.72$) and that their ratings varied significantly across sessions ($F(2,58) = 85.95$, $p < .001$, $\eta_p^2 = 0.75$, see Table A.2). There was also a Condition *

Session interaction ($F(2,58) = 82.34$, $p < .001$, $\eta_p^2 = 0.74$), which was driven by higher sleepiness ratings in the morning after sleep deprivation as compared to sleep (Delayed Session: $p < .001$, Bonferroni corrected).

Table A.2. Mean (± SEM) ratings on the Stanford Sleepiness Scale at each session per condition.

Condition	Immediate Session	Delayed Session	Follow-up Session
Sleep	2.80 (± 0.15)	2.27 (± 0.16)	2.17 (± 0.11)
Sleep Deprivation	2.63 (± 0.12)	5.37 (± 0.15)	2.20 (± 0.12)

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