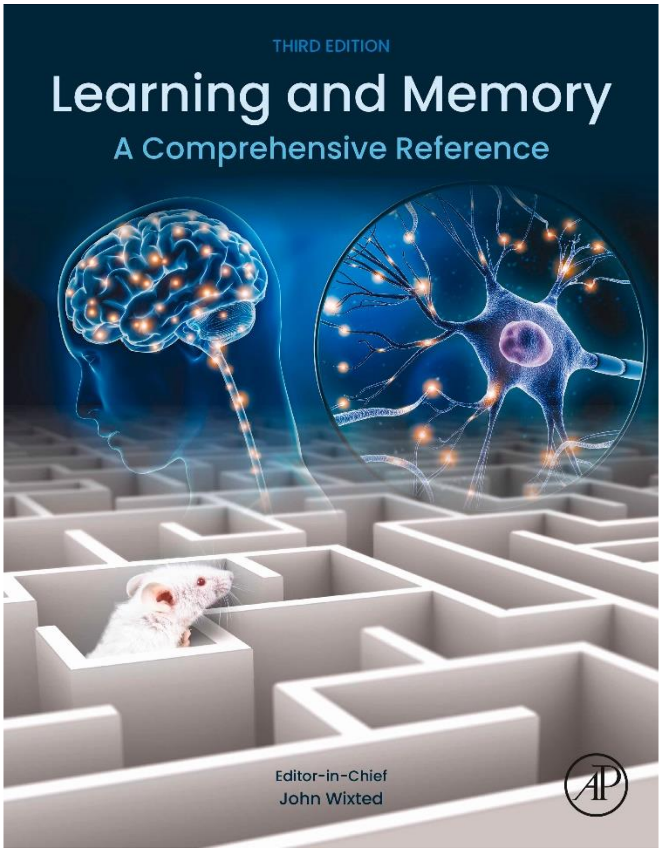

Platas, S.G.T., Yamazaki, E.M., Paller, K.A., Stickgold, R. and Schechtman, E. (2025) Memory evolution during sleep. In: Wixted, J (eds.) *Learning and Memory: A Comprehensive Reference, Third Edition*. vol. 3, pp. 413-433. UK: Elsevier.

dx.doi.org/10.1016/B978-0-443-15754-7.00077-8

3.24 Memory evolution during sleep

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Abstract

Consolidation is essential for enduring memories, but how and when consolidation transpires remains mysterious. Current views emphasize that memories change during certain stages of sleep in association with specific electrophysiological markers. Declarative memories, which pertain to the recall and recognition of facts and events, are gradually fortified and transformed via hippocampal-neocortical interactions. Although many aspects of this physiological process have yet to be elucidated, the stabilization of new memories is likely to entail integration of new knowledge with existing knowledge, selective strengthening of some memory features, concomitant loss of others, and potential transformation of knowledge. The method of Targeted Memory Reactivation is exceptionally valuable for making progress in understanding memory dynamics during sleep. Research on memory evolution during sleep is also valuable for generating insights into neurological and psychiatric disorders, corresponding treatment strategies, and ways to enhance memory generally.

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[*] Denotes equal contribution.

https://doi.org/10.1016/B978-0-443-15754-7.00077-8

Key points

- This chapter surveys leading approaches in the study of sleep's role in human memory.
- New findings challenge the formerly prominent idea that the only benefit of sleep is protection from interference.
- Memory consolidation depends on sleep-based neural replay of previously learned experiences.
- Relevant brain signals include hippocampal sharp-wave ripples, thalamocortical spindles, and cortical slow waves.
- Memory reactivation and consequent processing differ across sleep stages.
- Slow-wave sleep is particularly critical for consolidation of declarative memories, facilitating the subsequent recall and recognition of facts and events.
- Based on steady progress in this field, sleep-based applications with wearable technologies have high potential for improving sleep.

3.24.1 Introduction

Although humans spend about a third of their lives asleep, gaining a comprehensive scientific understanding of the functions of sleep is a supreme challenge. Sleep is essential for restoration of mental and physical capabilities, with an impact on almost every system in the human body. Sleep has been linked to neurological processes such as the clearance of Alzheimer-related proteins and to other neurological and psychiatric disorders (Irwin and Vitiello, 2019; Wang and Holtzman, 2020). Sleep has been associated with neural development (Tarokh et al., 2016; Coulson et al., 2024), inflammation (Besedovsky et al., 2019; Cao et al., 2020; Irwin, 2019), endocrine function (Morgan and Tsai, 2016; Duan et al., 2023), cardiovascular health (Avilez-Avilez et al., 2024), and emotional regulation (Palmer and Alfano, 2017; Yoo et al., 2007). Yet, memory consolidation is arguably one of the most extensively studied functions of sleep.

This chapter includes an overview of relevant characteristics of sleep and a review of the literature on sleep's role in stabilizing and transforming memory storage. Our use of the term *storage* is meant to denote the continued availability of information that was encoded, regardless of whether information is maintained by passive or active mechanisms and regardless of whether information is transformed through the process of consolidation. Whereas sleep can benefit both subsequent memory encoding and the status of previously acquired information, we focus on the latter in this chapter. Our review of the literature emphasizes studies on humans, but includes selected findings from the nonhuman animal neuroscience literature.

3.24.1.1 Sleep physiology

Human sleep is typically characterized by repeating cycles that last 90–120 min, as illustrated in Fig. 1. On the basis of the most readily apparent electrophysiological signs, orthodox categorization practices designate periods of sleep as either rapid eye movement (REM) sleep or one of three stages of non-REM sleep (NREM) known as N1, 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, while REM sleep occupies roughly 25%. Time spent in each stage changes systematically with age. One prominent change is that older adults spend less time in SWS. Although all stages of sleep can occur throughout the night, SWS is more prevalent in the first half of the night, whereas REM is more prevalent in the second half.

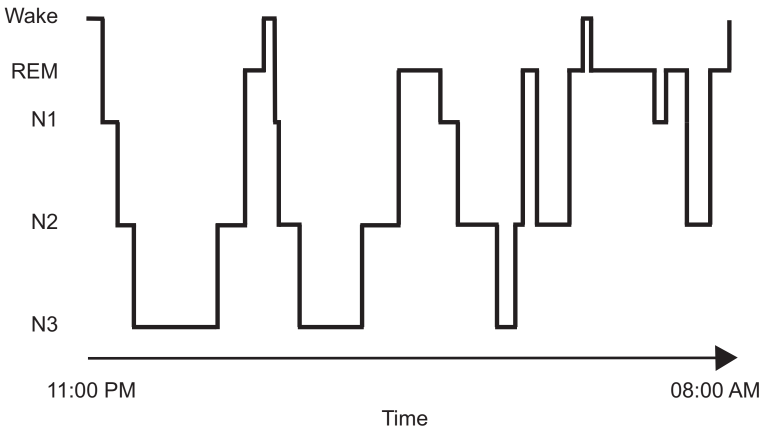

Fig. 1 The progression of sleep across a typical night, showing periods in REM and NREM sleep stages.

