Hippocampal Contributions to Declarative Memory Consolidation During Sleep

James W. Antony and Ken A. Paller

Abstract The human brain faces a fundamental information storage challenge—forming useful new memories while not over-writing important old ones. Memory consolidation, and the corresponding interplay between the hippocampus and neocortex, is a protracted process to adjudicate between these two competing factors. Converging evidence from behavioral, cellular, and systems neuroscience strongly implicates a special role for sleep in stabilizing new declarative memories. In this chapter, we review evidence that during sleep the reactivation of newly acquired neuronal traces has lasting implications for memory transformation and stabilization. We first summarize relevant theoretical issues in memory research and then outline the physiological properties of sleep that may allow for this reactivation. We consider many factors that affect spontaneous memory reactivation, and we highlight research showing that memories can be selectively targeted and modified using learning-related stimuli. Ultimately, the ability to rescue otherwise fleeting episodes from oblivion plays a vital role in human life. Research elucidating this ability will also be critical for understanding how memory breaks down in aging and disease.

During a young scientist's graduate school interviews, a senior researcher told her that she would not cut it in such a competitive field. At each major junction of her life—her first publication, first tenure-track job, a named professorship, and a lifetime achievement award—she remembered the researcher's exact words, his dismissive tone, and the seeds of doubt he planted about her career path as vividly as the day it happened.

Most learning requires repetition. A barrage of visual experience in early life is required for plasticity within the visual system (Wiesel and Hubel 1963). Hundreds to thousands of hours of practice are required to form expert procedural skills. So

J.W. Antony
Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08544, USA

K.A. Paller (✉)
Department of Psychology, Northwestern University, Evanston, IL 60208, USA
e-mail: kap@northwestern.edu

D.E. Hannula, M.C. Duff (eds.), *The Hippocampus from Cells to Systems*,
DOI 10.1007/978-3-319-50406-3_9

how can an event that occurred just once and took less than 3 s be stored in the connections of the brain for a full lifetime?

The answer appears to lie in the unique physiological properties of the hippocampus and its relationship with the neocortex. A personally important memory, though played out in the world only once, becomes repeatedly replayed after that one unique event by the networks of neurons involved in its formation and storage. A key feature of this ability lies in how much occurs outside of the agent's consciousness. Whereas the young scientist's memory of being told that she would never succeed in science likely returned to her consciousness when revisiting the memory in her mind or recounting the story to a friend, it seems that forming this lasting memory trace required nothing like the number of hours of experience or practice required for a highly refined skill. Thus, while most long-lasting experience-dependent changes in the brain require numerous repetitions to drive requisite changes in synaptic weights, episodic memories must become embedded in the brain and replayed on their own, without extensive efforts to re-live the experience over and over again.

This is not to say offline changes do not play a role in other types of memories. On the contrary, sensory and procedural memories benefit from offline processes, including sleep (Brawn et al. 2010b; Mednick et al. 2003). Additionally, there is evidence that the hippocampus may play a role in types of learning previously deemed to be hippocampal-independent (Albouy et al. 2013).

Nevertheless, something unique must occur that allows for lasting episodic memory traces. The following discussion will focus mostly on changes that occur to a memory trace after its initial formation, with consideration for how various factors operative at encoding might alter this process. We will take a historical perspective on the concept of memory consolidation and then consider the role by which memory reactivation influences consolidation. Although consolidation certainly occurs to some extent during wake, we will focus on the physiological properties present during sleep that create unique conditions for interactions between the hippocampus and neocortex.

Memory Consolidation

Brief Historical Perspective

In this section, we will discuss two major advancements in the concept of memory consolidation, specifically Müller and Pilzecker's (1900) original study that precipitated the creation of the concept and Scoville and Milner's (1957) research with patient H.M. (Fig. 1). We will finish by outlining what researchers theorize about the hippocampus and neocortex in explaining consolidation.

In a series of studies, Müller and Pilzecker (1900) taught participants lists of nonsense syllables and tested them after a delay of typically a few hours (Lechner et al. 1999). Between encoding and testing, they introduced other lists at various

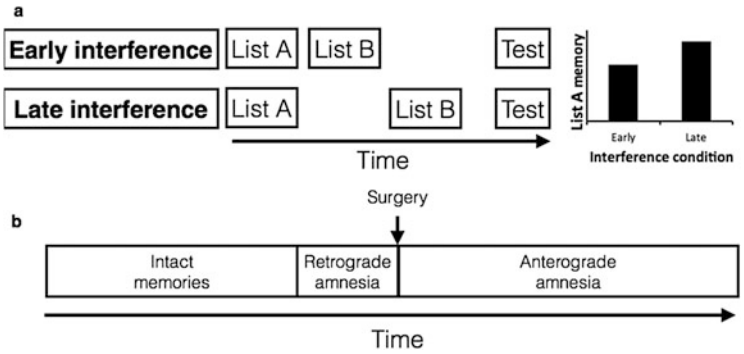

Fig. 1 Historical concepts in memory consolidation. (**a**) After encoding of a list of syllables (List A), introducing interfering information (List B) impairs List A memory when introduced sooner than later (Müller and Pilzecker 1900). A period of time without interference after learning is therefore beneficial for long-term memory stabilization. (**b**) Following medial temporal damage (such as when patient H.M. underwent surgery), the patient not only becomes unable to form new memories going forward (anterograde amnesia), but also cannot recall memories from an earlier time period (retrograde amnesia). Older memories remain largely intact. Therefore, during a prolonged period after learning, some declarative memories become independent of the medial temporal lobe

times within the delay interval and found that the later they gave the new lists, the better participants typically remembered the original information. Thus, they proposed a prolonged process eventually termed "consolidation" by which memories become increasingly resistant to interference. Their seminal finding remains a consistent and fundamental aspect of memory research today.

The next large piece of evidence about memory consolidation came from one of the most famous patients in the history of neuroscience known as H.M. (Scoville and Milner 1957). After H.M. had lived into his 20s with a form of epilepsy that resisted all other forms of treatment, the neurosurgeon William Scoville proposed performing brain surgery to remove the part of H.M.'s brain from which his seizures originated: a large portion of the medial temporal lobe, including the hippocampus. Little was known about this brain structure at the time, but the severity and frequency of his seizures seemed to warrant attempting such an experimental surgery. After removal of the hippocampus on both sides of his brain, the neuropsychologist Brenda Milner found H.M. could perform a whole host of mental functions and he retained many old memories. However, he forgot ones lasting up to a few years before his surgery and, critically, could no longer acquire new memories. He was thereafter, in the words of Suzanne Corkin (2013), trapped in a "permanent present tense."

H.M.'s impairment, while devastating, radicalized how researchers understood memory. The emerging theoretical picture suggested that when an event is learned, a confluence of information concurrently processed in the brain becomes bound together. This information enters the hippocampus from multiple neocortical streams specialized for processing highly detailed sensory inputs or thoughts as well as the spatial and temporal context in which the information arrives. The

hippocampus then rapidly binds together these distinct components. Initially highly susceptible to interference, new links reach a stable form in the neocortex only after a period of time. The relevant steps may require a certain number of reactivations rather than a certain period of time, per se. In either case, consolidation can progress such that networks within the neocortex are sufficient for retrieval—although whether some memories, or the full re-experience of some memories, then depend on only neocortical networks or on both neocortical and hippocampal networks remains a hotly debated issue (see Moscovitch et al. (2005) for one perspective and Squire and Bayley (2007) for another). In either case, converging data across many amnesic patients and animal models has forged agreement among researchers upon this basic conceptualization of consolidation.

Consolidation = Reactivation?

We will begin this section by outlining how memory retrieval acts to reactivate, strengthen, and reorganize a memory trace. We will then argue how this process resembles what occurs spontaneously in the gradual process by which memories become stabilized.

Cognitive psychological models of retrieval have long stressed the role of context on memory retrieval (Godden and Baddeley 1975; Jensen et al. 1971). For instance, psychology students often learn that studying information in the room where the test eventually occurs produces better results. An analogous mental trick is to try to create a mental context that allows for the successful retrieval of a memory. A series of neuroimaging studies have investigated how this phenomenon manifests itself in the brain. Unsurprisingly, neural reactivation patterns at retrieval tend to match those at encoding (Buchsbaum et al. 2012; Gelbard-Sagiv et al. 2008; Johnson and Rugg 2007; Nyberg et al. 2000; Polyn et al. 2005). Moreover, better matches predict better memory (Johnson et al. 2009; Manning et al. 2012; St-Laurent et al. 2014; Wing et al. 2015). A straightforward explanation of these findings follows from the reinstatement hypothesis (Tulving and Thomson 1973); the better the learning context is reinstated, the more likely a memory will be successfully remembered.

A vast psychological literature shows that memory retrieval does not simply involve finding a memory from storage and placing it back unaffected, as in retrieving a book from a library and later returning it in the same condition. Rather, successful retrieval produces better long-term enhancement than re-exposure to the material itself, a phenomenon known as the testing effect (for a thorough review, see Roediger and Karpicke 2006). During retrieval or during repeated study, stored information can be reactivated, leading in theory to superior storage. A straightforward prediction follows that better neural reactivation of an encoding context would produce better long-term memory at a later test. This prediction has been supported both during repeated study (Newman and Norman 2010; Xue et al. 2010)

and retrieval (Kuhl et al. 2010, 2012a, b; Vilberg and Davachi 2013; though see Karlsson Wirebring et al. 2015).

