Sleep and Memory

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Abstract

Sleep plays a crucial role in memory consolidation and has been shown to benefit various types of memory. These beneficial effects, once believed to originate from sleep's protection from external and internal interference, are now thought to stem primarily from reactivation of previously acquired memories during sleep. Sleep-based alterations in memory storage involve temporally synchronized brain waves: hippocampal sharp-wave ripple complexes, thalamocortical sleep spindles, and cortical slow waves. Mechanisms of memory reactivation differ across the classic stages of sleep, such as slow-wave sleep and rapid-eye-movement sleep. The unique contributions of each sleep stage are not fully understood, although slow-wave sleep appears to be particularly critical for the neocortical-based consolidation of declarative memories, facilitating the recall and recognition of facts and events. During sleep, a dynamic interaction between the hippocampus and neocortex can serve to gradually reinforce and transform cortical memory traces. Sleep can thus support stabilization of new memories, integration of new knowledge with existing knowledge, selective strengthening of aspects of some memories, and extraction of gist or discovery of rules within complex collections of memories. This chapter surveys the leading approaches to studying sleep's role in memory, and also examines the future potential of sleep-based applications and technologies that might prove useful for treating certain neurological and psychiatric disorders, or for general memory enhancement in healthy populations.

1 Introduction

Although humans spend about a third of their lives asleep, comprehensively understanding the functions of sleep is a supreme challenge. Sleep has been linked to neural development (Kurth et al., 2016; Mirmiran et al., 1983), immune function (Besedovsky, Lange, & Born, 2012), endocrine function (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005), clearance of Alzheimer-related proteins from the cerebrospinal fluid (Mander, Winer, & Walker, 2017; Xie et al., 2013), and emotion regulation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Yet, memory consolidation is arguably one of the most extensively studied function of sleep. In this chapter, we introduce relevant characteristics of sleep and review the literature on sleep's role in stabilizing and transforming different types of memory. Whereas sleep benefits both post-sleep memory encoding and the processing of previously acquired information, we focus on the latter in this chapter, emphasizing slow-wave sleep. We rely mostly on human studies but include some notable findings from the animal literature. A more comprehensive review of sleep and memory was published by Rasch and Born (2013).

1.1 Introduction to sleep

By convention, human sleep is divided into the stage of rapid eye movement (REM) sleep and three distinct stages of non-REM sleep: stages N1, N2 and N3. Although all three of these non-REM stages are different from REM sleep, the term non-REM or NREM commonly refers only to N2 and N3. Stage N1 is the shallowest stage of sleep, normally occurring immediately after sleep onset or following brief arousals, and lasting only a few minutes on each occasion. Stage N2 is the most dominant stage of sleep, typically occupying about 50% of total sleep time in adults. Stage N3, also termed slow-wave sleep (SWS), is the deepest stage of sleep and occupies about 20% of total sleep in young adults. REM sleep occupies a similar amount of time. Although all stages of sleep occur throughout the night, REM sleep is more prevalent in the second half of the night, whereas SWS is more prevalent in the first half. A night of sleep typically includes a series of REM/NREM cycles that each last 90-120 minutes (Figure 1).

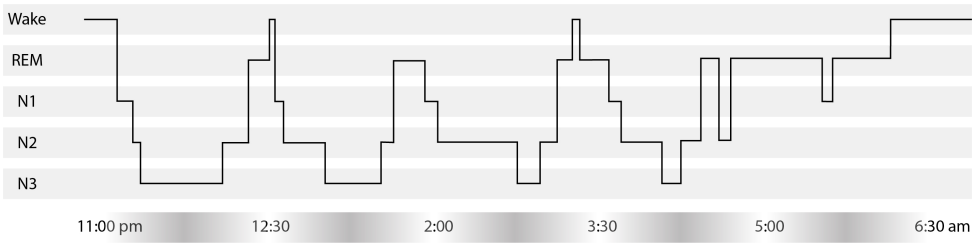

Figure 1: Stages of sleep over the course of a typical night.

Sleep stages are commonly characterized based on the electrical activity recorded using scalp electroencephalography (EEG), supported by electrooculography (EOG) and electromyography (EMG). The combined recording of these three forms of electrical activity during sleep is termed polysomnography (PSG).

Each stage of sleep is characterized by certain EEG waveforms (Figure 2). NREM sleep includes two characteristic EEG waveforms: K-complexes, which last about 1 second and include a sharp negative voltage peak; and sleep spindles, 11-16 Hz waveforms typically lasting 0.5-1 seconds. As its name suggests, SWS is characterized by slow (0.5-4 Hz), high-amplitude waves that dominate the EEG signal. The slowest of these waves, lasting 1-2 seconds (0.5-1 Hz), are often termed slow oscillations. During REM sleep, the EEG signal consists of mixed-frequency wake-like waveforms accompanied by intermittent bursts of rapid eye movements (Figure 2d) and a substantial decrease in muscle tone.

Another electrophysiological waveform of importance for our discussion is the hippocampal sharp-wave ripple complex (SWR; Figure 2e), although it is not specific to sleep and cannot be detected from the scalp EEG. SWRs are correlated with elevated hippocampal firing. During sleep, these 80-300 Hz waveforms are nested within spindle troughs (Clemens et al., 2011; Siapas & Wilson, 1998; Sirota, Csicsvari, Buhl, & Buzsaki, 2003). Spindles, in turn, are often nested in slow oscillations (Battaglia, Sutherland, & McNaughton, 2004; Clemens et al., 2007; Diekelmann & Born, 2010; Helfrich et al., 2019; Staresina et al., 2015). Slow oscillations can be divided into two parts, the positive half cycle or up-state, when neuronal firing in the cortex is high, and the negative half cycle or down-state, which is a period of widespread neuronal quiescence. Thus, spindles are phase-amplitude coupled with slow oscillations in that fast spindles (>13 Hz) occur mostly in the up-state and slow spindles (≤13 Hz) mostly in the hyperpolarizing down-state (Cox, van Driel, de Boer, & Talamini, 2014; Klinzing et al., 2016; Molle, Bergmann, Marshall, & Born, 2011). As discussed below, this temporal pattern of cross-frequency coupling has been associated with memory consolidation during NREM sleep.