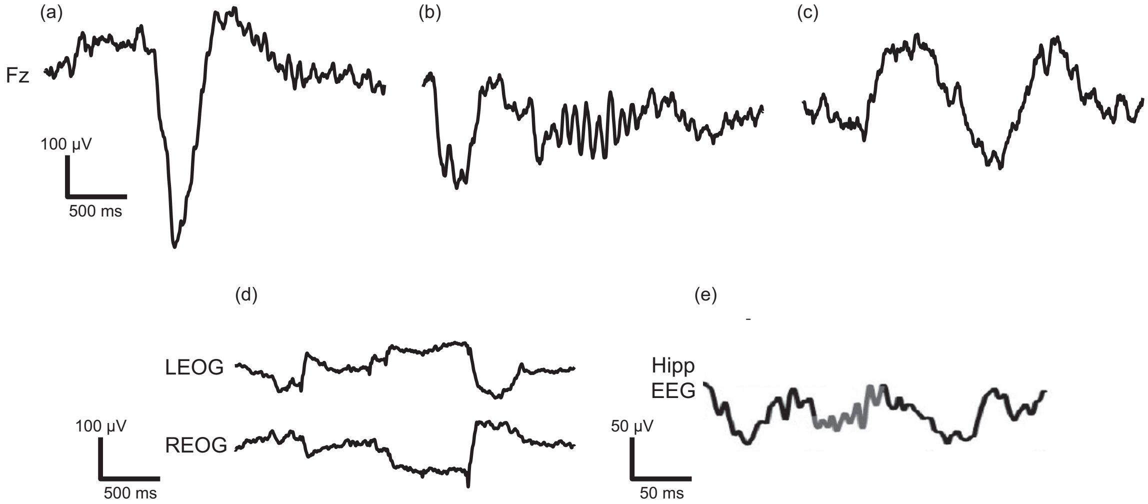

Fig. 2 Some of the typical electrophysiological signals observed during sleep. (a) K-complex. (b) Sleep spindle. (c) Slow wave. (d) Rapid eye movements. (e) Sharp-wave ripple complex. Data from electrode Fz (a–c), left and right EOG electrodes (d), and hippocampal depth electrodes (e) in humans. From Schechtman E, Stickgold R and Paller KA (2025) Sleep and memory. In: Grafman JH (Ed.), *Encyclopedia of the Human Brain*, 2nd edn., vol. 2, pp. 570–586, Elsevier; Panel (e) adapted from Zhang H, Fell J and Axmacher N (2018) Electrophysiological mechanisms of human memory consolidation. *Nature Communications* 9(1): 4103. https://doi.org/10.1038/s41467-018-06553-y.

Sleep stages are commonly identified based on the brain's electrical activity recorded using scalp electroencephalography (EEG), supported by electrooculography (EOG) that tracks eye movements, and electromyography (EMG) that tracks muscle activity. The combined recording of these three forms of electrical activity during sleep is termed polysomnography (PSG).

Each stage of sleep is characterized by waveforms such as those shown in Fig. 2. N1 sleep is characterized by low-amplitude EEG of mixed frequencies and by slow rolling eye-movements. N2 sleep includes two characteristic EEG waveforms, K-complexes and spindles. Each K-complex lasts about 1 s and includes a sharp negative voltage peak followed by a positive component. Sleep spindles are 11–16 Hz oscillations typically lasting 0.5–2 s. SWS, as its name suggests, is characterized by slow (0.5–4 Hz), high-amplitude waves that dominate the EEG signal and are generally at least 75 µV in peak-to-peak amplitude. The slowest of these waves, lasting 1–2 s (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 and a substantial decrease in muscle tone.

Another electrophysiological waveform of importance for this discussion is the sharp-wave ripple complex (SWR). SWRs are not specific to sleep. They are typically detected from intracranial electrodes in the hippocampus. In humans, SWRs are sharp, large-amplitude negative deflections together with high-frequency oscillatory patterns in the gamma range with a median frequency of 80–90 Hz (ripples), with a wider frequency range up to 250 Hz in animal studies (Kucewicz et al., 2024). Their generation has been explained as a result of coordinated input from CA3 pyramidal neurons that depolarize in synchrony, triggering activation of CA1 pyramidal neurons, producing a sharp wave in the striatum radiatum and a fast ripple in the CA1 pyramidal layer (Girardeau and Lopes-Dos-Santos, 2021). During sleep, reactivation of CA1 ensembles encoding new information is thought to strengthen connectivity to the neocortex, driving memory consolidation.

The temporal occurrence of slow oscillations, spindles, and SWRs appears crucial for memory reactivation during sleep. Spindles tend to occur in the up-state of slow oscillations, which is when neuronal firing in the cortex is high, coincident with the positive phase of these oscillations. The slow oscillation up-state alternates with the down-state, characterized by widespread neuronal quiescence. Ripples tend to occur in the trough of spindles (Staresina et al., 2023). Below we cover evidence associating such temporal patterns of cross-frequency coupling with memory consolidation during NREM sleep.

3.24.1.2 Historical highlights

After the momentous discovery of forgetting curves (Ebbinghaus, 1885), scientists began exploring the role of sleep in memory (e.g., Heine, 1914). Most notably, the systematic study by Jenkins and Dallenbach (1924) showed superior memory for a list of nonsense syllables following 8 h of nocturnal sleep than after an equivalent period of daytime wake. Following the identification of REM sleep (Aserinsky and Kleitman, 1953), the relationship between sleep and memory was more extensively studied, and generally REM sleep was emphasized, overshadowing consideration of the possible relevance NREM sleep.

One might consider that a modern age of research on consolidation during sleep started in the 1990s, prompted by the discovery of hippocampal replay during sleep in rodents (Pavlides and Winson, 1989; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994). The term *hippocampal replay* typically refers to the observation of learning-related activity in neural ensembles in the form of sequential place-cell firing patterns replicating patterns previously observed during waking exploration. However, replay was often studied without demonstrating consequences for changes in memory storage, and now the terms *replay* and *reactivation* are often used interchangeably in a more generic sense. Since the seminal discovery of hippocampal replay, 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 et al., 1995; Smith, 1995; Winson, 1985) gradually shifted to an emphasis on NREM sleep.

3.24.1.3 Memory terminology

The two main categories of memory are declarative memory and nondeclarative memory (setting aside working memory, immediate memory, iconic memory, echoic memory, etc.). Declarative memories are memories for events and facts that can be retrieved in explicit memory tests of recall and recognition (or spontaneously). Declarative memories can be retrieved in conjunction with an awareness of memory retrieval related to past events or acquired knowledge; awareness of memory retrieval is absent with a nondeclarative memory unless declarative memory retrieval occurs concurrently. Nondeclarative memory includes procedural motor skills, cognitive skills, habit memory, priming in many implicit memory tests, simple associative learning, and classical conditioning.

Memory encompasses three steps: encoding, storage, and retrieval. Memory storage is not a passive process and constitutes the continued availability of information that was encoded (regardless of whether information is maintained in a passive or active manner). The term *memory consolidation* has been used in diverse ways to describe the offline, post-encoding processes by which memories are stabilized, maintained, and transformed. Consolidation can unfold differently for different types of memory and can encompass several processes that alter memory storage. Consolidation of declarative memories is thought to rely on interactions between the hippocampus and neocortex, whereas nondeclarative memories also benefit from sleep but are generally not dependent on hippocampal function. Still, there are exceptions to such a strict dichotomy of hippocampal involvement (e.g., Schapiro et al., 2019).

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 strengthening neurons coding the representation 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. In this chapter, 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 (Brodt et al., 2023; Wamsley, 2022). Third, different types of memory undergo consolidation processes that are qualitatively different and rely on different neural substrates.