The above studies show how neural reactivation can counteract forgetting; we will now discuss how this relates to memory consolidation. We mentioned earlier how remote memories eventually become independent of the hippocampus. The gradual changes in activation from the hippocampus to the neocortex in animal data (Lesburguères et al. 2011; Maviel et al. 2004) and human data (Takashima et al. 2009) offer a mechanism by which this transfer occurs. Even stronger support comes from two studies showing that repeated reactivations render memories more quickly resistant to disruption following hippocampal damage (Lehmann and McNamara 2011; Lehmann et al. 2009). In these studies, rodents underwent contextual fear conditioning and then were (or were not) re-exposed to the learning context for 5 days after initial learning. After 5 days, they received sham or hippocampal damage. Without re-exposure, hippocampal damage strongly impaired memory, showing the memory was hippocampal-dependent. However, with repeated exposures, hippocampal damage had no effect on memory. This suggests that memory reactivation, and not time per se, causes memories to become hippocampal-independent. The overarching idea is that newly formed memories initially rely on the hippocampus and neocortex, whereas reorganization through repeated hippocampal-neocortical interaction produces neocortical networks that are sufficient for retrieval (Lesburguères et al. 2011; Redondo and Morris 2011; Squire et al. 2015; Tse et al. 2011).

In these studies reported by Lehmann and colleagues, animals were placed back into the original context, which was inferred to produce memory reactivation. However, behavioral (Craig et al. 2015a; b; Dewar et al. 2012) and neural evidence (Staresina et al. 2013; Tambini et al. 2010) suggests memories also undergo a stabilization process in the absence of overt retrieval. In studies that controlled for overt retrieval, increased resting functional connectivity patterns correlated with the amount of previous learning (Peigneux et al. 2006) and post-learning changes in hippocampal-cortical connectivity correlated with subsequent memory retention (Tambini et al. 2010). To strengthen this idea, it was even found that post-learning changes predicted memory during a non-learning control task (Staresina et al. 2013—but see Dewar et al. 2012, for evidence that rest benefits memories more than does performing non-learning control tasks). Additionally, strongly encoded items become the most preferentially reactivated (Tambini et al. 2010). Finally, it may be especially important that hippocampal processes occur immediately after learning. In humans, breaks between short video clips benefit memory, and allow for the onset of a strong post-clip hippocampal response that predicts memory (Ben-Yakov et al. 2013). Accordingly in rodents, replay occurs during learning (Davidson et al. 2009; Karlsson and Frank 2009) and correlates with memory measures (Dupret et al. 2010; Jadhav et al. 2012). Together, these studies provide a mechanism by which learning produces neural changes that in turn provide for stabilizing newly formed neural traces, presumably by assisting in hippocampal-neocortical transfer. In other words, in considering the findings of Müller and

Pilzecker over 100 years ago, these studies suggest consolidation may occur simply because of reactivation and the processes may be indistinguishable.

We have thus far outlined evidence for how wakeful memory reactivation contributes to stabilization. However, reactivation occurring during sleep plays an important and unique role as well. The following sections will outline the basics of sleep physiology and how it contributes to memory processing.

Characteristics of Sleep Physiology

The emergence of electroencephalographic investigations of sleep in the middle of the twentieth century showed that sleeping was an active process. Throughout the night, the brain progresses through cycles of distinctive stages of brain activity, each cycle lasting approximately 90 min. The physiological features of these stages provide clues about the functions of sleep in homeostasis and memory consolidation.

Typically, wakefulness transitions into stages of light sleep, known as stage-1 and stage-2, followed by the stage of deep sleep known as slow-wave sleep (SWS). To complete a full cycle, there will be a subsequent return to lighter stages, followed by rapid eye movement (REM) sleep. Stages of light and deep sleep are also known as non-rapid eye movement or NREM sleep (with Stage-1, Stage-2, and SWS sometimes termed N1, N2, and N3). In general, the character of these stages is influenced by factors such as circadian rhythms, such that cycles early in the night contain longer SWS periods, whereas later ones contain longer REM periods.

Physiological signals during wakefulness are chaotic. Fast, low-amplitude rhythms predominate in the EEG, muscle tension varies from moderate to high levels, and wakeful rest with the eyes closed produces a prominent occipital alpha rhythm, though with larger amplitudes in some people than in others. The alpha rhythm is most strongly observed over occipital regions, particularly during periods of rest with the eyes closed.

Stage-1 sleep appears at sleep onset with the appearance of quick vertex waves, rolling eye movements, and the decline of the alpha rhythm. This stage is considered to be the bridge between sleep and wakefulness, characterized by brief hallucinations and a low arousal threshold, meaning subjects can be easily awoken by external stimuli.

During stage-2 sleep, the predominant EEG rhythm is theta (4–8 Hz) with occasional *K-complexes*, which are high-amplitude deflections at approximately 0.8 Hz. Stage-2 also includes *sleep spindles*, which are short bursts of sigma activity at 11–16 Hz. Slow oscillations appear to originate in the frontal cortex (Cash et al. 2009), whereas spindles begin in the thalamus and continue as a series of reverberating thalamocortical oscillations (Morison and Bassett 1945). Arousal thresholds increase, which may connect to the findings that K-complexes and sleep spindles both coincide with reduced stimulus processing (Cote et al. 2000; Dang-Vu et al. 2010, 2011; Schabus et al. 2012). Stimuli can additionally elicit K-complexes and

spindles (Cash et al. 2009; Sato et al. 2007), and K-complexes are especially prominent after emotional or personally-relevant stimuli (e.g. one's own name) (Brain 1958; Bremer 1954; Oswald et al. 1960). For these reasons, K-complexes and spindles have been proposed to protect sleep by preventing unnecessary arousals from occurring. Because K-complexes in stage-2 sleep resemble slow oscillations in SWS in frequency, amplitude, and origin (Cash et al. 2009), stage-2 sleep can be considered a transitional bridge to SWS.

No naturally occurring brain state differs more from wakefulness than SWS. Slow, high-amplitude oscillations functionally segregate neuronal firing into discrete time bins, acting as the orchestrator of large-scale hyperpolarization and depolarization across the brain. Each oscillation has a down-state, during which there is a large-scale bias towards hyperpolarization and low neuronal firing, as well as an up-state, when there is bias towards depolarization and high neuronal firing (Mölle et al. 2011). Spindles persist into this stage, beginning most frequently during the slow oscillation up-state. Activation from neuromodulator systems prevalent during wake, such as those mediated by acetylcholine (ACh) and cortisol, wanes greatly during SWS (Diekelmann and Born 2010). Finally, arousal thresholds are highest in this stage (Rechtschaffen and Kales 1968).

After SWS, the brain progresses back towards lighter stages, and then to REM. Physiologically, REM resembles wakefulness in a number of ways. The EEG shows high-frequency, low-amplitude activity and neuromodulator levels for ACh and cortisol resemble their waking levels (Diekelmann and Born 2010). Subjectively, REM coincides with dreaming episodes more than any other stage (though dreaming also occurs in other stages). Despite these similarities between REM and wakefulness, there are obviously major differences. Muscle activity is nearly completely suppressed during REM. Brain areas involved in self-monitoring show dramatically lowered activity, whereas emotional areas reach higher levels than wake (Nir and Tononi 2010), likely corresponding to the emotionality and lack of self-awareness during dreams. Finally, arousal thresholds during REM vary widely, although the dreaming brain's ability to incorporate and re-interpret information coming from the outside world has been known at least since the days of Freud and postulated at least since Aristotle (Freud 1913).

In the following sections, we will discuss sleep's unique role in learning and memory processes.

Sleep as an Ideal State for Memory Reactivation

As with many important findings in psychology, studies on the role of sleep in memory began by accident (Jenkins and Dallenbach 1924). The story of this accident begins with Hermann Ebbinghaus, the German psychologist who pioneered experimental research on human memory in the late nineteenth and early twentieth centuries. His studies mostly consisted in presenting auditory strings of nonsense syllables and measuring how well they were remembered at various

retention intervals. Arguably his most influential finding came from what is known as the forgetting curve (Ebbinghaus 1885). Not only does memory fade over time, it does so in a systematic and mathematically predictable way. Forgetting occurs rapidly just after learning and less and less so over time, resulting in the curve he championed. However, in creating this curve an anomaly repeatedly crept in: forgetting was drastically lessened when the intervals included sleep than when they did not. Ebbinghaus largely ignored this, perhaps because he had no plausible explanation for it, but Jenkins and Dallenbach (1924) famously followed up the anomaly. Indeed, their extensive study showed that sleep, as compared to wake, benefits memory.

Approaches to Sleep Research and Multiple Types of Memory

Researchers have implemented three general approaches to isolating the importance of sleep: (1) testing memory retention across sleep versus wake intervals, (2) restricting sleep, either to particular parts of the night or to specific stages, (3) manipulating the conditions of intact sleep using pharmacology, sensory, or electrical stimulation. The first approach is effective for testing whether a task could be sleep-dependent; however, it produces rather limited conclusions given that sleep intervals can produce different arousal levels than wake intervals and that wake intervals can entail more interference than sleep intervals. Greater confidence can be reached using the second and third approaches. Indeed, these three approaches can provide increasingly more convincing evidence towards establishing causal relationships between sleep and memory.