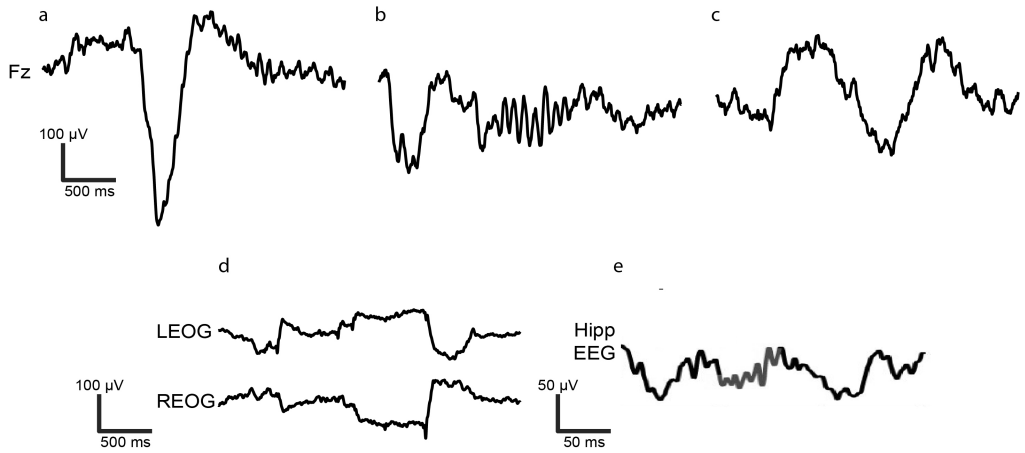

Figure 2: Typical electrographic waveforms observed during sleep. (a) K-complex. (b) Sleep spindle. (c) Slow waves. (d) Rapid eye movements. (e) Sharp-wave ripple complexes (blue trace). Data from electrode Fz (a-c), the left and right EOG electrodes (d), and hippocampal EEG in humans. Panel (e) adapted from Zhang, Fell, and Axmacher (2018), use permitted under Creative Commons license: http://creativecommons.org/licenses/by/4.0.

1.2 A brief historic review of research on sleep and memory

The oldest known statement regarding sleep's beneficial role for memory is from the first century CE Roman rhetorician, Quintilian, who observed that "a single night will greatly increase the strength of memory." But it was only after Ebbinghaus' (1885) momentous discovery of forgetting curves that several studies explored the role of sleep in memory (e.g., Heine, 1914). The first systematic study backing Quintilian's claim was provided by Jenkins and Dallenbach (1924), who showed that memory for a list of nonsense syllables was better following eight hours of nocturnal sleep than after an equivalent period of daytime wake. Jenkins and Dallenbach's results were originally interpreted as evidence for sleep's passive, protective role in preventing the effects of interference on previously acquired memories. It wasn't until the 1960s, after the identification of REM sleep (Aserinsky & Kleitman, 1953), that the relationship between sleep and memory was more extensively studied. The idea of passive protection through sleep has continued to be relevant for this research, along with the intriguing idea that sleep actively shapes memory through yet-to-be elucidated mechanisms.

The modern age of research in the field started in the 1990s, with the discovery of hippocampal replay (i.e., the reactivation of learning-related neural ensembles during sleep, first revealed in rodents; Pavlides & Winson, 1989; Wilson & McNaughton, 1994). Importantly, this finding fits with the idea of active memory processing during sleep, rather than sleep simply sheltering memories from interference (see Section 3 for further discussion). Since that seminal discovery, a series of major advances have shaped our understanding of memory consolidation during sleep. The focus on REM sleep's importance for consolidation (e.g., Hennevin, Hars, Maho, & Bloch, 1995; Smith, 1995; Winson, 1985) gradually shifted to an emphasis on NREM sleep. A major milestone in these studies was the development of targeted memory reactivation (TMR), a paradigm involving the unobtrusive presentation of learning-related stimuli during sleep, putatively triggering the reactivation of the memory trace in a manner akin to replay. TMR has been shown to improve memory on various tasks, demonstrating that memory reactivation during sleep can strengthen memory in humans (Rasch, Buchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009).

1.3 The evolution of memory during sleep

The term "memory consolidation" has been used in diverse ways to describe the off-line, post-encoding processes by which memories are stabilized, maintained, and transformed. Despite its prevalence, the term is rather ambiguous. Consolidation can unfold differently for different types of memory and can encompass a number of processes that alter memory storage.

Several considerations can help clarify the different meanings of consolidation. First, consolidation is classically divided into synaptic consolidation (the process by which synapses are shaped by long-term potentiation over a period of hours) and systems consolidation (the process by which memory traces are modified and shaped at the systems level over time scales ranging from several hours to several weeks or longer). For the sake of our discussion, we will emphasize the latter meaning. Second,

consolidation is not limited to sleep; at present, the relationship between consolidation during waking periods and sleeping periods is not clear (Tambini & Davachi, 2019). Third, different types of memory undergo consolidation processes that are qualitatively different and rely on different neural substrates. For example, consolidation of declarative memories (i.e., memories for facts and events) is thought to rely on the hippocampus, whereas consolidation of nondeclarative memories (e.g., motor skill expertise or the utilization of statistical regularities) is not. Still, there are exceptions to such a strict dichotomy, in that memories can be dependent on a combination of two memory systems (e.g., Schapiro et al., 2019).

Finally, the term consolidation may refer to different processes that memories undergo. For example, a plethora of studies reviewed below have shown that sleep not only stabilizes memories, but can also enhance them, integrate them into networks of preexisting memories, and extract gist or rules from larger ensembles of newly learned information, fostering subsequent creative insight. In addition, sleep can selectively maintain or enhance some memories or even parts of memories while allowing other memories and parts of memories to be forgotten. The use of a single umbrella term – consolidation – to describe these many processes may therefore be misleading. This led Walker and Stickgold (2010) to suggest the term "memory evolution" to describe this assemblage of off-line memory processing mechanisms. For simplicity and consistency with previous literature, we use the term "consolidation" in this chapter to encompass all these diverse forms of processing, but these complexities should be kept in mind.