Finally, the term consolidation may refer to different memory processes. 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. Walker and Stickgold (2010) suggested the term *memory evolution* to describe this assemblage of offline 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.

3.24.2 The leading hypothesis about sleep strengthening memory storage

3.24.2.1 Development of the notion of active consolidation

The notion of a process of consolidation can be traced back to Ebbinghaus (1885) and then Müller and Pilzecker (1900), who concluded that newly acquired memories can stabilize over time after initial encoding. Strong positions were not taken on whether the process transpired automatically, in a passive sense, perhaps through inexorable biochemical transformations, or in the course of memory retrieval, in an active sense. Another four decades passed before Duncan (1949) demonstrated that consolidation could be interrupted by electroconvulsive shock in a time-dependent manner.

The earliest proposal for a two-stage model of memory consolidation can be ascribed to Marr (1971). Marr hypothesized that new memories are first encoded and stored using a so-called fast-learning system through a process taking place in the hippocampus. Memories could then be gradually strengthened and stabilized by a slower process in the neocortex. This model was later expanded to describe the manner in which the hippocampus and the neocortex interact in encoding and storing memories (Cowan et al., 2020; McClelland et al., 1995; Squire and Alvarez, 1995). 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 this reactivation creates the cortical infrastructure supporting enduring storage of a memory that need no longer depend on the hippocampus for recall. This basic model remains highly influential, despite being challenged by evidence of a more sustained role for the hippocampus (Nadel and Moscovitch, 1997; but see Barry and Maguire, 2019; Gilmore et al., 2021).

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 and Born, 2013). Building on Marr's (1971) two-stage model, the active systems

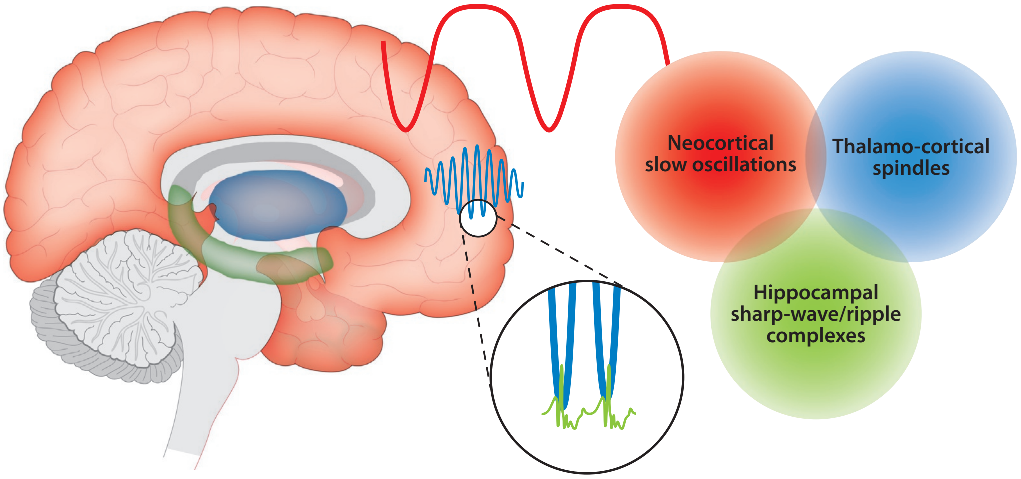

Fig. 3 During sleep, phase-locked neural oscillations support memory reactivation and consolidation. Hippocampal sharp-wave ripples coincide with the troughs of thalamo-cortical spindles, which tend to be time locked to the up-states of neurocritical slow-oscillations. Reproduced with permission from Paller KA, Creery JD and Schechtman E (2021) Memory and sleep: How sleep cognition can change the waking mind for the better. *Annual Review of Psychology* 72(1): 123–150. https://doi.org/10.1146/annurev-psych-010419-050815.

consolidation hypothesis asserts that the shaping of cortical memory traces based on hippocampal activity takes place predominantly during SWS, a privileged state devoid of external distraction when hippocampal-cortical communication is engaged through interactions among slow waves, spindles, and SWRs (Fig. 3). Hippocampal reactivations coincide with SWRs in the hippocampus, which occur during the troughs of thalamocortical spindles (Siapas and Wilson, 1998; Wilson and McNaughton, 1994), which in turn occur during the up-state of cortical slow waves (Helfrich et al., 2019; Latchoumane et al., 2017). Over time, neocortical memories become more stable and can lose their reliance on the hippocampus for successful recall.

According to the active systems consolidation hypothesis, memories benefit from sleep through a selective, active mechanism. Accordingly, some memories may benefit while others fade because they are not reactivated. A wide variety of factors can influence which memories are reactivated (Lewis and Bendor, 2019).

3.24.2.2 SWS and memory consolidation

3.24.2.2.1 Correlations and manipulations for declarative memory

Initial studies examining the different roles of human REM sleep and SWS used a split-night design, in which participants acquired new memories before either the first or second half of the night and were subsequently tested after sleeping for half the night. Memory retrieval for these two groups was compared with that of control groups comprising participants who learned and were tested in similar ways but spent the intermediate half-night period awake. The split-night strategy takes advantage of the higher prevalence of SWS sleep in the first half of the night and of REM in the second half. N2 sleep is generally similar across both halves and therefore has relatively little effect on the comparison. Using such an experimental design, Yaroush et al. (1971) showed that participants improved more in recall of word pairs after SWS-rich sleep than after REM sleep or wake. This dependency of declarative memories on SWS has been repeatedly and consistently shown in split-night studies (e.g., Daurat et al., 2007; Plihal and Born, 1997).

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 measures. The amount of slow-wave activity can be quantified using EEG spectral power in the 0.5–4 Hz range, for example. Consonant with split-night studies, these correlational studies consistently found positive correlations between memory benefits and SWS measures (e.g., Atherton et al., 2016; Backhaus et al., 2007; but see Cordi and Rasch, 2021).

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 linked with improved gist extraction and generalization (Lewis and Durrant, 2011), as well as the development of explicit knowledge regarding hidden rules and patterns embedded in motor tasks (Verleger et al., 2013). On the other hand, these types of memory benefits have also been associated with REM sleep (Barsky et al., 2015; Pereira et al., 2023) or even inversely with SWS (Payne et al., 2009).

3.24.2.2.2 Sleep and nondeclarative memory

Evidence linking SWS with nondeclarative memory consolidation is not as consistent as with declarative memory. Nondeclarative learning is not hippocampus-dependent (Cohen and 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 (Holz et al., 2012; Rakowska et al., 2021) and specifically for spindles occurring during both SWS and N2 (Astill et al., 2014; Nishida and Walker, 2007; Rasch et al., 2009; Wilhelm et al., 2012). Several studies suggest, however, that N2 plays a more significant role in procedural learning of motor skills relative to SWS (Laventure et al., 2016; Peters et al., 2008).

Some evidence has linked REM sleep with consolidation, specifically with regard to a type of learning termed "complex cognitive procedural" learning by Carlyle Smith. Here, a multi-step process facilitates acquiring a cognitive ability through repeated practice, as in the Tower of Hanoi task (Smith and 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). These results suggest that hippocampal function may contribute to consolidation during sleep even when not needed for initial learning (Sawangjit et al., 2018).