Since Jenkins and Dallenbach's (1924) landmark study showing sleep benefits for declarative memories, sleep has been shown to affect nearly every type of memory. Well-established research paradigms have been used to show that sleep benefits (1) motor sequence learning (Barakat et al. 2011; Brawn et al. 2010a; Cohen et al. 2005; Fischer et al. 2002; Fogel and Smith 2006; Gulati et al. 2014; Korman et al. 2007; Kuriyama et al. 2004; Manoach et al. 2009; Maquet et al. 2000; Morin et al. 2008; Nishida and Walker 2007; Rasch et al. 2009; Robertson et al. 2004; Song and Cohen 2014; Walker et al. 2002b, 2003, 2005; Wamsley et al. 2012); (2) procedural memory (Huber et al. 2004; Landsness et al. 2009; Plihal and Born 1997; Smith and MacNeill 1994; Tamaki et al. 2008); (3) visual perceptual learning (Frank et al. 2001; Gais et al. 2000; Karni et al. 1994; Mednick et al. 2002, 2003, 2008; Stickgold et al. 2000); and (4) auditory perceptual learning (Brawn et al. 2010b, 2013; Fenn et al. 2003; Gaab et al. 2004; Shank and Margoliash 2009). Other aspects of cognition that show improvement across sleep include anagram problem-solving (Walker et al. 2002b), statistical learning (Batterink et al. 2014; Batterink and Paller 2015; Durrant et al. 2011), language abstraction in infants (Gómez et al. 2006; Lany and Gómez 2008), and creative insight (Wagner et al. 2004; Yordanova et al. 2012). And of course, sleep replenishes attention, processing speed, rational decision-making, and many other cognitive processes that go beyond the scope of this chapter.

Understanding the mechanisms underlying these findings depends on elucidating how memory relates to hallmarks of sleep physiology. It has often been tempting to seek simplistic assignments between sleep stages and memory types, as if there were always one-to-one relationships. Varying methods, contradictory findings, and lumping disparate tasks into a single category have accounted for much of the confusion on this point. Countless other factors have likely had blurring effects as well—task difficulty and extent of learning influence sleep, which likely influences sleep's role in retention (Gais et al. 2002; Kuriyama et al. 2004); species differences in their learning aptitudes and sleep physiology (Buzsáki et al. 2013); human population and individual differences (Fenn and Hambrick 2012); the time between learning and sleep (Benson and Feinberg 1977); circadian differences between nap sleep and nocturnal sleep (Payne et al. 2008, 2012). However, a few general patterns have emerged, and relationships between sleep stages and learning may actually add nuances to how we understand differences between various learning categories.

Early on in sleep/memory investigations, the research focus rested entirely on REM sleep. This focus made intuitive sense, as the benefits of memory rehearsal were established, and a reasonable assumption would be that if a sleep benefit existed it would most likely come about through the reactivation of memories during dreams. Indeed, dreams were seen as a necessary phenomenon, as depriving REM sleep caused more subsequent entrances into it, as if it were a homeostatic need (Dement 1960). (The same homeostatic pressure can be observed for SWS). Accordingly, REM boosts were reported in the context of procedural learning prior to sleep, including avoidance conditioning (Smith et al. 1980), Morse code learning (Mandai et al. 1989), trampolining (Buchegger and Meier-Koll 1988), and other types of procedural learning (see Smith 2001 for a more extensive review). Later studies showed that REM sleep deprivation negatively affected learning on avoidance learning (Fishbein 1971), operant conditioning (Smith and Wong 1991), complex problem-solving tasks (Smith 1995), and visual discrimination (Karni et al. 1994). Furthermore, playing learning-related cues during subsequent REM sleep was found to strengthen complex procedural learning tasks such as Morse code learning (Guerrien et al. 1989), a complex logic task (Smith and Weeden 1990) and fear conditioning (Hars et al. 1985). These findings implicated a strong role for REM in procedural learning tasks.

This one-to-one relationship between procedural memory and REM sleep seemed to provide a clear and simple principle for sleep/memory theorizing, but it eventually broke down. For example, simpler motor tasks, such as explicit motor sequence learning and visual rotor pursuit, relied on NREM stages, especially stage 2 (Nishida and Walker 2007; Smith and MacNeill 1994; Tamaki et al. 2008; Walker et al. 2002a; though see Fischer et al. 2002, where performance in an identical task correlates with REM). In addition, pharmacological REM suppression boosted, rather than impaired, this type of learning (Rasch et al. 2009). To preserve some sort of REM sleep mapping, one way to potentially account for these findings was to invoke the idea that simpler procedural memory tasks rely on NREM sleep, whereas more complex ones rely on REM sleep (Smith et al. 2004).

On the other hand, the story grew yet more complex with new evidence implicating SWS in procedural tasks. For example, performance in a motor adaptation task correlated with measures of SWS (Huber et al. 2004), and impairments were found after SWS deprivation (Landsness et al. 2009). Also, some procedural knowledge acquired with awareness of learning can be modulated by learning-related cues during SWS (Antony et al. 2012; Cousins et al. 2014; Schönauer et al. 2014).

Finally, the preponderance of extant evidence indicates that NREM sleep underlies the consolidation of declarative memories. This is presented with a caveat that declarative memories are nearly universally studied now as item or paired associations. Studies investigating SWS and REM deprivation separately showed that, while REM deprivation had no effect on simple associations, it impaired declarative memory for full stories (Empson and Clarke 1970; Scrima 1982; Tilley and Empson 1978). Full stories are arguably more complex than associations, which accords with the role of REM in other complex cognitive tasks, such as complex procedural learning (see above), creativity in the remote associates task (Cai et al. 2009), solving anagrams (Walker et al. 2002a), Tower of Hanoi problems (Smith and Smith 2003), and categorical probabilistic learning (Djonlagic et al. 2009). Therefore, the role of REM sleep in declarative memory could be understated by the choice in tasks typically employed in these studies.

We will now delve deeper into the role of sleep, particularly NREM sleep, in declarative memory processing. We will again take a historical perspective and cover a wide range of converging evidence using different methods.

Passive vs. Active Role for Sleep in Declarative Memory

In the early part of the century, retrograde interference was one of the better-known characteristics of memory (Müller and Pilzecker 1900). As a result, Jenkins and Dallenbach (1924) ascribed sleep only a passive role in memory, in providing a temporary reprieve from constant encoding during wake. This hypothesis was plausible; indeed, an alternative view only became prominent a half-century later.

The first counter-evidence came with a pair of studies in the 1970s. First, Yaroush et al. (1971) measured memory retention over three 4-h intervals: the first half of the night, containing large amounts of deep NREM sleep; the second half of the night, containing large amounts of REM; and during 4 h of daytime wakefulness. Retention over the first 4 h of sleeping consistently trumped that for the other two conditions, indicating there may be something to NREM sleep physiology that specifically reduced forgetting. However, it was possible the effects could be explained by circadian factors, contributions from less predominant stages, or that NREM offered more of a release from interference, especially as the EEG during REM more resembled wakefulness and possibly interference from dreams. This partial sleep restriction method has also been used successfully (Plihal and Born 1997; Smith et al. 2004) to replicate the link between early, NREM-rich

sleep and declarative memory while showing that procedural memories benefit more from the later, REM-rich part of the night. The second 1970s study investigated memory retention with an equivalent amount of sleep and wakefulness, but allowed for sleep to come immediately or later on in the 24-h interval (Benson and Feinberg 1977). Better memory after immediate sleep showed that the total amount of overall interfering wakefulness could not alone explain the role of sleep in memory [a finding replicated by Gais et al. (2006), Payne et al. (2012), and Talamini et al. (2008)].

Converging evidence for memory replay during sleep accrued from neuronal reactivation in cellular physiology in the 1980s–1990s and human behavioral manipulations performed in the 2000s. The findings from cellular physiology will be discussed in the next section. First, it is helpful to cover how the behavioral studies have unfolded.

In Ellenbogen et al. (2006), Ellenbogen and colleagues set out to test whether sleep helped stabilize a memory by experimentally inducing interference. Participants learned A–B paired associates and then experienced a 12-h sleep, 12-h wake, or 24-h sleep-then-wake interval (among other conditions). Subsequently, they returned to the lab and learned A–C associates before tests on the original A–B pairs. As predicted, comparing 12-h conditions revealed superior memory for sleep over wake. However, if sleep protected memories from interference, the investigators argued, participants in the 24-h sleep-then-wake interference condition should perform better than the 12-h wake condition, even though the interval was longer and they had more time awake. This is indeed what they found.

Additional evidence for memory replay during sleep that included data on sleep physiology was produced by directly manipulating the conditions of NREM sleep. Gais and Born (2004) studied the role of low ACh levels during NREM sleep. They found that administering ACh agonists to prevent these low levels interfered with retention. Along with evidence that cholinergic activity suppresses output from the hippocampus to extrahippocampal regions (Chrobak and Buzsáki 1994; Hasselmo and McGaughy 2004), these findings suggest the low ACh levels during NREM sleep create an important state for consolidation. Using a novel approach to link SWS with memory processing, Marshall et al. (2006) directly manipulating slow oscillations using transcranial direct current stimulation at 0.8 Hz. This oscillating current, compared with sham stimulation, significantly boosted both slow oscillations and declarative memory, and thus strongly linked slow oscillations to memory consolidation.