2 The leading hypothesis – sleep selectively strengthens memory

2.1 The active systems consolidation hypothesis

The notion of an active memory consolidation process can be traced back to Ebbinghaus (1885) and then Müller and Pilzecker (1900), who concluded that memories can develop over time after initial encoding. Another four decades passed before Duncan (1949) demonstrated that consolidation could be interrupted by electroconvulsive shock, and then it was another decade before Flexner, Flexner, and Stellar (1963) showed consolidation to be an active process dependent on protein synthesis.

The earliest proposal for a two-stage model of memory consolidation can be ascribed to Marr (1971), who hypothesized that new memories are first encoded and stored using a so-called "fast learner" and only later are strengthened and stabilized by a slower, but more stable, learner. This model was later expanded to describe the manner in which the hippocampus and the neocortex interact in encoding and storing declarative memories (McClelland, McNaughton, & O'Reilly, 1995; Squire & Alvarez, 1995; Norman, Newman, & Perotte, 2005). The two separate stores of information, in the hippocampus and neocortex, enable the system to keep forming new memories without overwriting previously learned ones. A major pillar of this hypothesis is that memories that are indexed by the hippocampus are repeatedly reactivated over time and that these reactivations create the cortical infrastructure supporting enduring storage of a memory that is no longer dependent on the hippocampus for recall. This basic model remains highly influential, despite being challenged by evidence of a more sustained role for the

hippocampus for certain highly recollective memories (Nadel & Moscovitch, 1997; but see Barry & Maguire, 2019; Gilmore et al., 2020).

One of the most important achievements of the last 25 years of research on sleep and memory was the elaboration of the active systems consolidation hypothesis (Rasch & Born, 2007, 2013). Building on Marr's two-stage model (Marr, 1971), the active systems consolidation hypothesis asserts that the shaping of cortical memory traces based on hippocampal traces takes place predominantly during SWS, when hippocampal-cortical communication is engaged through interactions among slow waves, spindles, and SWRs. Hippocampal reactivations coincide with SWRs in the hippocampus, which occur during the troughs of thalamocortical spindles (Coon et al., 2019; Siapas & Wilson, 1998; Wilson & McNaughton, 1994), which in turn occur during the up-state of cortical slow waves (Helfrich et al., 2019; Latchoumane, Ngo, Born, & Shin, 2017). Over time, the neocortical memories become more stable and can lose their reliance on the hippocampus for successful recall. A similar idea was put forward by Paller and Voss (2004), without an emphasis on the physiology of SWS, but with the idea that declarative memories change by virtue of reactivation during sleep that engages neocortical-hippocampal interaction. They postulated that "memories may not lie dormant during sleep, but rather may be receiving regular exercise… sleep is essentially a nightly session of psychotherapy… the many hours we spend sleeping may actually serve to boost the usefulness of memory change" (Paller & Voss, 2004, p. 667, 669).

According to the active systems consolidation hypothesis, memories benefit from sleep through a selective, active mechanism, such that some memories benefit and others do not. Factors found to increase the probability for a sleep-related benefit include: (a) memory strength (i.e., memories must not be over-trained, but need to be sufficiently encoded to support reactivation; Cairney, Lindsay, Sobczak, Paller, & Gaskell, 2016; Creery, Oudiette, Antony, & Paller, 2015; Schapiro, McDevitt, Rogers, Mednick, & Norman, 2018; Stickgold, 2009); (b) the emotional intensity associated with the memory (Lipinska, Stuart, Thomas, Baldwin, & Bolinger, 2019; Schoch, Cordi, & Rasch, 2017); and (c) the perceived relevance of the memory for future behavior (Fischer & Born, 2009; Wilhelm et al., 2011; van Dongen et al., 2012).

2.2 SWS and memory consolidation

The first studies examining the different roles of REM sleep and SWS in humans used a half-night design (also called a split-night design), in which participants acquire new memories before either the first or second half of the night and are subsequently tested after sleeping for half the night. Memory retrieval performance for these two groups is commonly compared with performance of participants in two control groups, who learned and were tested in a similar way but spent the intermediate time period awake. This design takes advantage of the higher prevalence of SWS sleep in the first half of the night and of REM in the second half (whereas N2 is equivalent across both halves and therefore has relatively little effect on the comparison). Using this design, Yaroush, Sullivan, and Ekstrand (1971) showed that participants improve more in a declarative, word-pairs task after SWS-rich sleep than after REM sleep or wake. This dependency of declarative memories on SWS has been repeatedly and consistently shown in half-night studies (e.g., Daurat, Terrier, Foret, & Tiberge, 2007; Plihal & Born, 1997, 1999).

Another approach for studying the significance of SWS for declarative memory is to allow a full night of sleep and correlate memory benefit with duration of SWS or amount of slow-wave activity (defined as EEG spectral power in the 0.5-4 Hz range). Consonant with half-night studies, these studies consistently found positive correlations between memory benefits and these SWS measures (e.g., Atherton et al., 2016; Backhaus et al., 2007; Lau, Tucker, & Fishbein, 2010; Figure 3). Finally, electrical or sensory stimulation used to boost slow-wave activity during SWS has concurrently strengthened declarative memory (Marshall, Helgadottir, Molle, & Born, 2006; Ngo et al., 2015; Papalambros et al., 2017). This result shows that not only is this stage of sleep important for memory consolidation, but also the waveforms themselves are of importance.