3.24.2.3 Physiological correlates of memory reactivation during SWS sleep

According to the active systems consolidation hypothesis, oscillatory EEG interactions during SWS are crucial for declarative memory consolidation. The key oscillations identified to date are slow waves, spindles, and SWRs, as discussed above. Different methods, such as functional MRI (fMRI), EEG, magnetoencephalography, and positron emission tomography, have produced evidence for reactivation of memory-related patterns in both the hippocampus and cortex during sleep. The results of these studies have cumulated in the current understanding of the physiological correlates of memory reactivation during sleep (Alm et al., 2019; Cairney et al., 2018; Deuker et al., 2013; Liu et al., 2019; Peigneux et al., 2004; Schapiro et al., 2018; Schechtman, 2022; Schechtman et al., 2023; Schreiner et al., 2021; Schuck and Niv, 2019; Tambini and Davachi, 2013).

3.24.2.3.1 Slow waves

Slow waves have been linked to memory benefits both in correlational studies and in studies that may inform causal interpretations by 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 et al., 2013; Ong et al., 2016; Papalambros et al., 2017; but see Harrington et al., 2021; Henin et al., 2019). Non-invasive procedures for slow-wave entrainment using transcortical electrical stimulation have shown post-sleep declarative memory benefits in the laboratory (Barham et al., 2016; Marshall et al., 2004, 2006). Such studies provide evidence for a causal role of slow-wave activity in memory consolidation and may pave the way towards interventions to improve the memory benefits of sleep.

3.24.2.3.2 Spindles

Sleep spindles have been studied extensively over many decades. Spindles have been found to originate in the thalamic reticular nucleus and have been associated with subsequent memory benefits for declarative memory (Antony et al., 2018; Eschenko et al., 2006; Schreiner et al., 2015) and nondeclarative memory (Antony et al., 2012; Astill et al., 2014; Lustenberger et al., 2016; Nishida and Walker, 2007; Rasch et al., 2009; Schechtman et al., 2023; 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 et al., 2002), visuospatial learning (Clemens et al., 2006) and procedural learning (Milner et al., 2006; Nishida and Walker, 2007). Sleep spindles also seems to benefit the generalization of learned material (Chatburn et al., 2021) and the integration of new material to existing knowledge (Tamminen et al., 2010).

The observation of spindles in sleep EEG in association with consolidation may reflect the reactivation, strengthening, and potentially updating of previously encoded memories (Antony et al., 2019). Neuroimaging studies using both fMRI and EEG recently showed that neural activity occurring in conjunction with spindles carries information regarding previously acquired memories (Cairney et al., 2018; Jegou et al., 2019; Schechtman et al., 2023; Schönauer et al., 2017), further supporting the idea that spindles play a role in consolidation. Some scalp EEG studies differentiate fast spindles prominent in frontal regions (>13 Hz) and slow spindles prominent in central and parietal regions (<13 Hz). Using fMRI and EEG, only fast spindles were associated with activity and functional connectivity between the hippocampus and cortex (Andrade et al., 2011; Schabus et al., 2007). Extending this finding, fast spindles have been closely linked to improvements in declarative memory (Cousins et al., 2014; Lustenberger et al., 2015; Molle et al., 2011) and nondeclarative memory (Barakat et al., 2011; Cousins et al., 2014; Tamaki et al., 2008). A causal role of spindles for the enhancement of declarative memories in humans has also been inferred based on pharmacological approaches (Kaestner et al., 2013; Mednick et al., 2013) and transcranial stimulation (Barham et al., 2016; Lustenberger et al., 2016; Marshall et al., 2006), as these manipulations could both alter.

3.24.2.3.3 Rodent place cells

The discovery of offline replay in rodents arguably marked the beginning of a new age of research on sleep-based memory change. Place cells are neurons that fire when an animal is in a specific location, presumably part of the formation of a neural representation of the environment. Initially, replay was found to involve the reactivation of previously activated hippocampal place cells during SWS in rodents (Pavlides and Winson, 1989; Wilson and McNaughton, 1994). Since that discovery, however, sequential replay of patterns of place cell activation has been observed during waking rest (Karlsson and Frank, 2009; Kudrimoti et al., 1999) and REM sleep (Louie and Wilson, 2001); in other brain areas including the cortex (Ji and Wilson, 2007; Olafsdottir et al., 2016); and in other species, including songbirds (Dave and Margoliash, 2000) and macaques (Hoffman and McNaughton, 2002). Direct evidence for replay on the cellular level in the human hippocampus during sleep is lacking.

3.24.2.3.4 Sharp-wave ripples

SWRs, which have been causally related to memory consolidation in rodent models (Girardeau et al., 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 and Zugaro, 2011; Rothschild et al., 2017). Recordings from the human hippocampus during sleep (Helfrich et al., 2019; Staba et al., 2002; Zhang et al., 2018) have identified SWRs that may parallel observations of SWRs in nonhuman animals (Wilson and McNaughton, 1994). A study of human hippocampal SWRs during NREM sleep showed that they 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.

3.24.2.3.5 Interplay of oscillations

Multiple studies have revealed the interplay between spindles and slow waves (Battaglia et al., 2004; Clemens et al., 2007; Goldi et al., 2019; Klinzing et al., 2016; Sirota et al., 2003). Helfrich et al. (2019) reported that 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. Additionally, the specific phase of the slow wave at the time of a spindle predicted memory reactivation during sleep (Schreiner et al., 2021). Intracranial deep-brain stimulation on the active phase of the slow wave increased coupling of thalamocortical fast spindles and MTL ripples, which was correlated with overnight recognition memory (Geva-Sagiv et al., 2023), further supporting the importance of oscillatory coupling. Together, these findings suggest that the benefits of spindles on memory are dependent on their precise timing relative to slow waves. Going beyond neural oscillations, phase of the respiratory cycle has also been shown be systematically related to these neural oscillations during sleep (Schreiner et al., 2023).

3.24.2.4 Targeted memory reactivation

3.24.2.4.1 Nudging the sleeping brain

Although many studies in humans and rodents have demonstrated correlations between reactivation and memory enhancement, this correlative evidence does not necessarily imply that the relationship is causal, that memory improvement is a consequence of reactivation. With targeted memory reactivation (TMR; Oudiette and Paller, 2013; Paller, 2024; Paller et al., 2021) 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 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. Post-sleep spatial memory 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.

Many subsequent studies replicated this finding of altered memory performance after a period of sleep with TMR, as confirmed by a meta-analysis (Hu et al., 2020). TMR has been shown to improve not only spatial memory, but also vocabulary learning (Neumann et al., 2020; Schreiner and Rasch, 2015), skill learning (Antony et al., 2012; Johnson et al., 2020; Schönauer et al., 2014) and even to reduce social biases (Hu et al., 2015; but see Humiston and Wamsley, 2019; Xia et al., 2023a).

Fig. 4 illustrates the design and results from one recent study to exemplify TMR research. The study addresses a fundamental question about memory reactivation. Outside of the laboratory, memories are presumably formed for numerous events each day while only a small subset is reactivated during sleep. Does sleep reactivation resemble conscious rehearsal such that there are distinct limits on how many memories can be brought to mind at once? Or does sleep reactivation occur in a less restricted manner? In the study conducted by Schechtman et al. (2021), reactivation appeared to take place in parallel for groups of distinct memories, with no decline as the number of memories increased (Fig. 4c). These findings suggest that reactivation is not limited the same way waking conscious rehearsal is limited; it can occur in parallel for multiple memories at the same time, with corresponding electrophysiological indicators of reactivation that scale with the number of memories reactivated (Fig. 4d).