These slow oscillations are not the only facet of sleep physiology apparently playing a role in memory processing. Despite the abundance of divergent theories about sleep spindles, as described above, they have emerged as a key physiological factor in memory consolidation. Numerous studies have demonstrated correlations between spindles and motor memory consolidation (Barakat et al. 2011; Kurdziel et al. 2013; Nishida and Walker 2007; Rasch et al. 2009; Tamaki et al. 2008; Walker et al. 2002a), as well as with declarative memory consolidation (Clemens et al. 2005, 2006; Cox et al. 2012; Schabus et al. 2004; Studte et al. 2015; van der Helm et al. 2011). However, these correlations are complicated by another line of

research showing that spindles positively correlate with general cognitive abilities (Bódizs et al. 2009; Fenn and Hambrick 2015; Schabus et al. 2006, 2008), leaving open the possibility that any memory effects are merely secondary to general cognitive effects that indirectly influence learning.

Evidence for a causal role for spindles in memory consolidation has slowly accumulated. Many researchers have employed intra-subject measures comparing learning and non-learning (control) sleep to control for individual differences. Gais et al. (2002) first showed that learning boosted spindle density during subsequent sleep. Spindle density correlated with memory at both pre- and post-nap tests, but not memory change across the nap. Schabus et al. (2004, 2008) found no boost from learning, but did find a correlation between experimental-control group density and memory retention, meaning that individuals with increased spindles showed better improvements. Schmidt et al. (2006) found that difficult learning (though not easy learning) boosted and correlated with sleep spindles, suggesting that spindles may effect changes depending on cognitive demands. Finally, learning-related spindle boosts arise in the rodent EEG (Eschenko et al. 2006) and in human epilepsy patients undergoing novel training on a brain-computer interface (Johnson et al. 2012). In a heroic effort, Bergmann et al. (2012) showed using combined fMRI-EEG that spindle amplitude increased in a specific set of brain regions related to learning but in other areas unrelated to learning. However, this increase correlated with pre-sleep memory but not with memory change across the nap.

Another indirect line of support for spindles comes from methods aimed at boosting slow oscillations. Marshall et al. (2006) could not measure spindle activity during stimulation due to artifacts caused by the current, but did find enhanced slow oscillatory activity between successive 5-min stimulation periods. Intriguingly, during these 1-min non-stimulation periods, slow spindle power was enhanced. Bolstering these findings, a later study found that playing two auditory noise bursts in time with slow oscillation up-states can similarly boost slow oscillatory power and memory (Ngo et al. 2013). This auditory stimulation protocol also boosted fast spindles, which positively correlated with memory retention. Using a different variation on this general methodology, Ong et al. (2016) also showed that acoustic stimulation to increase slow oscillations also produced an increase in fast spindles. In another follow-up experiment, Ngo et al. (2015) showed that playing four auditory bursts during up-states had no greater effect on memory than the two-burst condition, and did not elicit a further boost in fast spindle power. Altogether, these studies show that spindles may represent an essential factor mediating the effect of increased slow oscillatory power on memory enhancement.

Using a very different approach, Mednick et al. (2013) delivered the most convincing causal evidence that spindles benefit memory to date. They found that delivering zolpidem (Ambien) boosts spindle density without increasing slow oscillation power. Furthermore, spindle density increases under zolpidem predicted within-subject memory retention improvements. Although zolpidem increased time in SWS, neither this SWS measure nor slow oscillatory power predicted memory improvements under zolpidem. In a follow-up study, a similar effect of zolpidem was found on emotional memories (Kaestner et al. 2013).

In summary, there is good evidence that slow oscillations and spindles benefit memory. We will now discuss how these measures of cortical activity fit together with events occurring in the hippocampus, where newly formed memories stir.

Memory Replay During Sleep

By the 1980s, it was clear the hippocampus played an important role in forming new memories and that memories underwent a period of consolidation. However, the specific hippocampal mechanisms responsible for driving this process were largely unknown. György Buzsáki et al. (1983) described a physiological process consisting of a sharp wave in the local field potential followed by a high frequency burst (150–250 Hz, termed a ripple) occurring uniquely in the hippocampus. Intriguingly, these events were most prevalent during NREM sleep (Buzsaki 1986; Hartse et al. 1979). Buzsaki (1989) prophetically proposed that they played a role in memory consolidation. However, it was difficult to corroborate this view at the time, as evidence linking sharp-wave/ripples (SWRs) to specific memory traces was lacking.

The evidence for replay came in steps. First, Pavlides and Winson (1989) showed that hippocampal place cells with enhanced activation during wake continued to show enhanced activation during sleep. While intriguing, there remained the possibility that each cell simply kept firing on its own as a homeostatic mechanism without any relation to other cells. Wilson and McNaughton's (1994) seminal study put this concern to rest and largely legitimized future studies on sleep and memory relationships. They recorded from numerous hippocampal place cells in the hippocampus before, during, and after a rat explored a novel spatial environment. Remarkably, cell pairs that fired together while the rat explored the environment similarly fired together during post-learning sleep. Because these cells did not fire together during pre-learning sleep, the post-learning results can be attributed to learning rather than merely a function of neurons that were already highly connected.

Wilson and McNaughton's findings inspired numerous studies that expanded upon how and when replay occurred. Not only do previously co-activated place cells correlate during post-learning sleep, they fire in the same order (though with less fidelity), as if one could read out the spatial location the rat was traversing during sleep (Louie and Wilson 2001; Skaggs and McNaughton 1996). Replay of place-cell firing patterns occur most commonly during hippocampal SWRs (Dupret et al. 2010; Kudrimoti et al. 1999; O'Neill et al. 2006, 2008; Pennartz et al. 2004; Peyrache et al. 2009). Enhanced co-firing of cell pairs during wake increases replay during sleep (O'Neill et al. 2008). In relation to activity in other parts of the brain, SWRs overlap with and slightly precede sleep spindle events in other areas such as the ventral striatum (Lansink et al. 2009) and neocortex (Siapas and Wilson 1998). Moreover, wakeful hippocampal-neocortical (Ji and Wilson 2007) and neocortical-neocortical (Hoffman and McNaughton 2002) firing patterns replay during sleep.

Other details about the speed, conditions, and timing of replay have also been uncovered. Place-cell replay patterns become compressed by a factor of 6–7x during sleep (Euston et al. 2007), occur for extended events spanning as long as 10 m of track over 60 s (replaying at approximately 8 m/s) across multiple SWRs (Davidson et al. 2009), and also occur, though to a lesser extent, during wake (Carr et al. 2011; Diba and Buzsáki 2007; Dupret et al. 2010; Karlsson and Frank 2009).

Though ensemble reactivations occur most frequently during SWRs, one could argue that the large-scale synchrony that encompassed SWR events reflected previous neuronal firing without relating to memory. However, a few findings speak against this idea. First, learning (Eschenko et al. 2008; Ramadan et al. 2009) and LTP (Behrens et al. 2005; Buzsaki 1984) boost SWRs during subsequent NREM sleep. Second, reactivation events are specific to learning-related ensembles (Dupret et al. 2010; Peyrache et al. 2009) and correlate with memory retention (Dupret et al. 2010). Third, and most definitively, manipulating SWRs alters memory. Imposing replay with artificial stimulation during SWS SWRs enhances fear memory (Barnes and Wilson 2014). Suppressing SWRs impairs memory both when done during learning in a spatial working memory task (Jadhav et al. 2012) and during subsequent sleep when rodents learn a maze over a series of days (Ego-Stengel and Wilson 2009; Girardeau et al. 2009). These studies provide a crucial causal link to the role of hippocampal SWRs and memory consolidation. Since hippocampal replay occurs most frequently during SWRs, they constitute strong indirect evidence for the role of replay in memory consolidation.

Early neuroimaging studies using positron emission tomography gave the first and currently most illustrative evidence of reactivation on a systems-level. Maquet et al. (2000) showed learning-specific activation of brain areas during REM sleep that were previously activated by motor-sequence learning. In a similar vein, Peigneux et al. (2004) showed learning-specific hippocampal activation after learning a novel spatial environment, and this activation correlated with memory improvement. However, these studies showed enhanced activity over a long time scale. In contrast, one recent study (Deuker et al. 2013) enlisted multivariate methods to decode whether newly formed memories were reactivated during sleep and wake after learning. Possible reactivation patterns were observed, though puzzlingly only during stage-1 sleep. One shortcoming of this study relates to the difficulty participants had reaching deep sleep, but the presence of an effect nevertheless offers encouragement for pursuing these sorts of approaches.

Across a wide range of neuroscientific techniques, there is strong evidence that replay reflects learning. However, not all learning events are remembered in the long-term, so there must be a mechanism by which memories become differentiated over time. Below, we will cover how various factors influence spontaneous memory reactivation and how these influences may play a role in determining which memories endure.

Factors Influencing Spontaneous Reactivation

Humans form far more episodic memories than they can remember after some time passes, suggesting there are computational limits on the hippocampal-neocortical system. Thus, human memory is cluttered with competition among memories, forcing the system to devise a mechanism by which it can keep the memories deemed to be of the greatest future use, even if it comes at the expense of other, less relevant memories. Over the last decade, it has become increasingly clear that sleep plays a role in this prioritization (Fischer and Born 2009; Rauchs et al. 2011; Saletin et al. 2011; van Dongen et al. 2012b; Wilhelm et al. 2011; though see Baran et al. 2013).

A prominent theory suggests that memories of higher importance become "tagged" during wake by the hippocampus to undergo further consolidation during sleep (Morris 2006; Redondo and Morris 2011). The "synaptic tagging and capture" hypothesis (Morris 2006) suggests there are at least two steps in the consolidation process: an early-LTP process occurring at encoding that rapidly decays and a late-LTP process that involves hippocampal-neocortical dialogue and results in a relatively persistent neural trace. Central to this idea is that a molecular "tag" influenced by the early process (albeit not deterministically) signals the late process to enact enduring changes that occur during offline periods like sleep.