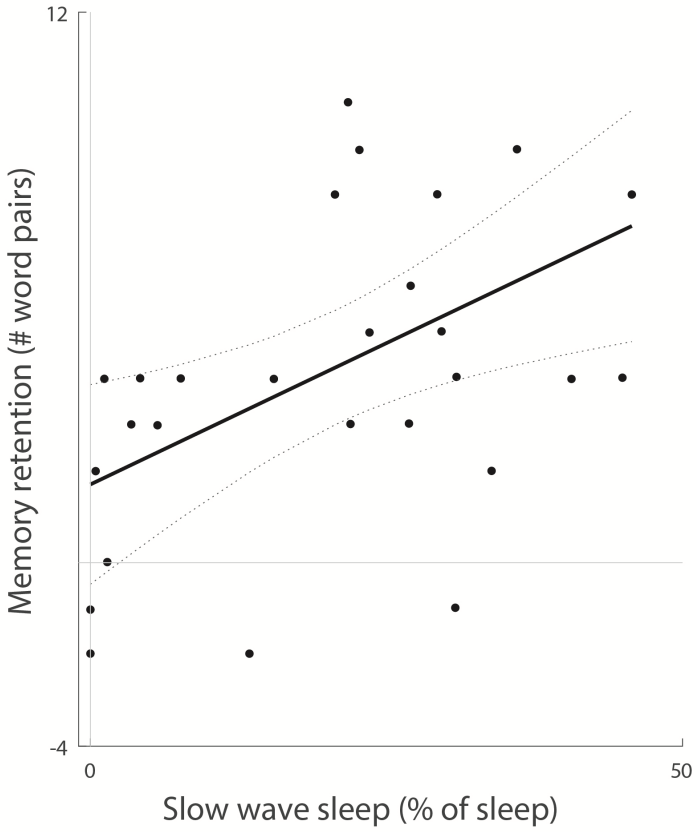

Figure 3: Memory retention over sleep is correlated with the percentage of time spent in slow-wave sleep during a night of sleep (adapted from Backhaus et al., 2007; copyright 2021 by Cold Spring Harbor Laboratory Press).

Taken together, these findings provide strong evidence for the causal role of SWS in sleep-dependent declarative memory consolidation. In addition to these associations with memory benefits, SWS has also been associated in some studies with improved gist

extraction and generalization (Lewis & Durrant, 2011), as well as the development of explicit knowledge regarding hidden rules and patterns embedded in motor tasks (Verleger, Rose, Wagner, Yordanova, & Kolev, 2013), although these have also been associated with REM sleep (Barsky, Tucker, & Stickgold, 2015) or even inversely with SWS (Payne et al., 2009).

Evidence linking SWS with nondeclarative memory consolidation is not as consistent. Nondeclarative learning is not hippocampus-dependent (Cohen & Squire, 1980), but may nevertheless depend on reactivation-based mechanisms of consolidation that are similar to the mechanism described in the active systems consolidation hypothesis. Some studies have found evidence for a beneficial role for SWS in procedural tasks (Huber, Ghilardi, Massimini, & Tononi, 2004; Landsness et al., 2009; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000b), and specifically for spindles occurring during both SWS and N2 (Astill et al., 2014; Nishida & Walker, 2007; Rasch, Pommer, Diekelmann, & Born, 2009; Wilhelm, Metzkow-Meszaros, Knapp, & Born, 2012). Several studies suggest, however, that stage N2 plays a more significant role in procedural learning of motor skills relative to SWS (Laventure et al., 2016; Peters, Ray, Smith, & Smith, 2008; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002a). Also, as noted above, REM sleep appears to play a major role in the consolidation of what Carlyle Smith has called "complex cognitive procedural" learning, such as for the Tower of Hanoi task (Smith & Smith, 2003). A major challenge for studies of nondeclarative memory is to avoid contamination from explicit learning that may produce declarative memories that interact with the nondeclarative ones. One recent study used a nondeclarative motor-sequence task and found that, unlike healthy controls, hippocampal amnesic patients showed no evidence of sleep-dependent memory enhancement (Schapiro et al., 2019), suggesting that hippocampal function normally contributes to consolidation during sleep even when not needed for initial learning (Sawangjit et al., 2018).

2.3 Memory reactivation during sleep

As noted above, the discovery of offline replay in rodents marked the beginning of a new age of sleep and memory research. Initially, replay was found to involve the reactivation of previously activated hippocampal place cells (i.e., neurons sensitive to specific locations) during SWS in rodents (Pavlides & Winson, 1989; Wilson & McNaughton, 1994). Since that discovery, however, sequential replay of patterns of place cell activation has been observed during waking rest (Karlsson & Frank, 2009; Kudrimoti, Barnes, & McNaughton, 1999) and REM sleep (Louie & Wilson, 2001); in other areas of the brain, including the cortex (Ji & Wilson, 2007; Olafsdottir, Carpenter, & Barry, 2016); and in other species, including songbirds (Dave & Margoliash, 2000) and macaques (Hoffman & McNaughton, 2002). Replay, at least in nonhuman animals, is involved not only in memory but also in planning and decision making (Olafsdottir, Bush, & Barry, 2018; Vikbladh et al., 2019).

Direct evidence for replay on the cellular level in humans is lacking. However, recordings from the human hippocampus during sleep (Helfrich et al., 2019; Staba, Wilson, Bragin, Fried, & Engel, 2002; Zhang et al., 2018) have exhibited SWRs, similar to replay on the cellular level in nonhuman animals (Wilson & McNaughton, 1994). A recent study in humans found that hippocampal SWRs during NREM sleep triggered the reactivation of

stimulus-specific neural activity for subsequently remembered items (Zhang et al., 2018), suggesting that SWRs play a similar role in consolidation for humans as in nonhuman animals.

Adopting a different approach to examining memory reactivation in humans, studies using multivariate pattern classification analyses in functional MRI (fMRI), magnetoencephalography, and positron emission tomography have produced evidence for reactivation of memory-related patterns in both the hippocampus and cortex during sleep and awake rest (Alm, Ngo, & Olson, 2019; Deuker et al., 2013; Liu, Dolan, Kurth-Nelson, & Behrens, 2019; Peigneux et al., 2004; Schapiro et al., 2018; Schuck & Niv, 2019; Tambini & Davachi, 2013; see Tambini & Davachi, 2019 for review of wake reactivation studies). These findings suggest that memory reactivation occurs in humans, but the neural substrates and mechanism supporting this process are still being explored. Whether these activations occur predominantly during SWS (see Peigneux et al., 2003 for reactivation during REM) and whether these neural events are causally linked to sleep-based memory consolidation remain open questions.