3.24.2.4.2 Mechanisms of reactivation

TMR is thought to function by activating specific memory traces during sleep to preferentially promote their consolidation. Electrophysiological responses to stimuli during sleep provide some support for this hypothesis, including evidence of an increase in fast spindle power (Cairney et al., 2018; Schechtman et al., 2021; Wang et al., 2019). In an intracranial study of TMR during SWS (Creery et al., 2022), learning-associated sounds elicited hippocampal activity beyond that produced by irrelevant sounds, with activity in the gamma frequency range predicting the magnitude of post-sleep improvements in spatial recall due to TMR. In an fMRI-TMR study using olfactory stimulation during sleep (Shanahan et al., 2018), odor presentation provoked learning-related patterns of cortical activity, lending support to the hypothesis that TMR activates cortical memory traces (see also Van Dongen et al., 2012).

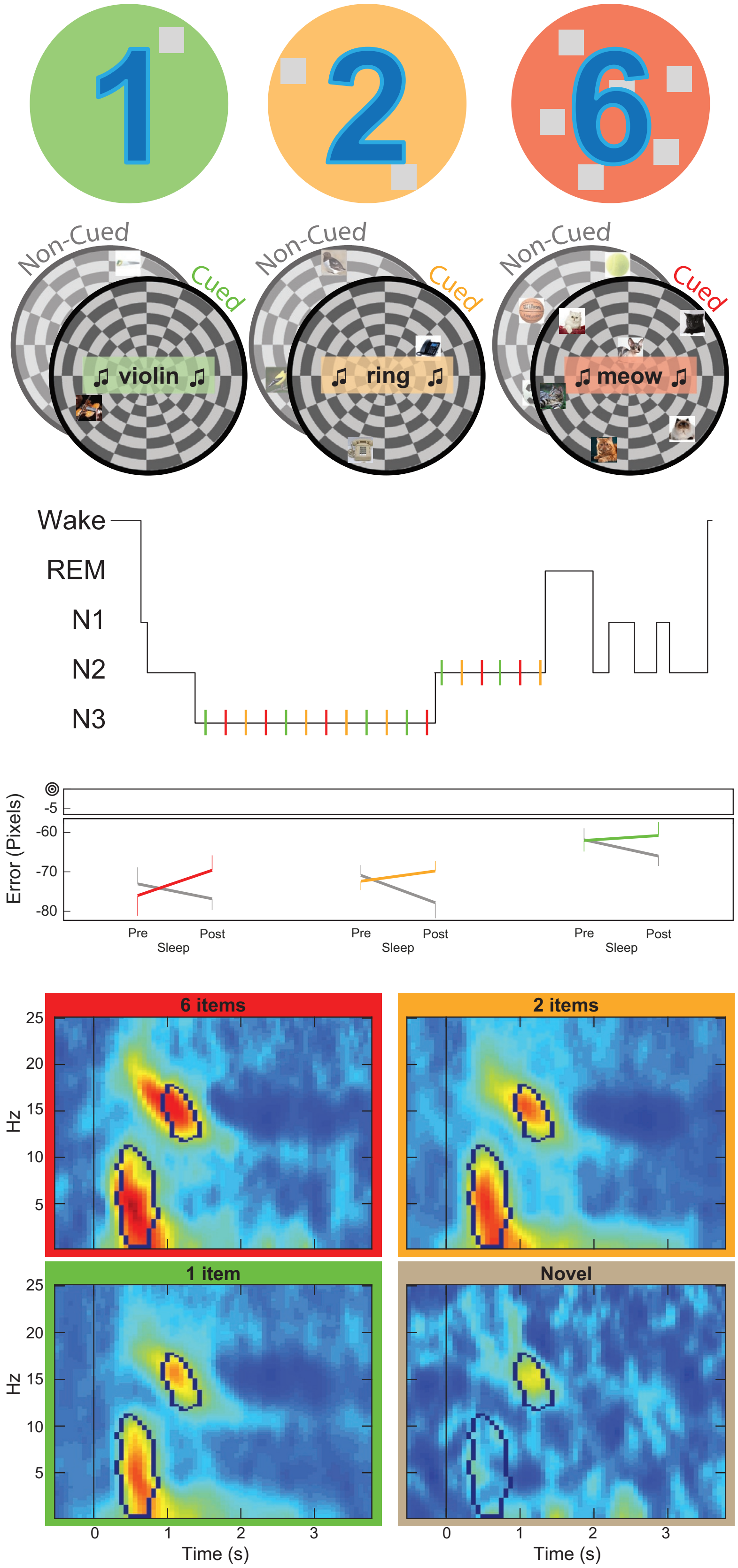

Fig. 4 An example of the procedure of Targeted Memory Reactivation (TMR) as applied with spatial learning (Schechtman et al., 2021). (a) Participants learned the locations of object images on a circular grid. Images belonged to a set of one, two, or six items in the same categories (e.g., one instrument, two phones, or six cats). The objects were accompanied by sounds (e.g., that of an instrument, phone, or cat). (b) Sounds from the colored sets, but not the gray sets, were then unobtrusively presented during N2 and N3 sleep. (c) The locations of cued objects were recalled with less error if cued than if not cued, whether from a set of one (green), two (yellow), or six cued items (red). That is, TMR produced a similar memory benefit regardless of the number of object-location associations associated with each sound. (d) During sleep, the sounds elicited EEG activity in the slow-wave and spindle range, and these effects increased in amplitude with the number of sound associations. Modified from Schechtman E, Antony JW, Lampe A, Wilson BJ, Norman KA and Paller KA (2021) Multiple memories can be simultaneously reactivated during sleep as effectively as a single memory. *Communications Biology* 4(1): 25. https://doi.org/10.1038/s42003-020-01512-0.

TMR investigators generally devote considerable attention to presenting cues that do not disrupt sleep. Importantly, several studies showed that when TMR cues cause behavioral or EEG signs of arousal from sleep, the specific memories associated with those cue can be weakened (Goldi and Rasch, 2019; Whitmore et al., 2022a; Whitmore and Paller, 2023). A recent follow-up study showed that this memory weakening when cues were too loud was not evident when the memories in question had been formed a week earlier, which suggests that recent memories are preferentially liable to disruption (Whitmore et al., 2024). These results are in keeping with the notion that communication between the hippocampus and cortex in the sleep state is necessary for the strengthening of recently formed memories, and that TMR provides a way to influence this process.

3.24.2.5 REM sleep and memory consolidation

In the decades after Aserinsky and Kleitman (1953) described REM sleep, it 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 (Fishbein and Gutwein, 1977; Smith, 1985; Smith and Rose, 1996). A recent study in mice suggests that neuronal activity in the medial septum during REM sleep may contribute to memory consolidation (Boyce et al., 2016). However, the link between REM and the consolidation of declarative memories is debatable. Although several studies implicated REM in emotional declarative memory (Nishida et al., 2009; Schäfer et al., 2020; Wagner et al., 2001), this topic has not been investigated sufficiently. Nevertheless, research on REM sleep led to the development of the "sleep to forget and sleep to remember" hypothesis (Cabrera et al., 2024), which suggests that REM sleep has a dual role in emotional memory processing. By this account, REM can strengthen emotionally charged memories (Kleinsmith and Kaplan, 1963; LaBar and Phelps, 1998; Nishida et al., 2009), while decreasing the physiological reactivity to these memories, which can benefit emotional regulation (Hutchison et al., 2021).