At the molecular level, some relationships have been worked out between early- and late-LTP, memory persistence, and NMDA- and dopamine receptor-dependence within the hippocampus (Wang et al. 2010). The amount of cell co-firing within 50 ms of learning during spatial exploration resulted in enhanced SWRs (O'Neill et al. 2008), and we previously mentioned links between learning and LTP on SWRs. Therefore, replay of tagged memories could provide a mechanism by which memories differentially persist.

Electrophysiological oscillations during wake that group neuronal activity across regions may play a role in the tagging process. At the cellular level, prefrontal neuron assemblies producing high theta coherence during learning were preferentially replayed during sleep SWRs (Benchenane et al. 2010). Similarly, a recent study in humans (Heib et al. 2015) showed theta power during word-pair encoding mediated the positive relationship between fast spindles and memory retention. Thus, theta power may reflect an effective encoding process that tags memories to undergo further consolidation.

Further evidence for differential memory tagging comes from experimental manipulations that alter the future relevance, reward, or emotional content of various items. Sleep benefits memory items that participants are directed to remember at encoding (Rauchs et al. 2011; Saletin et al. 2011), directed to bring to mind (Fischer et al. 2011), told later would be important (van Dongen et al. 2012), or would even be tested at all (Wilhelm et al. 2011). Importantly, sleep physiology appears to become biased in conjunction with this memory prioritization. Participants who expected to be tested showed a pronounced increase in slow oscillatory power and the number of spindles in relation to a control night (Wilhelm et al.

2011), and sleep spindles correlated positively with memory change for to-be-remembered items and also negatively with that for to-be-forgotten items (Saletin et al. 2011). Using a similar paradigm with fMRI, Rauchs et al. (2011) found that hippocampal activity at encoding predicted overnight changes in memory only for to-be-remembered items. Crucially, this activity failed to predict overnight changes for a separate group of subjects who were sleep-deprived. These results support the idea that memories tagged during wake undergo further processing during sleep (Morris 2006).

In rodents, a few studies found replay during SWRs occurs more frequently for memory traces that are motivationally relevant, as assessed by the presence or absence of reward (Lansink et al. 2008, 2009; Peyrache et al. 2009). Moreover, one study showed reactivation does not occur when rewarded locations are cued and no learning is required (Dupret et al. 2010), showing it relates directly with memory importance. Dopaminergic (DA) fiber bundles emanating from the ventral tegmental area (VTA) heavily control reward processes. The VTA contains fiber bundles that innervate the hippocampus and these have been shown to affect long-term potentiation within the hippocampus (Bethus et al. 2010; Lisman and Grace 2005). Additionally, one study found activity in the VTA and hippocampus predicts memory for high-reward cues (Wittmann et al. 2005), and another found functional interactions between these regions predicts long-term memory formation (Adcock et al. 2006). Therefore, DA may modulate hippocampal reactivation as a function of reward during offline periods such as sleep.

Indeed, a recent study showed direct links between VTA-hippocampal stimulation, neuronal reactivation, and memory retention (McNamara et al. 2014). The authors found that VTA neurons increased their firing rate while rats explored a novel environment. Optogenetic stimulation of VTA-hippocampal fibers increased subsequent reactivation of related memory traces, which could be blocked by administering DA antagonists before learning. Finally, this optogenetic stimulation improved memory retention. Another recent study showed that new memories could be implanted by pairing VTA-hippocampal firing with spontaneous place cell reactivation (de Lavilléon and Lacroix 2015). First, the authors separately found hippocampal place cells while rats explored a spatial environment and stimulations of VTA ensembles that animals found rewarding. Next, during offline periods of wake or sleep, spontaneous place cell reactivation was assessed online and paired with rewarding VTA-hippocampal fiber stimulation. When rats were re-introduced into the environment, they spent more time immediately in the location represented by the place cell undergoing co-activation with VTA-hippocampal fibers. Therefore, interactions between DA inputs to the hippocampus appear to strongly influence reactivation and subsequent memory retention (Atherton et al. 2015; but see Berry et al. 2015).

Two pharmacological studies support this idea by specifically highlighting the role dopamine plays in reward-enhanced consolidation. Wang et al. (2010) found that strong rewards induced persistent memory when weak rewards did not, and this enhancement could be blocked with dopamine antagonists. Additionally, in a study with human subjects, Feld et al. (2014) showed participants a number of objects

preceded by a high or low reward while administering either a dopamine agonist or placebo to participants. Under the placebo condition, high reward items were remembered better after sleep, but this difference was eliminated when participants received the dopamine agonist. These results suggest that high reward items would receive preferential processing during sleep under normal conditions, but the presence of the dopamine agonist made low items receive further processing.

Another biologically adaptive way some memories will be given priority comes from their level of emotional content (Richter-Levin and Akirav 2003). In some experimental paradigms, sleep appears to play a role in this prioritization. For instance, Payne et al. (2008) showed participants a series of pictures with a neutral or emotional central image against a neutral background (e.g., an undamaged car or a wrecked car, respectively, against a city backdrop). They tested participants after encoding and then again after 30 min, 12 h of wake, or 12 h of sleep. They found that sleep resulted in an enhanced selective benefit for emotional over neutral items relative to both the 30-min and 12-h wake intervals, demonstrating specificity for sleep in prioritizing maintenance of emotional material. The same research group has repeatedly replicated this effect (Bennion et al. 2015; Payne et al. 2012, 2015; Payne and Kensinger 2011), and other paradigms have produced comparable evidence supporting a role for sleep in emotional memory (Hu et al. 2006; Nishida et al. 2009; Wagner et al. 2001), with differential sleep effects lasting up to at least 4 years (Wagner et al. 2006).

Current conceptions of the mechanisms underlying emotional memory consolidation accord with this idea. Generally for emotional memories, amygdala activation leads to enhanced memory retention (Cahill et al. 1996; Canli et al. 2000), and enhanced amygdala-hippocampal interactions at encoding leads to better memory (Dolcos et al. 2004). Furthermore, elevated levels of the stress hormone cortisol predict higher levels of amygdala activity for negative pictures (van Stegeren et al. 2005) and predict enhanced levels of selective memory enhancement for negative stimuli after sleep (Bennion et al. 2015). Thus, a plausible mechanism is that cortisol modulates amygdala activity, which, via interactions with the hippocampus, tags memories for further rehearsal during sleep (Bennion et al. 2015).

Emotional memory consolidation presents an intriguing case for the role of emotions in REM sleep. In dream reports, REM sleep is frequently associated with greater emotional content than other stages (Fosse et al. 2001) and REM sleep also shows higher levels of amygdala activity than NREM sleep and wakefulness (Maquet et al. 1996). Accordingly, several studies have found that emotional memory retention correlates with REM sleep (Nishida et al. 2009; Payne et al. 2012; Wagner et al. 2001). These findings may, however, appear surprising, as the emotional information would certainly be categorized as an example of declarative memory, which otherwise is linked with the involvement of NREM sleep. Indeed, unlike the case with nocturnal sleep, when participants take afternoon naps they typically only attain NREM sleep, and emotional memory retention correlates with SWS measures during the nap (Payne et al. 2015). There may be more to decipher about these disparate findings, as they hint at the complexity of competing and/or complementary processes operative during the various stages of sleep.

Illuminating findings have also arisen in the context of investigations showing that sleep does not selectively benefit emotional memories. Baran et al. (2012) and Lewis et al. (2011) found no interaction between emotional versus neutral information and sleep versus wake. Additionally, Atienza and Cantero (2008) found that sleep deprivation hurt memory for emotional items less than for neutral information, suggesting that in some paradigms emotional memories are simply less susceptible to interference and may remain robust with reactivation processes that occur during wake.

These apparently contradictory findings can be reconciled. The interaction of emotion and memory is complex, and the general assertion that emotions enhance memory is by no means universal (Mather and Sutherland 2011). For instance, memories can become enhanced or inhibited depending on numerous factors at encoding, such as whether they occur before, after, or simultaneously with emotional information, their level of association with the emotional content, the level of perceptual contrast, or the relevance of the information for current goals (see Mather and Sutherland 2011, for an extensive review). Furthermore, a complex set of hormonal factors (McGaugh 2000), interactions between the amygdala and the hippocampus (Dolcos et al. 2004) or vmPFC (Bennion et al. 2015), and emotional learning during consolidation (Dunsmoor et al. 2015) can affect memory beyond the time of encoding. The type of molecular tag, including the strength of the tag and what does or does not become tagged alongside emotional information likely differs based on experimental paradigm, and this will affect what role offline processes play in memory. This research topic deserves much further attention, as it could aid treatment for disorders such as depression and post-traumatic stress disorder (LaBar and Cabeza 2006).

In this section, we have outlined some major factors that naturally influence memory reactivation. In the next section, we will discuss a relatively new method that involves artificially targeting memories for reactivation at specific times during sleep.

Targeted Declarative Memory Reactivation

As with many aspects of science and human thought, speculations and unexplained findings supported the idea that TMR could work long before it became part of established and accepted ways of thinking. In the late 1980s and early 1990s, a few studies showed altered memory after linking a stimulus with a learning episode and re-administering the stimulus as a memory cue during EEG-verified sleep. In some of the first successful studies employing TMR, Hars et al. (1985) enhanced active avoidance conditioning in rats by cueing during REM, whereas Hennevin and Hars (1987) impaired the same type of learning by cueing during SWS. Hars and Hennevin (1990) again found an effect for REM stimulation impairing spatial memories. In human participants, Smith and Weeden (1990) enhanced Morse code learning by re-playing learning-related auditory clicks during REM sleep.