A different line of inquiry regarding reactivation in humans postulates that if memory-reactivation occurs during sleep, these memories may be incorporated into dreams. Dreams occur during both REM and NREM sleep, with the former being generally more vivid and bizarre (Foulkes, 1962). Several studies have shown that recent memories are incorporated into dreams, especially in reports collected from sleep onset (Kusse, Shaffii, Schrouff, Matarazzo, & Maquet, 2012; Stickgold, Malia, Maguire, Roddenberry, & O'Connor, 2000a). A recent study found evidence for memory-related content during all stages of sleep, and these putative reactivations were correlated with subsequent post-sleep memory improvements (Wamsley, Perry, Djonlagic, Reaven, & Stickgold, 2010; Wamsley & Stickgold, 2019). The extant evidence thus suggests that dreams may reflect memory reactivation as part of consolidation in the broadest sense.

2.4 Targeted memory reactivation

Although many studies in humans and rodents have shown a correlation between reactivation and memory enhancement, this evidence does not necessarily mean that the relationship is causal — that memory improvement is a consequence of reactivation. With targeted memory reactivation (TMR; Oudiette & Paller, 2013), learning-associated stimuli are used to induce reactivation during sleep. In their seminal study, Rasch and colleagues (2007) incorporated a specific odor during spatial learning and exposed participants to the same odor during subsequent SWS to reactivate the odor-related memories. They found an increase in spatial memory performance under these conditions, but not in control groups. Rudoy and colleagues (2009) extended these findings to the auditory modality by pairing related sounds with each of 50 objects displayed on a two-dimensional grid. Subjects were trained on object locations and then unobtrusively presented with half of these sound cues during N2 and N3 (Figure 4). Post-sleep testing revealed a relative increase in spatial memory performance for the subset of objects that had been cued during sleep compared to the non-cued objects. These findings showed that the TMR method can selectively reactivate individual memories, not just sets of memories, and that auditory stimuli can be effective, not just olfactory cues.

In the decade since these initial studies, TMR has been shown to improve not only spatial memory, but also vocabulary learning (Schreiner & Rasch, 2015), skill learning (Antony, Gobel, O'Hare, Reber, & Paller, 2012; Schönauer, Geisler, & Gais, 2014) and even to reduce social biases (Hu et al., 2015; but see Humiston & Wamsley, 2019; Xia, Antony, Paller, & Hu, Under review). TMR is thought to function by activating specific memory traces during sleep and selectively promoting their consolidation. In a recent fMRI-TMR study using olfactory stimulation during sleep (Shanahan, Gjorgieva, Paller, Kahnt, & Gottfried, 2018), odor presentation provoked learning-related patterns of cortical activity, lending support to the hypothesis that TMR activates cortical memory traces.

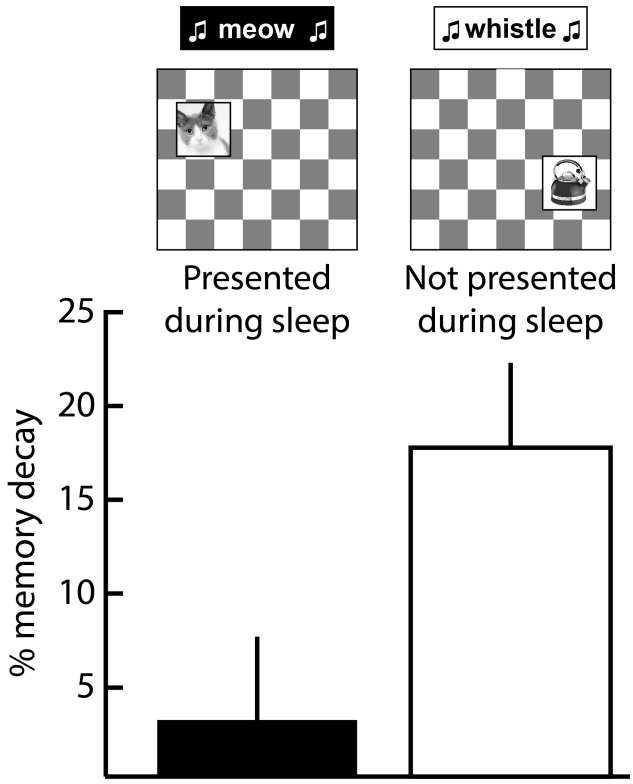

Figure 4: Targeted memory reactivation paradigm applied with spatial learning. Participants learned the locations of object images on a screen (top). The objects were accompanied by sounds and half of these sounds were later unobtrusively presented during sleep. The locations of cued objects were subsequently better remembered (bottom). Adapted from Rudoy et al. (2009) with permission.

2.5 Physiological correlates of sleep-based consolidation

The active systems consolidation hypothesis proposes that the interactions between SWRs, spindles, and slow waves are crucial for declarative memory consolidation. SWRs, which are causally related to memory consolidation in rodent models (Girardeau,

Benchenane, Wiener, Buzsaki, & Zugaro, 2009), play an important role in the memory-enhancing interplay between the hippocampus and the neocortex both in humans (Helfrich et al., 2019) and in nonhuman animals (Girardeau & Zugaro, 2011; Rothschild, Eban, & Frank, 2017).

In humans, SWRs can only be detected using invasive recordings and their contribution to memory is therefore relatively poorly understood. In contrast, sleep spindles are easily detectible in scalp EEG and their role in human memory consolidation has been studied extensively. Spindles, which originate in the thalamic reticular nucleus, have been associated with subsequent memory benefits for declarative memory (Antony et al., 2018; Eschenko, Molle, Born, & Sara, 2006; Schreiner, Lehmann, & Rasch, 2015) and nondeclarative memory (Antony et al., 2012; Astill et al., 2014; Lustenberger et al., 2016; Nishida & Walker, 2007; Rasch et al., 2009; Wilhelm et al., 2012). Higher spindle density (number per minute) following learning has been associated with better memory performance on various tasks, such as word pair learning (Gais, Molle, Helms, & Born, 2002), visuospatial learning (Clemens, Fabo, & Halasz, 2006) and procedural learning (Milner, Fogel, & Cote, 2006; Nishida & Walker, 2007).