Various other memory-related roles for REM have been suggested, including in problem solving (Cai et al., 2009; Walker et al., 2002a, 2002b), statistical learning (Barsky et al., 2015), and complex cognitive learning (Smith and Smith, 2003). REM has also been linked with nondeclarative memory, including priming (Plihal and Born, 1999), skill learning (Abdellahi et al., 2023; Plihal and Born, 1997), and perceptual learning (Karni et al., 1994). Evidence from studies that examined both SWS and REM suggested that these two stages may operate in a complementary fashion in promoting consolidation (Batterink et al., 2017; Diekelmann et al., 2011; Mednick et al., 2003; Pereira and Lewis, 2020; Sifuentes Ortega and Peigneux, 2024; Stickgold et al., 2000b).

REM enhancement via auditory stimulation and effects on memory consolidation have been explored in humans less frequently compared to the SWS studies. Guerrien et al. (1989) presented auditory stimulation during REM sleep after participants learned Morse code. They found that stimulation during the phasic period of REM (when rapid eye movements are evident) led to better retention (Guerrien et al., 1989). A more recent study also using auditory stimulation during phasic REM found a positive effect of stimulation on performance on a visual task but a negative effect on motor performance (Navarrete et al., 2024).

Despite a wealth of intriguing ideas, there is currently no consensus regarding the mechanisms by which REM influences memory consolidation. The neural architecture for REM-based consolidation may parallel that proposed for SWS by the active systems consolidation model. On the other hand, the mechanisms may differ fundamentally or there may be some similarities and some differences. In the same vein, REM TMR has also been explored to address questions related to the manipulation of emotional memories (Rihm and Rasch, 2015), rule abstraction (Pereira et al., 2023), memory generalization (Sifuentes Ortega and Peigneux, 2024), and a motor task (Abdellahi et al., 2023), but its efficacy in biasing memory is also variable. Future attempts to improve our understanding of REM-related memory processes should utilize the tools that have been successful in NREM investigations (Peigneux et al., 2003). Additionally, the complementary roles of NREM and REM sleep should be fully explored in tasks involving a wider variety of memory types to reveal how within-sleep dynamics serve to consolidate memories.

3.24.2.6 Dreams

Dreams occur during both REM and NREM sleep, although REM dreams are generally more vivid and bizarre (Foulkes, 1962). The association between memory consolidation and dreams has been a matter of controversy. In humans, evidence on memory-incorporation into dreams (Kusse et al., 2012; Stickgold et al., 2000a) suggests that the neural substrate for dreams and waking life operate in a similar fashion (Decety, 1996; Dresler et al., 2011). Whereas recent memories are incorporated during dreams earlier in the night, dreams from later in the night have memory sources that are more remote (Picard-Deland et al., 2022), suggesting that dreams may leverage recent memories to form novel associations between recent events and previously acquired memories. Indeed, a model known as NEXTUP (Network Exploration to Understand Possibilities) suggests that dreaming is a distinctive type of sleep-related memory processing whereby new knowledge is extracted from existing memories through the discovery and strengthening of previously unexplored weak associations (Zadra and Stickgold, 2021). Multiple memories are blended to create dream narratives that explore unexpected and sometimes bizarre connections. According to this model, the blending process aids in making sense of past experiences, interpreting them, and preparing for potential future scenarios. Furthermore, the emotional response to the narrative reflects the significance of these events and associations.

Historically, dreaming has been strongly associated with REM, but recent investigations have taken on board that mental content is regularly reported after awakenings from NREM sleep stages (e.g., Picard-Deland et al., 2022). Results from many studies support an association between memory-related dream content and subsequent post-sleep memory improvements, irrespective of the sleep stage of the dream (Wamsley et al., 2010; Wamsley and Stickgold, 2019; see Hudachek and Wamsley, 2023), but results in this territory have been inconsistent.

Individuals who are aware of dreaming within the narrative context of the dream are experiencing a so-called *lucid dream*. Lucid dreams typically occur in REM sleep (Baird et al., 2019). Studies of lucid dreaming allow for additional research strategies to elucidate dreaming (Mallett et al., 2024). For example, motor skills has been studied during lucid dreams, revealing that dreamers who practice a task (finger tapping or dart throwing) in a lucid dream gain performance improvements compared controls who sleep without lucid dreaming (Schädlich et al., 2017; Stumbrys et al., 2016). In a REM TMR study, researchers found that dreaming of a procedural learning task was associated with greater post-sleep improvement on the task (Picard-Deland et al., 2021). Perhaps dreams that include practicing of a nondeclarative learning task engaged during waking can enhance task performance whether the dream is lucid or nonlucid, but further studies are needed to explore such possibilities. Mallett et al. (2024) described several methodological advances, including the use of variants of the TMR method, that have expanded the possibilities for studying dreams and possible relationships with learning.

3.24.2.7 Sleep learning

Acquiring knowledge during sleep has been desired by many throughout history and featured regularly in science-fiction. Several possibilities for such a shortcut to learning have been tested. Results to date support modest learning with a few tasks of implicit memory. In these cases, de novo associations were successfully formed during sleep and evident during post-sleep testing.

For example, using partial-reinforcement trace conditioning, Arzi et al. (2012) created associations between odors and sound stimuli during sleep. When the odors were unpleasant, sleeping participants inhaled less compared to when exposed to pleasant odors. After sleep, participants exposed to the sounds inhaled less for those sounds associated with unpleasant compared to pleasant odors, demonstrating new learning during sleep.

Others studies have induced implicit vocabulary learning during sleep by playing known words with either translated or pseudowords (Andrillon and Kouider, 2016; Koroma et al., 2022; Ruch et al., 2014; Schmidig et al., 2024; Züst et al., 2019). Whether such associations can persist over long periods of time is still unexplored. Implicit learning to discriminate auditory noise patterns during sleep has also been observed (Andrillon et al., 2017). The literature on sleep-based new learning is thus firmly situated within nondeclarative memory.

The generalization that sleep learning concerns only simple materials or simple types of learning, however, may be subject to notable exceptions. In particular, declarative learning during sleep can be demonstrated through interactive dreaming (Konkoly et al., 2021). During interactive dreaming, as demonstrated in this initial report of the phenomenon, people in REM sleep and in the context of a lucid dream perceived stimuli delivered by an experimenter and expressed volitional responses with pre-designated signals through eye movements, sniffs, or muscle twitches. One example included the following sequence of events. (a) The participant signaled that he was having a lucid dream. (b) The experimenter then delivered a spoken stimulus constituting a simple math problem. (c) The participant then signaled the correct answer. (d) Upon awakening, the participant was able to recall the episode of interacting with the experimenter with impressive accuracy. Although most of this recall could be considered merely ordinary dream recall, key parts of the interaction constituted the experimenter's input. As such, the dreamer recalled the novel information provided by the experimenter during PSG-verified sleep. The available evidence does not tell us whether this sort of learning is feasible beyond the context of lucid dreaming. Nevertheless, such instances of sleep learning — forming a contextually rich declarative memory based in part on external input during sleep, and then successfully recalling the episode upon awakening — suggest that we should keep an open mind regarding the possibilities for learning new information acquired during sleep.