To understand why these studies were largely ignored, it is important to note these studies preceded much of the reactivation literature that grounded sleep and memory at the neuronal level. Furthermore, the mechanisms at work during the various sleep stages were largely unknown. To be sure, the mechanisms for each of these effects are still somewhat mysterious, though with current knowledge of neuronal reactivation mechanisms in TMR, it is easier to envision their workings.

In a seminal study, Rasch et al. (2007) revived TMR and bolstered the idea that memories are actively reprocessed during sleep. Participants learned pairs of pictures on a spatial grid akin to a memory game, all while smelling a rose odor. Next, they slept in the lab, and some subjects received the rose odor again upon entering SWS. After waking up, those receiving the rose odor remembered significantly more pairs than those who did not. This method failed to boost memory when the rose cue was delivered during wake, or during REM, or when the rose odor was delivered during SWS but was not present during learning, demonstrating the specificity of reactivation of the learning episode.

Rudoy et al. (2009) followed up on this finding to investigate its specificity for individual memories (Fig. 2a). Participants learned 50 object-location associations against a background grid and a semantically related sound cue played concurrently with each visual object presentation (e.g. cat image—"meow" sound). During a subsequent afternoon nap, Rudoy used 25 sounds to cue half of the object locations during SWS. After the nap, participants recalled locations more accurately for objects associated with those sounds, in comparison to objects associated with sounds not presented during sleep, showing that TMR can be used to reactivate individual memories.

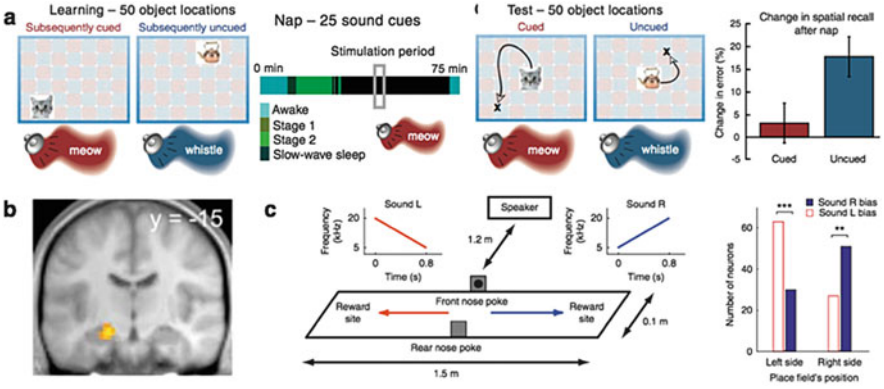

Fig. 2 Mechanisms of targeted declarative memory reactivation during sleep. (**a**) After unique auditory cues were paired with individual items, presenting those cues during subsequent SWS significantly enhanced memory (Rudoy et al. 2009). (**b**) Targeting memories using olfactory stimuli resulted in enhanced activity in the hippocampus (Rasch et al. 2007). (**c**) After unique cues were paired with different locations in a rectangular grid, presenting the cues during sleep resulted in enhanced firing of corresponding place cells (Bendor and Wilson 2012). Such biased cellular firing patterns presents a plausible mechanism by which targeting memories results in differential memory performance

Numerous other studies have subsequently shown TMR benefits and begun to elucidate the corresponding neural mechanisms. TMR enhances spatial memories via specific odors (Rihm et al. 2014), otherwise forgotten low-priority memories (Oudiette et al. 2013), memories of moderate initial strength (Creery et al. 2014), emotional memories (Cairney et al. 2015), and vocabulary words with the words as cues (Schreiner and Rasch 2014; Schreiner et al. 2015). It reduces subsequent retroactive interference (Diekelmann et al. 2011) and accelerates the consolidation process (Diekelmann et al. 2012). Additionally, stimulation boosts spindle power over learning-related regions (Cox et al. 2014), and enhances parahippocampal-mPFC connectivity (van Dongen et al. 2012a), implicating spindles and dialogue with the neocortex as possible underlying mechanisms.

In line with the expectation that targeted memory reactivation should resemble spontaneous memory reactivation, four studies suggest a role for replay in TMR. The first showed that cueing a bird's own newly-learned song during post-learning sleep elicited replay of neurons involved in forming the memory (Dave and Margoliash 2000). The second showed with fMRI that odor presence enhanced activity in the hippocampus relative to its absence (Rasch et al. 2007; Fig. 2b). The third involved cueing different sounds as rats explored the two sides of a rectangular environment (Bendor and Wilson 2012; Fig. 2c). Upon subsequent sleep, the sounds elicited corresponding place cell activity for each respective side of the grid, suggesting the cues directly activated the neurons involved in forming those memories. The fourth showed that patients with bilateral hippocampal lesions did not benefit from TMR and that memory benefits from TMR correlated inversely with amount of hippocampal damage (Fuentemilla et al. 2013), offering causal evidence that the hippocampus plays an important role in TMR.

Finally, TMR has been shown to influence other types of cognition such as creativity (Ritter et al. 2012), procedural memories (Antony et al. 2012; Cousins et al. 2014; Schönauer et al. 2014), fear memories (Barnes and Wilson 2014; Hauner et al. 2013; Rolls et al. 2013), and learning to reduce implicit social biases (Hu et al. 2015).

Basic Model of Sleep Reactivation and Major Open Questions

The aforementioned lines of evidence can be integrated into a basic model of declarative memory consolidation (Fig. 3). Hippocampal SWRs time-lock to slow wave up-states (Mölle et al. 2006), neocortical spindles time-lock to slow wave up-states (Mölle et al. 2011), and SWRs time-lock to spindle down-states during the slow-wave up-state (Ayoub et al. 2012; Siapas and Wilson 1998; Staresina et al. 2015). This scheme suggests that slow waves coordinate reactivation in the form of hippocampal-neocortical dialogue, like a conductor leading an orchestra (Mölle and Born 2011). However, there are major open questions and a few possible contradictions about the processes underlying reactivation.

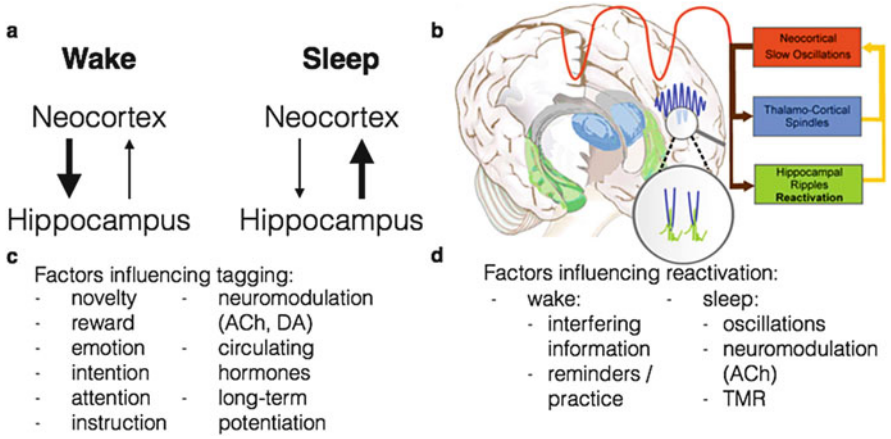

Fig. 3 Overview of sleep-dependent declarative memory consolidation. (**a**) Newly-encoded neural traces formed in the hippocampus become reactivated and consolidated via interactions with the neocortex. (**b**) Prominent theories suggest slow oscillations group hippocampal SWRs and thalamocortical spindles to coordinate hippocampal-neocortical transfer (from Born and Wilhelm 2012). (**c**) Numerous factors influence the filtering process determining which memories become later reactivated. (**d**) Reactivation processes operate on tagged neural traces to influence the later stability of the memory trace. Many of the factors in (**c**) and (**d**) are highly interrelated concepts from different levels of analysis

One major question involves the role of various parts of NREM sleep in declarative memory consolidation. A recent review (Genzel et al. 2013) argues there is likely a difference between lighter NREM sleep (stage-2 sleep and early SWS) and deep NREM sleep (late SWS). Slow oscillations are more frequently global in nature during light NREM sleep (Nir et al. 2011), which likely improves coordination between disparate brain areas such as the hippocampus and neocortex. Furthermore, SWRs (Clemens et al. 2007) and spindles (de Gennaro and Ferrara 2003) occur more frequently during lighter NREM stages, though this could be due to analysis issues with respect to identifying spindles by eye when they are superimposed on predominant slow oscillations (Cox et al. 2012). Efforts to boost memory via inducing slow oscillations with stimulation have begun in stage-2 sleep (Marshall et al. 2006; Ngo et al. 2013), creating the possibility that changes crucial for memory occurred in early NREM stages. Additional confusion might have arisen due to differences in sleep-stage terminology in humans and animal models, whereby SWS has been used as a term for all of NREM sleep (Genzel et al. 2013). Altogether, considering physiological differences in the hippocampus and neocortex, the distinction of early and late NREM for declarative memory is plausible and well worth further investigation.