The role of spindles in the consolidation process appears to be to reactivate previously encoded memories, which are thereby strengthened and updated (Antony, Schönauer, Staresina, & Cairney, 2019). The causal role of spindles for the enhancement of declarative memories in humans has been established using pharmacological approaches (Kaestner, Wixted, & Mednick, 2013; Mednick et al., 2013) and transcranial stimulation (Barham, Enticott, Conduit, & Lum, 2016; Marshall et al., 2006) to alter spindle activity and, consequently, memory. Neuroimaging studies using both fMRI and EEG have recently shown that neural activity occurring in conjunction with spindles carries information regarding previously acquired memories (Cairney, Guttesen, El Marj, & Staresina, 2018; Jegou et al., 2019; Schonauer et al., 2017), supporting the idea that spindles play a role in consolidation. Spindles were also shown in an fMRI study to coincide with regional activations in the neocortex and hippocampus, further solidifying their role in active systems consolidation (Bergmann, Molle, Diedrichs, Born, & Siebner, 2012).

Multiple studies have revealed the interplay between spindles and slow waves (Battaglia et al., 2004; Clemens et al., 2007; Goldi, van Poppel, Rasch, & Schreiner, 2019; Klinzing et al., 2016; Sirota et al., 2003). Helfrich et al. (2019) recently reported cortical spindles were coupled with slow waves near the slow wave peak, with maximal SWR activity nested in cortical spindle troughs. The amplitude of this coupled ripple activity was maximal when the spindle peaked during the slow wave up-state. In schizophrenia patients, the later in the slow-wave upstate that spindles peaked and the more reliable this phase relationship, the greater the overnight improvement on a procedural motor sequence task (Demanuele et al., 2017). Together, these findings suggest that the benefits of spindles on memory are dependent on their precise timing relative to slow waves.

As reviewed above, slow waves have been linked to memory benefits both in correlational studies and, causally, in studies using direct manipulations to enhance them (Backhaus et al., 2007; Marshall et al., 2006; Molle et al., 2011; Ngo et al., 2015;

Papalambros et al., 2017). Delivering unobtrusive auditory stimuli phase-locked to slow waves can entrain slow-wave activity and improve verbal, declarative memory (Ngo, Martinetz, Born, & Molle, 2013; Ong et al., 2016; Papalambros et al., 2017; but see Henin et al., 2019; Harrington et al., 2021). Such studies provide evidence for the causal role of slow-wave activity in memory consolidation and may pave the way towards interventions to improve the memory benefits of sleep.

2.6 REM sleep and memory consolidation

In the first decades after its discovery (Aserinsky & Kleitman, 1953), REM sleep was believed to be crucial for memory consolidation. This hypothesis gained support from rodent studies, with evidence of a crucial role for REM in both conditioning and contextual memory (Boyce, Glasgow, Williams, & Adamantidis, 2016; Fishbein & Gutwein, 1977; Smith, 1985; Smith & Rose, 1996). In humans, however, the link between REM and consolidation remains unclear. REM has not been consistently associated with consolidation of declarative memories, except in a few studies investigating emotional declarative memory (Nishida, Pearsall, Buckner, & Walker, 2009; Wagner, Gais, & Born, 2001). Research exploring the role of REM sleep in emotional memories has led to the development of the "sleep to forget and sleep to remember" hypothesis (Walker & van der Helm, 2009), which suggests that REM sleep has a dual role in emotional memory processing: it strengthens emotionally charged memories (Kleinsmith & Kaplan, 1963; LaBar & Phelps, 1998; Nishida et al., 2009), but decreases the physiological reactivity to these memory and helps with emotional regulation.

Various other memory-related roles for REM have also been suggested over the years, including in problem solving (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Walker, Liston, Hobson, & Stickgold, 2002b), statistical learning (Barsky et al., 2015), and complex cognitive learning (Smith & Smith, 2003). REM has also been linked with other forms of nondeclarative memory, including priming (Plihal & Born, 1999), skill learning (Plihal & Born, 1997), and perceptual learning (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994). Evidence from studies that examined both SWS and REM suggest that these two stages may operate in a complementary fashion in promoting consolidation (Batterink, Westerberg, & Paller, 2017; Diekelmann, Buchel, Born, & Rasch, 2011; Mednick, Nakayama, & Stickgold, 2003; Stickgold et al., 2000b).

Despite this wealth of intriguing ideas, the role of REM in memory consolidation remains poorly understood in comparison to that of NREM sleep. There is currently no consensus regarding the mechanisms by which memories are consolidated during REM. The neural architecture for consolidation may parallel that proposed by the active systems consolidation model, it may be similar in only some respects, or it may be something else altogether. Future studies should utilize the tools successfully used to investigate NREM memory contributions (e.g., cross frequency coupling to reveal nested oscillations; examination of cortical reactivation) to improve our understanding of REM-related memory processes (Peigneux et al., 2003). Additionally, the complementary roles of NREM and REM sleep should be fully explored in tasks involving different types of memory to reveal how within-sleep dynamics serves to consolidate memories.

3 Other hypotheses proposing to explain sleep's effect on memory

3.1 Sleep shelters memories from interference

For decades, forgetting was hypothesized to occur as a result of retroactive interference (i.e., newly learned memories would interfere with previously learned memories; McGeoch, 1932). In this context, sleep's beneficial influence on memory was attributed to the lack of new information that could otherwise interfere with prior memories (Jenkins & Dallenbach, 1924). Not only would sleep shelter against potentially disruptive effects of external stimuli, it would also limit internal, endogenous interference (e.g., as a result of mind wandering or self-generated thoughts and ideas). Additionally, since memory retrieval is dependent on the similarity between the encoding and retrieval contexts (McGeoch, 1942), sleep may make memories more accessible upon waking up by limiting contextual changes. Proponents of this view argued that sleep generally doesn't improve declarative memories, it merely decreases forgetting (Fenn & Hambrick, 2013; Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011; Schönauer & Born, 2017). Similarly, sleep has recently been hypothesized to preserve memories by minimizing contextual interference after encoding, thus protecting memories from the interfering effects of other events occurring in the same context (Yonelinas, Ranganath, Ekstrom, & Wiltgen, 2019).