3.24.2.8 Sleep forgetting

Forgetting is fundamental to healthy brain function but has primarily been studied in people while they're awake. Remembering recent events, such as what happened within the past few days, while forgetting events from many months ago, is adaptive. Such forgetting could decrease interference, thereby facilitating new learning, and in many cases could help with emotional regulation. It has been hypothesized that, without forgetting, memory systems would become overloaded with unwanted memories, and the saturation of neural networks would hinder new encoding and consolidation (Anderson and Hulbert, 2021).

Because our treasured human memories tend to be connected to many interwoven experiences, we depend on overlapping networks of memories rather than unique, isolated event storage (Eichenbaum, 2000). Retrieval itself relies on the links among memories. The retrieval of one memory can trigger the activation of another, and another, eventually leading to valuable information. Furthermore, retrieval entails inhibitory control, such that we can bring specific information to mind without all the potentially related information. Inhibition enables humans to override habitual responses or avoid the most accessible information, allowing retrieval of desired information unsullied by all their associated counterparts. Retrieving a selected memory further triggers forgetting of associated but not-selected memories, as recognized by the phenomenon of retrieval-induced forgetting (Anderson and Hulbert, 2021). Memories can be forgotten because they share an associated cue with others that are consistently retrieved.

To what extent are these memory mechanisms operative during sleep? A viable possibility is that all the same mechanisms of memory reactivation and adaptive forgetting operate during sleep. For example, memories that share the same cue may undergo retrieval competition, leading to the weakening of associated memories. In this way, memory reactivation during sleep would weaken competing memories. In a similar fashion, TMR may not only enhance the retrieval of selected memories but also induce forgetting by weakening other components of the experience. In other words, a similar mechanism to retrieval-induced forgetting may operate during sleep (Cairney and Horner, 2024; Joensen et al., 2022).

This sort of memory interaction was shown in a TMR study by Oyarzún et al. (2017). Auditory cues were associated with new memories at learning. Overlapping object-location pairs were encoded in succession, either contiguously within 5-min or with a 3-h delay. The researchers found a decrease in recall of the first encoded pairs when auditory cues associated with the second pairs were presented during NREM sleep. This effect occurred only with the 3-h delay. When encoding was contiguous, TMR instead resulted in an increase in memory accuracy for the first encoded pairs. This result suggests that TMR promotes the strengthening and weakening of overlapping memories based on their relative encoding strength (Oyarzún et al., 2017). This idea has also been supported by other studies showing that TMR can lead to both strengthening and forgetting of overlapping pairs, depending on their encoding order (Joensen et al., 2022). This evidence supports the findings of increased retention and forgetting for overlapping pairs when presented with a common sound cue during SWS, suggesting that reactivation-induced forgetting with TMR may be useful for inducing forgetting of unwanted or aversive memories.

Although intentional suppression can be used to weaken unpleasant memories with TMR in healthy populations (Schechtman et al., 2020; Simon et al., 2018), some research has focused on sleep-based strategies for forgetting unwanted memories. This type of strategy could be useful in conditions like post-traumatic stress disorder, where aversive memories cannot be volitionally forgotten. A recent study by Xia et al. (2024) showed that aversive memories can be strategically re-edited and weakened using positive memories to mediate interference. The effect was produced using TMR cues during sleep that reactivated positive memories. Moreover, cue-elicited theta brain rhythms during sleep predicted the recall of positive memories, suggesting that cue-elicited theta power may track cue-triggered memory reactivation during sleep (Xia et al., 2024). With the objective of changing the affective content of aversive memories to be more positive, these researchers used strategic pairing of positive words and memory cues during sleep. They found a reduction in negative affective judgments in post-sleep tests, suggesting that the recalled events were perceived as less aversive. It is suggested that positive emotional valence is modulated by an increase in EEG theta and sigma (spindle) power. In particular, when the onset of positive words (cueing) coincided with the up-phase of slow oscillations, affective updating was more successful (Xia et al., 2023b).

Together, these studies fit with the notion that memories are not only reactivated and strengthened during sleep, but also that reactivation of memories can lead to forgetting of associated memories both in wakefulness and sleep. Moreover, these memory-interaction mechanisms during sleep can be manipulated to produce small changes in the affective power of unwanted memories.

3.24.3 Conceptions of sleep's effect on memory storage beyond memory reactivation

3.24.3.1 Sleep shelters memories from interference

Theoretically, forgetting could result from retroactive interference, whereby new learning impedes storage based on previous learning (McGeoch, 1932). Sleep could be beneficial merely because of a lack of new learning while we sleep (Jenkins and Dallenbach, 1924). Proponents of this view argued that sleep merely decreases forgetting (Fenn and Hambrick, 2013; Mednick et al., 2011; Schönauer and Born, 2017), or that sleep merely reduces contextual interference (Yonelinas et al., 2019). These arguments, however, do not cast doubt on the evidence summarized above implicating memory reactivation during sleep.

(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 et al., 2014) 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 et al., 2006; Talamini et al., 2008); (3) periods of sleep not only reduce forgetting but also increase resistance to interference (Ellenbogen et al., 2006; but see Zhang et al., 2022); (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; Zhang et al., 2022); (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 et al., 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; Schönauer et al., 2014; Walker et al., 2002a). On the other hand, it may not be feasible to create an entirely interference-free waking environment, on a 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 complete explanation for why sleep is beneficial for memory.

3.24.3.2 Sleep weakens memories

Crick and Mitchison (1983) suggested that REM sleep, and dreaming in particular, may act to eliminate irrelevant memories. A related idea is that the forgetting of specific episodic memories during sleep could help with creating gist-like schemas (Poe, 2017). Another position is that a generic sleep-based mechanism for weakening memories could be essential for maintaining synaptic homeostasis (Tononi and Cirelli, 2003, 2014). The fundamental idea of this synaptic homeostasis hypothesis is that a compensatory process during SWS could assure that synapse strengths do not become too high for effective new learning. Interestingly, when certain brain regions are employed in demanding learning tasks, synaptic downscaling during sleep seems to be concentrated in those same regions (Geva-Sagiv and Nir, 2019; Hanlon et al., 2009; Huber et al., 2004). These ideas about sleep-based forgetting seem to coincide with the principle that forgetting can be adaptive. A summary of the evidence for and against these hypotheses is beyond the scope of this chapter. Rather, we note simply that, either way, these hypotheses are not in conflict with the core idea of this chapter that memory reactivation during sleep benefits memory storage.

3.24.4 Sleep and memory in clinical populations

Sleep disturbances in aging and in many neurological and psychiatric disorders are associated with memory deficits and cognitive decline. Sleep-related memory issues may thus contribute to the symptoms of many disorders. 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 (Borghese et al., 2022; Freeman et al., 2017; Papalambros et al., 2019). Non-invasive manipulations to enhance sleep (e.g., auditory stimulation of slow waves) and to enhance memory-processing (e.g., TMR) could pave the way for developing new treatments for specific populations (Paller et al., 2021).