The open issue above highlights another set of troubling complexities with respect to the role of spindles. As reviewed above, much of the evidence on spindles to date could be attributed to correlation rather than causation. Despite this, converging evidence from four sources implicates a direct role of spindles in

stabilizing memories: (1) methods showing causal roles for slow oscillations in memory also boost spindle power, suggesting that spindles could mediate the effect of slow oscillations on memory (Marshall et al. 2006; Ngo et al. 2013, 2015), (2) TMR induces spindle amplitude enhancements for learning-specific brain regions (Cox et al. 2014), (3) spindles have specifically been shown to enhance long-term potentiation between synapses *in vitro* (Rosanova and Ulrich 2005), and (4) a pharmacological method to induce spindles enhances memory (Kaestner et al. 2013; Mednick et al. 2013). However, none of these findings show that spindles benefit memory directly. For example, the pharmacological results could reflect changes in other underlying processes (e.g., hippocampal SWRs) that indirectly influence spindles. Additionally, real-time evidence for the role of spindles in reactivation remains obscure, and questions remain about whether neural measures of reactivation precede, become embedded in, or follow the spindle itself.

Other key questions arise about the nature of reactivation. On the cellular level, there is at least a basic understanding that hippocampal replay re-emerges during post-learning sleep and affects later memory retention (Ego-Stengel and Wilson 2009; Girardeau et al. 2009). To date, researchers investigating relationships between replay and behavior have understandably focused on the fidelity of offline reactivation to learning episodes. However, in addition to memory, sleep aids the generalization and abstraction of information, which may rely on reactivation (Stickgold and Walker 2013). In this light, findings in rodents (Karlsson and Frank 2009) that replay has higher fidelity during wake than sleep may prove illuminating. It would be interesting to discover if these abilities rely not on high-fidelity replay, but on some intermediate level of replay fidelity that allows for the incorporating the trace into other semantic networks or statistically similar episodes.

A different line of research has begun to outline the molecular mechanisms required for long-term plasticity (Takeuchi et al. 2014). However, it is currently unknown how cellular reactivation interacts with plasticity on the single neuron level. Specifically, would blocking reactivation (for instance, using optogenetics) prevent placticity? Or vice versa, would blocking plasticity, as with protein synthesis inhibitors and/or post-translational modification regulators (Routtenberg and Rekart 2005) reduce reactivation?

On the systems level, there is no clear picture for what constitutes reactivation. Over a full night of sleep, learning-related neural activity becomes enhanced (Deuker et al. 2013; Maquet et al. 2000; Peigneux et al. 2004) and correlates with memory retention (Deuker et al. 2013; Peigneux et al. 2004), and TMR/fMRI studies have also implicated enhanced activity in medial temporal lobe structures (Rasch et al. 2007; van Dongen et al. 2012a). However, we currently lack solid real-time evidence of systems-level reactivation to correspond with results from neuronal reactivation, although methods such as EEG or MEG hold promise in this regard. Also, it remains unclear exactly how reactivation events are connected to hallmarks of sleep physiology such as slow oscillations and spindles.

Finally, the timescale for systematic changes in the neural locus of memories is not understood. Mander et al. (2011) showed that sleep, as opposed to wake, can

promote the acquisition of new declarative memories, and this improvement correlates with spindle activity. Sleep may therefore act as a way to "refresh" the hippocampus to learn anew the next day, which accords with findings that sleep enhances activation in the neocortex while reducing it in the hippocampus (Takashima et al. 2009). However, discrepancies exist between this model and the effects of hippocampal damage, which typically cause retrograde amnesia for memories formed over much longer time periods. Critically, there is scant experimental evidence on the extent to which reactivation occurs for memories more than a single day old. How long does it take for memories to become independent of the hippocampus? And does sleep reactivation continue to play a role beyond even the first day of memory formation?

Concluding Thoughts

In 2005, *Science* magazine released a list of the 125 biggest questions the field of science had yet to answer. Among them was, "Why do we sleep?" and "Why do we dream?" Both remain perplexing. Why we spend a third of our lives in near-complete inactivity has thus far eluded scientists. This is likely because, as with many solutions to environmental pressures during evolution, there is no singular purpose but rather a series of co-opted adaptations that best fit ecological niches.

Some lines of evidence suggest that sleep protects an agent from predators (Siegel 2009) and aids brain metabolism and restoration (Silva et al. 2004; Vyazovskiy et al. 2008, 2009, 2011; Xie et al. 2013; see Vyazovskiy and Harris 2013 and Tononi and Cirelli 2014 for helpful reviews). More pertinent to this chapter, a recent theory posited that certain types of brain plasticity may only become possible after the organism becomes detached from the environment, so sleep may be the price paid for plasticity (Tononi and Cirelli 2014). Considering the presence of circadian rhythms and sleep patterns in organisms without our complex system of memory (Cirelli and Tononi 2008), the argument that sleep evolved originally and primarily for memory is not strong.

However, that sleep plays a unique role in learning and memory has gradually become an irrefutable position. Throughout evolution, many organs and networks of cells originally evolved for one purpose and have later been used for another. The inner ear originally evolved in early vertebrates for balance, but later became involved in hearing (Torres and Giraldez 1998). The brain itself evolved to coordinate movement, but has clearly taken on numerous other abilities. Thus, it seems highly plausible that sleep originally evolved for purposes other than plasticity, but became co-opted later as new selection pressures incentivized the need for greater plasticity.

Behavioral, cellular, and systems level evidence suggests NREM sleep plays a special role, though perhaps not an exclusive role, in consolidating declarative memories. Reactivation is instrumental to our ability to retain information from a single, unique episode. One could easily envision a world in which no moment

effectively lived beyond the present. Humans forget most of their life's episodes, as the natural, entropic fate of any episode is oblivion. However, offline reactivation can rescue otherwise fleeting episodes, especially those of high priority like the experience of the young scientist on her interview outlined at the beginning of this chapter. That the hippocampal-neocortical system has evolved a way to solidify experiences that were formed only once is a marvel, and that it co-opted natural sleep processes to effect its end is another testament to nature's ability to find unique solutions to adaptation challenges.

Acknowledgements Parts of this chapter were adapted from James Antony's Ph.D. thesis. We offer special thanks to Paul Reber for his insightful comments and Aryeh Routtenberg for his willingness to discuss these topics in detail. This work was supported by NIMH grant F31MH100958 and Princeton University's C.V. Starr Fellowship to JWA and NSF grants NSF BCS-1461088 and BCS-1533512 to KAP.

References

Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JDE (2006) Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron 50(3): 507–517. doi:10.1016/j.neuron.2006.03.036

Albouy G, King BR, Maquet P, Doyon J (2013) Hippocampus and striatum: dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. Hippocampus 23(11):985–1004. doi:10.1002/hipo.22183

Antony JW, Gobel EW, O'Hare JK, Reber PJ, Paller KA (2012) Cued memory reactivation during sleep influences skill learning. Nat Neurosci 15(8):1114–1116. doi:10.1038/nn.3152

Atherton LA, Dupret D, Mellor JR (2015) Memory trace replay: the shaping of memory consolidation by neuromodulation. Trends Neurosci 38(9):560–570. doi:10.1016/j.tins.2015.07.004

Atienza M, Cantero JL (2008) Modulatory effects of emotion and sleep on recollection and familiarity. J Sleep Res 17:285–294. doi:10.1111/j.1365-2869.2008.00661.x

Ayoub A, Mölle M, Preissl H, Born J (2012) Grouping of MEG gamma oscillations by EEG sleep spindles. NeuroImage 59(2):1491–1500. doi:10.1016/j.neuroimage.2011.08.023

Barakat M, Doyon J, Debas K, Vandewalle G, Morin A, Poirier G et al (2011) Fast and slow spindle involvement in the consolidation of a new motor sequence. Behav Brain Res 217(1): 117–121

Baran B, Pace-Schott EF, Ericson C, Spencer RMC (2012) Processing of emotional reactivity and emotional memory over sleep. J Neurosci 32(3):1035–1042. doi:10.1523/JNEUROSCI.2532-11.2012

Baran B, Daniels D, Spencer RMC (2013) Sleep-dependent consolidation of value-based learning. PLoS One 8(10):e75326. doi:10.1371/journal.pone.0075326

Barnes DC, Wilson DA (2014) Slow-wave sleep-imposed replay modulates both strength and precision of memory. J Neurosci 34(15):5134–5142. doi:10.1523/JNEUROSCI.5274-13.2014

Batterink LJ, Paller KA (2015) Sleep-based memory processing facilitates grammatical generalization: evidence from targeted memory reactivation. Brain Lang. Available online Oct 3, 2015 [Epub ahead of print]. doi:10.1016/j.bandl.2015.09.003

Batterink LJ, Oudiette D, Reber PJ, Paller KA (2014) Sleep facilitates learning a new linguistic rule. Neuropsychologia 65(2014):169–179. doi:10.1016/j.neuropsychologia.2014.10.024

Behrens CJ, van den Boom LP, de Hoz L, Friedman A, Heinemann U (2005) Induction of sharp wave-ripple complexes in vitro and reorganization of hippocampal networks. Nat Neurosci 8(11):1560–1567. doi:10.1038/nn1571

Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, Battaglia FP, Wiener SI (2010) Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. Neuron 66(6):921–936. doi:10.1016/j.neuron.2010.05.013

Bendor D, Wilson MA (2012) Biasing the content of hippocampal replay during sleep. Nat Neurosci 15(10):1439–1444. doi:10.1038/nn.3203

Bennion KA, Mickley Steinmetz KR, Kensinger EA, Payne JD (2015) Sleep and cortisol interact to support memory consolidation. Cereb Cortex 25(3):646–657

Benson K, Feinberg I (1977) The beneficial effect of sleep in an extended Jenkins and Dallenbach paradigm. Psychophysiology 14(4):375–384