However, several lines of converging evidence argue against the sheltering hypothesis and instead support the active systems consolidation hypothesis. (1) Several forms of nondeclarative learning, ranging from visual (Karni et al., 1994) and motor (Walker et al., 2002a) skill learning to complex cognitive procedural tasks such as the Tower of Hanoi (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2014; Smith, 1995) and probabilistic learning (Barsky et al., 2015) have shown absolute improvement after a period of sleep that is not seen after equivalent periods of wake; (2) for declarative learning, sleep is more beneficial immediately after learning than at a later point, even when testing occurs after equal amounts of wake, which should match interference in the two conditions (Gais, Lucas, & Born, 2006; Talamini, Nieuwenhuis, Takashima, & Jensen, 2008); (3) periods of sleep not only reduce forgetting but also increase resistance to interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006); (4) declarative memory benefits from sleep even when the total wake time between encoding and recall is equivalent to that of the control wake group (Ellenbogen et al., 2006; Gais et al., 2006); (5) SWS, N2, and REM provide differential benefits across a range of memory tasks, indicating that sleep is not uniform in its benefits across different memory systems; and (6) similarly, the importance of specific electrographic waveforms, such as sleep spindles and slow waves, to memory consolidation would not be predicted by the sheltering hypothesis. Together, these finding overwhelmingly support the active systems consolidation hypothesis over the sheltering hypothesis.

A fallback position for those supporting the sheltering hypothesis has been offered by Mednick et al. (2011), who proposed that sleep acts to shelter memories from interference and allow for uninterrupted, "opportunistic" consolidation (Mednick et al., 2011). Specifically, the proposal is that the consolidation of "hippocampal-dependent memories might not depend on SWS *per se*," instead occurring "opportunistically … whenever the hippocampus is not otherwise occupied by the task of encoding new memories" (p 504). Supporting this argument, a recent study in drosophila has shown that circuits involved in active forgetting are suppressed in sleep, hypothetically

"guarding" these memories from wake-related forgetting that is associated with retroactive interference (Berry, Cervantes-Sandoval, Chakraborty, & Davis, 2015).

However, the model suggested by Mednick et al. (2011) does not fare much better than the classic sheltering hypothesis. Several studies have tried to minimize wake interference in various ways, and have consistently found that sleep is more beneficial than wake, even when interference is at minimum (Mednick et al., 2002; Schonauer, Pawlizki, Kock, & Gais, 2014; Walker et al., 2002a). On the other hand, it may not be feasible to create an entirely interference-free waking environment, on par with SWS, which would be necessary to fully dissociate the effects of sleep and sheltering from interference. Another difficulty for the model is in explaining why benefits vary with sleep stage—such as when declarative memory consolidation is preferentially associated with SWS, or when emotional memory consolidation benefits particularly from REM rather than NREM sleep. The apparent participation of sleep spindles, coupled both with hippocampal SWRs and with cortical slow oscillations, in memory consolidation during sleep, argues that more than the simple absence of encoding of new memories is required for this sleep-dependent memory processing. Finally, the enhancement of specific memories through TMR cannot be explained by such a model. Nevertheless, there is merit to the notion that sleep can minimize new encoding and internal interference, and therefore these factors should be considered as part of any explanation for why sleep is beneficial for memory.

3.2 Sleep selectively weakens certain memories

Whereas the hypotheses discussed thus far have focused on memory strengthening, a different line of research has focused primarily on forgetting. Crick and Mitchison (1983) suggested that REM sleep, and dreaming in particular, may act to eliminate irrelevant memories. Although this theory has not gathered much support, some results indicate that, at least in animals, sleep-induced forgetting during REM sleep may play a role in creating gist-like schemas by diminishing item-specific memories (see Poe, 2017, for review). Additionally, some human studies have used TMR with forgetting-related cues (sounds associated with the instruction to forget) to weaken memories during sleep (Simon, Gomez, & Nadel, 2018; Schechtman et al., 2020).

A different perspective on sleep's role in weakening memories is that such degradation is necessary to maintain synaptic homeostasis (Tononi & Cirelli, 2003; Tononi & Cirelli, 2014). The synaptic homeostasis hypothesis (SHY) is premised on the claim that learning during wake involves the enhancement of synapses across the neocortex (Bushey, Tononi, & Cirelli, 2011). To avoid reaching a state of saturation, potentially causing "catastrophic interference" (French, 1999), a SWS-specific compensatory process is initiated, during which synapse strength is downscaled in a quasi-proportional manner, so that cortex-wide summed synaptic weights return to the baseline levels of the morning before (de Vivo et al., 2017; Diering et al., 2017; Tononi & Cirelli, 2003; Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). More recent versions of SHY acknowledge that certain memory traces could be reactivated so as to be preserved and perhaps even enhanced to some degree (Tononi & Cirelli, 2014; Tononi & Cirelli, 2019). Importantly, slow waves are thought to be causally involved in the downscaling process, with averaged synaptic strength indexed by slow-wave amplitudes (Vyazovskiy

et al., 2008). Moreover, slow waves in brain regions that were previously employed in demanding learning tasks could increase locally in the service of downscaling in those regions (Geva-Sagiv & Nir, 2019; Hanlon, Faraguna, Vyazovskiy, Tononi, & Cirelli, 2009; Huber et al., 2004). Accordingly, SHY explains the benefits of sleep to memory as a consequence of increased signal-to-noise ratios due to selective downscaling of synaptic strength (Nere, Hashmi, Cirelli, & Tononi, 2013).

A major challenge for SHY is to connect downscaling with mounting evidence linking memory benefits with memory reactivation during sleep and awake rest. Although the idea of renormalization of synaptic weights is gaining attention, the details of SHY are still hotly debated. One controversial issue concerns the sleep stage in which downscaling occurs, with recent evidence linking REM and not SWS to synapse pruning and firing rate renormalization (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsaki, 2012; Li, Ma, Yang, & Gan, 2017). Other major issues that are discussed in this context are which cortical and subcortical areas show downscaling, what the role of cortical slow waves is in this downscaling, what determines which synapses are downscaled and which are spared, and whether this spared set is strengthened or simply preserved (Niethard & Born, 2019).