3.24.4.1 Aging

Natural aging is associated with decreased SWS duration and memory decline (Mander et al., 2017). The altered microstructure of SWS is characterized by a reduction in slow-wave power, decreased spindle power, and diminished coupling between slow waves and sleep spindles (Helfrich et al., 2018; Mander et al., 2013, 2014). Decline in slow wave power in older adults, attributed to gray matter atrophy, is associated with decreased retention of memories (Mander et al., 2013). Similarly, diminished SWS neuro-oscillatory coupling in older adults is linked to decreased memory retention, which is also explained by brain atrophy (Helfrich et al., 2018; Muehlroth et al., 2019). As in younger adults, enhancing slow waves and coupling to spindles using transcranial stimulation or auditory stimulation (Papalambros et al., 2017; Wunderlin et al., 2024) can improve memory retention in older adults. The size and consistency of such effects requires additional longitudinal research focused on these questions. Some initial explorations of TMR procedures has begun in older adults, but so far memory enhancement has not been evidenced in motor tasks (Nicolas et al., 2024) or in vocabulary learning (Cordi et al., 2018). Many parameters of the procedures may not be optimal in older populations, and adequate testing may require longitudinal studies carried out in the home environment, as discussed further below in Section 5.

3.24.4.2 Dementia

Alzheimer's disease (AD) and its prodromal syndrome, Mild Cognitive Impairment (MCI), are associated with insomnia, reduced slow-wave power, and fragmented sleep (Peter-Derex et al., 2015; Westerberg et al., 2012). AD patients exhibit 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). In patients with MCI, Papalambros et al. (2019) used auditory stimulation to enhance slow waves and consequently found a positive association between slow-wave power and overnight memory improvement. The usage of TMR in AD or MCI populations is yet to be explored.

3.24.4.3 Psychiatric conditions

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 (Göder et al., 2015) and nondeclarative memory (Wamsley et al., 2012), thereby contributing to cognitive symptoms of the disorder (Manoach and Stickgold, 2019). Both thalamocortical hyperconnectivity (Avram et al., 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. 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).

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 (Pace-Schott et al., 2015). Various experimental approaches could thus be useful for elucidating the specific mechanisms whereby sleep can influence memories for traumatic experiences. To date, meta-analyses suggest that sleep can have a protective effect in the form of sleep decreasing the frequency of intrusive memories after a traumatic event (Schäfer et al., 2023; Larson et al., 2023). 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). Currently, 50% of patients suffering from PTSD do not respond to first-choice exposure-based psychotherapies, such as eye movement desensitization and reprocessing (EMDR). In a recent study, TMR was used to try to strengthen the therapeutic memories associated with EMDR through cueing during the up-states of slow oscillations during sleep (van der Heijden et al., 2024). Results showed an increase in slow-oscillation power and spindle dynamics. These brain dynamics correlated positively with reductions in PTSD symptoms, suggesting that TMR may have enhanced the consolidation of the EMDR treatment memory, but there was no overall benefit from TMR. In patients with social anxiety disorder, TMR cues presented during REM sleep to reactivate the context of their therapy showed signs of improved clinical outcomes after TMR (Borghese et al., 2022). Further work along these lines thus holds promise for using TMR as an adjuvant therapy in some circumstances.

Patients suffering from major depressive disorder exhibit shorter REM latencies, more overall REM, and less SWS (Pillai et al., 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, further evidence is needed to substantiate links between their sleep differences and memory processing during sleep (Harrington et al., 2018). Nevertheless, manipulations of sleep are worth exploring given the ample evidence that behavioral methods for changing sleep in depression can be helpful.

3.24.4.4 Sleep disorders

Nightmares are distressing during the dream and can be distressing even after awakening from them. Nightmare disorder (ND) is characterized by social and occupational distress caused by frequent nightmares. One treatment that is often effective for ND is imagery rehearsal therapy (IRT), a cognitive behavioral therapy where the storyline of a recurring nightmare is formally rewritten to create a more positive ending. After patients repeatedly rehearse the new storyline with their therapist, their nightmare distress can be reduced, even if the new storyline does not materialize in their dreams. In one study, a sound cue associated with the new storyline during IRT was presented during REM sleep, and adding this TMR procedure to IRT was found to enhance its effectiveness compared to IRT alone (Schwartz et al., 2022).

Another study used a different approach to nightmare treatment and applied it in people with narcolepsy (Mundt et al., 2024). These individuals often experience nightmares, but the associated symptoms are frequently overlooked. People with narcolepsy also tend to have lucid dreams more often than the general population. Accordingly, Mundt et al. (2024) employed a variation of TMR called Targeted Lucidity Reactivation. This procedure uses an auditory cue from a waking session when people learn to associate it with a lucid mindset, when they practice carefully examining their experiences for signs of dreaming. Cues are then played quietly during REM sleep to help people recognize a dream as a dream. Three narcoleptic patients received IRT along with cues during REM sleep, with preliminary indications of post-treatment reductions in symptoms. However, the study was designed only to investigate the feasibility and potential of the method, which must be explored in larger studies to determine whether it is advantageous compared to standard IRT alone.

Sleep deficiencies manifested in neurological disorders are mirrored by memory deficiencies manifested in sleep disorders. For example, sleep apnea, characterized by the partial or full cessation of respiration during sleep, is associated with poorer sleep-dependent memory consolidation (Cunningham et al., 2023; Djonlagic et al., 2021). Treatments to reduce sleep apnea and improve sleep for 3 months also improved overnight memory retention (Djonlagic et al., 2021; Zimmerman et al., 2006). A comprehensive review of memory consolidation in sleep disorders delves into some of these issues further (Cellini, 2017).

3.24.5 Monitoring and manipulating sleep for memory benefits in the home

Although polysomnography is the gold standard of investigating sleep, recent technological developments allow for studying memory processing during sleep in other ways. Wireless sleep monitoring in the home is less obtrusive and less labor-intensive, while more comfortable and ready-to-use for participants. Various combinations of actigraphy, EKG, and headband or in-ear EEG are used to detect sleep stages (Kwon et al., 2021). These methods are increasingly used by the public overnight to keep track of various sleep parameters.

Such methods can also be used to adapt TMR procedures from the sleep laboratory, with protocols to determine when to present TMR cues in the home. Studies in healthy adults have shown that memory can be influenced with these methods (Goldi and Rasch, 2019; Whitmore et al., 2022b). There is thus great potential to use such methods to improve clinical outcomes in patient populations (Borghese et al., 2022; Schwartz et al., 2022). In the future, as these technologies become cheaper, smaller, and more precise, they may be incorporated into treatment plans for individuals as precision medicine enters the sleep-medicine field (Lim et al., 2020). Technical advances can also expand the possibilities for memory research, including longitudinal studies. Whereas multiple nights in the sleep lab are seldom feasible, home-based recordings could be conducted over a larger number of nights. Such studies could focus on types of learning that develop gradually, such as language learning. There will also be opportunities for overnight interventions over many nights, which could be critical given that many nights of TMR could lead to memory changes much larger than those found over a single night.

3.24.6 Conclusions

More than 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 and of cross-stage interactions 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 must be investigated both to gain a better understanding of the fundamental functions of the sleeping brain as well as to determine how memories are maintained and ultimately utilized.

Acknowledgments

We gratefully acknowledge support from the USA-NIH (T32-NS047987, T32-HL007909; R00-MH122663, R01-MH048832, R01-NS112942, and DP1-HL179370), USA-NSF (BCS-1829414, BCS-1921678, and BCS-2048681), the McKnight Foundation, the Mind and Life Institute, and the Mind Science Foundation. Portions of this chapter were adapted from the chapter by Schechtman, Stickgold, and Paller (2025) in the *Encyclopedia of the Human Brain*, 2nd edition.

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