4 Sleep and memory in psychiatric and neurological disorders

Many neurological disorders, and most psychiatric disorders, are associated with disturbances in sleep patterns. In some cases, these disturbances are believed to disrupt the memory function of sleep and thereby contribute to the symptoms of the disorder. For example, patients suffering from schizophrenia typically display sleep-related symptoms, most commonly insomnia. Patients with schizophrenia also manifest spindle deficits that correlate with impairments in sleep's benefit for both declarative memory (Goder et al., 2015) and nondeclarative memory (Wamsley et al., 2012), thereby contributing to cognitive symptoms of the disorder (Manoach & Stickgold, 2019). Both thalamocortical hyperconnectivity (Avram, Brandl, Bauml, & Sorg, 2018; Ferri et al., 2018) and spindle deficits (Ferrarelli et al., 2010; Manoach et al., 2014; Wamsley et al., 2012) have been shown to correlate with positive symptoms in schizophrenia, which include hallucinations, delusions, and confused thinking, suggesting a wide impact of the spindle deficit in schizophrenia symptomatology.

Another psychiatric condition characterized by sleep disturbances, possibly in relation to memory processing, is post-traumatic stress disorder (PTSD). Sleep disturbances after a traumatic event, such as insomnia and fragmented REM sleep, can predict the future progression of the disorder, though not every traumatic event results in PTSD (Pace-Schott, Germain, & Milad, 2015). One model of sleep's contribution to PTSD suggests that these disturbances disrupt extinction learning, a memory function deemed critical for successfully coping with the traumatic memory (Pace-Schott et al., 2015). Another suggests more pervasive interruptions of REM-sleep-dependent memory processing, including integration of the trauma memory with older memories, reduction of associated affect, and selective forgetting of inessential trauma details (Stickgold, 2008).

The relevance of sleep-related memory impairments in other psychiatric disorders is yet to be clarified, although there are some intriguing hints. Patients suffering from major depressive disorder exhibit shorter REM latencies, more overall REM, and less SWS (Pillai, Kalmbach, & Ciesla, 2011). Patients with depression also tend to exhibit a tendency for over-general episodic memory recall, and effective therapies often change sleep and/or memory. Yet, evidence is lacking to link their sleep differences to any memory abnormality (Harrington, Johnson, Croom, Pennington, & Durrant, 2018).

Several neurological conditions are also characterized by sleep deficits. Alzheimer's Disease and its prodromal syndrome, Mild Cognitive Impairment, for example, are associated with insomnia, reduced slow-wave power, and fragmented sleep (Peter-Derex, Yammine, Bastuji, & Croisile, 2015; Westerberg et al., 2012). Of importance, Alzheimer's patients have fewer fast sleep spindles and this deficit predicts their poorer declarative memory (Rauchs et al., 2008). The potential causal involvement of sleep alterations in the etiology of the disorder is under active investigation (Lucey et al., 2019). Patients suffering from amnesia due to focal bilateral hippocampal lesions also show abnormal sleep patterns, including less SWS, and less slow-wave activity during N2 relative to matched controls (Spanò et al., 2020). Sleep deficiencies manifested in neurological disorders are mirrored by memory deficiencies manifested in sleep disorders. For example, sleep apnea is associated with poorer sleep-dependent memory consolidation (Djonlagic, Saboisky, Carusona, Stickgold, & Malhotra, 2012).

Most studies exploring the relationship between sleep and neurological or psychiatric disease are correlational by nature. However, the idea that non-optimal sleep patterns may contribute to such disorders has recently been supported by studies directly manipulating sleep (Freeman et al., 2017; Papalambros et al., 2019). Together with non-invasive manipulations designed to improve sleep efficiency, interventions designed to specifically enhance memory-related characteristics of sleep (e.g., slow waves) could pave the way for developing new treatments for neurological and psychiatric illnesses.

5 Technologies for increasing sleep's memory benefits

The growing appreciation of sleep's beneficial role for memory consolidation, along with the evolving mechanistic understanding of the neurophysiological processes behind these benefits, have resulted in multiple lines of research on sleep interventions to improve sleep-dependent memory consolidation. Non-invasive procedures for slow-wave entrainment using transcortical electrical stimulation (Barham et al., 2016; Marshall et al., 2006; Marshall, Molle, Hallschmid, & Born, 2004) and auditory stimulation (Ngo et al., 2013) have shown post-sleep declarative memory benefits in the laboratory, and attempts to adapt them for home use are underway (Debellemaniere et al., 2018; McConnell et al., 2019). TMR, which has been used to selectively enhance specific memories in the laboratory, is also being considered for use at home (Cellini & Mednick, 2019; Goldi & Rasch, 2019; Paller, 2017).

A major challenge for home-based sleep interventions has been the identification of the appropriate sleep stage without the use of polysomnography equipment, which people can find obtrusive or uncomfortable. Additionally, the equipment traditionally needed for high-quality recordings is prohibitively expensive. However, newly developed technologies may reduce both the cost and discomfort involved in polysomnographic recordings without significantly sacrificing sleep-staging quality by using measures such as actigraphy, EKG, and dry EEG

electrodes. If this endeavor proves successful, these non-invasive methods may be able to selectively enhance memory not only in clinical populations, but in healthy populations as well (e.g., older adults; Papalambros et al., 2017).

6 Conclusions

Almost a century has passed since sleep's role in memory was first systematically examined. Over the years, the focus of research has shifted dramatically — from conceptualizing sleep as merely protecting memories passively to appreciating its active role; and from singling out REM sleep, to emphasizing NREM sleep, to seeking a more nuanced view of the distinct physiological contributions made during each stage of sleep. The discovery of neuronal replay within the hippocampus was a major impetus for the development of the active systems consolidation hypothesis, which states that declarative memory reactivation during slow-wave sleep shapes cortical memory traces based on hippocampal associations. The documentation of absolute improvements in nondeclarative learning following periods of sleep also had a major impact on the field. Whereas it is now widely agreed that sleep benefits many types of learning, the putative roles of each sleep stage are actively debated. Recent years have shown major advances both in understanding the forms of memory processing engaged during sleep and in thinking about how we might optimize these memory functions. Although largely hidden from view, covert alterations of memory traces during sleep can and should be investigated to shed light on the fundamental operation of the sleeping brain as well as on how memories are maintained and ultimately utilized.

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