Ben-Yakov A, Eshel N, Dudai Y (2013) Hippocampal immediate poststimulus activity in the encoding of consecutive naturalistic episodes. J Exp Psychol Gen 142(4):1255–1263. doi:10.1037/a0033558

Bergmann TO, Mölle M, Diedrichs J, Born J, Siebner HR (2012) Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. NeuroImage 59(3):2733–2742

Berry JA, Cervantes-Sandoval I, Chakraborty M, Davis RL (2015) Sleep facilitates memory by blocking dopamine neuron-mediated forgetting. Cell 161(7):1656–1667. doi:10.1016/j.cell.2015.05.027

Bethus I, Tse D, Morris RGM (2010) Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. J Neurosci 30(5):1610–1618. doi:10.1523/JNEUROSCI.2721-09.2010

Bódizs R, Körmendi J, Rigó P, Lázár AS (2009) The individual adjustment method of sleep spindle analysis: methodological improvements and roots in the fingerprint paradigm. J Neurosci Methods 178(1):205–213

Born J, Wilhelm I (2012) System consolidation of memory during sleep. Psychol Res 76(2):192–203

Brain R (1958) The physiological basis of consciousness: a critical review. Brain 81(3):426–455. doi:10.1093/brain/81.3.426

Brawn TP, Fenn KM, Nusbaum HC, Margoliash D (2010a) Consolidating the effects of waking and sleep on motor-sequence learning. J Neurosci 30(42):13977–13982. doi:10.1523/JNEUROSCI.3295-10.2010

Brawn TP, Nusbaum HC, Margoliash D (2010b) Sleep-dependent consolidation of auditory discrimination learning in adult starlings. J Neurosci 30(2):609–613. doi:10.1523/JNEUROSCI.4237-09.2010

Brawn TP, Nusbaum HC, Margoliash D (2013) Sleep consolidation of interfering auditory memories in starlings. Psychol Sci 24(4):439–447. doi:10.1177/0956797612457391

Bremer F (1954) The neurophysiological problem of sleep. In: Adrian E, Bremer F, Japser H (eds) Brain mechanisms and consciousness. Blackwell, Oxford, pp 137–162

Buchegger J, Meier-Koll A (1988) Motor learning and ultradian sleep cycle: an electroencephalographic study of trampoliners. Percept Mot Skills 67(1972):635–645

Buchsbaum BR, Lemire-Rodger S, Fang C, Abdi H (2012) The neural basis of vivid memory is patterned on perception. J Cogn Neurosci 24(9):1867–1883

Buzsaki G (1984) Long-term changes of hippocampal sharp-waves following high frequency afferent activation. Brain Res 300(1):179–182. doi:10.1016/0006-8993(84)91356-8

Buzsaki G (1986) Hippocampal sharp waves: their origin and significance. Brain Res 398:242–252

Buzsaki G (1989) Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 31(3):551–570

Buzsáki G, Lai-Wo SL, Vanderwolf CH (1983) Cellular bases of hippocampal EEG in the behaving rat. Brain Res Rev 6(2):139–171. doi:10.1016/0165-0173(83)90037-1

Buzsáki G, Logothetis N, Singer W (2013) Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. Neuron 80(3):751–764. doi:10.1016/j.neuron.2013.10.002

Cahill L, Haiert RJ, Fallon J, Alkirei MT, Tangii C, Keatorii D et al (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proc Natl Acad Sci USA 93:8016–8021

Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC (2009) REM, not incubation, improves creativity by priming associative networks. Proc Natl Acad Sci 106(25):10130–10134

Cairney SA, Durrant SJ, Power R, Lewis PA (2015) Complementary roles of slow-wave sleep and rapid eye movement sleep in emotional memory consolidation. Cereb Cortex 25(6): 1565–1575. doi:10.1093/cercor/bht349

Canli T, Zhao Z, Brewer J, Gabrieli JD, Cahill L (2000) Event-related activation in the human amygdala associates with later memory for individual emotional experience. J Neurosci 20(19):RC99 20004570 [pii]

Carr MF, Jadhav SP, Frank LM (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. Nat Neurosci 14(2):147–153. doi:10.1038/nn.2732

Cash SS, Halgren E, Dehghani N, Rossetti AO, Thesen T, Wang C et al (2009) The human K-complex represents an isolated cortical down-state. Science 324(5930):1084–1087. doi:10.1126/science.1169626

Chrobak JJ, Buzsáki G (1994) Selective activation of deep layer (V-VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. J Neurosci 14(10):6160–6170

Cirelli C, Tononi G (2008) Is sleep essential? PLoS Biol 6(8):1605–1611

Clemens Z, Fabó D, Halász P (2005) Overnight verbal memory retention correlates with the number of sleep spindles. Neuroscience 132(2):529–535

Clemens Z, Fabó D, Halász P (2006) Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 403(1-2):52–56

Clemens Z, Mölle M, Eross L, Barsi P, Halász P, Born J (2007) Temporal coupling of parahippocampal ripples, sleep spindles and slow oscillations in humans. Brain 130: 2868–2878

Cohen DA, Pascual-Leone A, Press DZ, Robertson EM (2005) Off-line learning of motor skill memory: a double dissociation of goal and movement. Proc Natl Acad Sci USA 102(50): 18237–18241. doi:10.1073/pnas.0506072102

Corkin S (2013) Permanent present tense. Basic Books, New York, NY

Cote K, Epps T, Campbell K (2000) The role of the spindle in human information processing of high-intensity stimuli during sleep. J Sleep Res 9:19–26

Cousins JN, El-Deredy W, Parkes LM, Hennies N, Lewis PA (2014) Cued memory reactivation during slow-wave sleep promotes explicit knowledge of a motor sequence. J Neurosci 34(48): 15870–15876. doi:10.1523/JNEUROSCI.1011-14.2014

Cox R, Hofman WF, Talamini LM (2012) Involvement of spindles in memory consolidation is slow wave sleep-specific. Learn Mem 19(7):264–267

Cox R, Hofman WF, de Boer M, Talamini LM (2014) Local sleep spindle modulations in relation to specific memory cues. NeuroImage 99:103–110 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24852461

Craig M, Dewar M, Della Sala S, Wolbers T (2015a) Rest boosts the long-term retention of spatial associative and temporal order information. Hippocampus 25:1017–1027. doi:10.1002/hipo.22424

Craig M, Dewar M, Harris MA, Della Sala S, Wolbers T (2015b) Wakeful rest promotes the integration of spatial memories into accurate cognitive maps. Hippocampus. doi:10.1002/hipo.22502

Creery JD, Oudiette D, Antony JW, Paller KA (2014) Targeted memory reactivation during sleep depends on prior learning. Sleep 38(5):755–763 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25515103

Dang-Vu TT, McKinney SM, Buxton OM, Solet JM, Ellenbogen JM (2010) Spontaneous brain rhythms predict sleep stability in the face of noise. Curr Biol 20(15):R626–R627

Dang-Vu TT, Bonjean M, Schabus M, Boly M, Darsaud A, Desseilles M et al (2011) Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. Proc Natl Acad Sci USA 108(37):15438–15443

Dave A, Margoliash D (2000) Song replay during sleep and computational rules for sensorimotor vocal learning. Science 290(5492):812–816. doi:10.1126/science.290.5492.812

Davidson TJ, Kloosterman F, Wilson MA (2009) Hippocampal replay of extended experience. Neuron 63(4):497–507. doi:10.1016/j.neuron.2009.07.027
de Gennaro L, Ferrara M (2003) Sleep spindles: an overview. Sleep Med Rev 7(5):423–440
de Lavilléon G, Lacroix MM (2015) Explicit memory creation during sleep demonstrates a causal role of place cells in navigation. Nat Neurosci 18:493–495. doi:10.1038/nn.3970
Dement W (1960) The effect of dream deprivation. Science 131(3415):1705–1707. doi:10.1126/science.131.3415.1705
Deuker L, Olligs J, Fell J, Kranz TA, Mormann F, Montag C et al (2013) Memory consolidation by replay of stimulus-specific neural activity. J Neurosci 33(49):19373–19383. doi:10.1523/JNEUROSCI.0414-13.2013
Dewar M, Alber J, Butler C, Cowan N, Della Sala S (2012) Brief wakeful resting boosts new memories over the long term. Psychol Sci 23(9):955–960. doi:10.1177/0956797612441220
Diba K, Buzsáki G (2007) Forward and reverse hippocampal place-cell sequences during ripples. Nat Neurosci 10(10):1241–1242. doi:10.1038/nn1961
Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11(2):114–126
Diekelmann S, Büchel C, Born J, Rasch B (2011) Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nat Neurosci 14(3):381–386. doi:10.1038/nn.2744
Diekelmann S, Biggel S, Rasch B, Born J (2012) Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. Neurobiol Learn Mem 98(2):103–111. doi:10.1016/j.nlm.2012.07.002
Djonlagic I, Rosenfeld A, Shohamy D, Djonlagic I, Rosenfeld A, Shohamy D, Myers C, Gluck M, Stickgold R (2009) Sleep enhances category learning. Learn Mem 16:751–755
Dolcos F, Labar KS, Cabeza R (2004) Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. Neuron 42:855–863
Dunsmoor JE, Murty VP, Davachi L, Phelps EA (2015) Emotional learning selectively and retroactively strengthens memories for related events. Nature 520:345–348. doi:10.1038/nature14106
Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J (2010) The reorganization and reactivation of hippocampal maps predict spatial memory performance. Nat Neurosci 13(8):995–1002. doi:10.1038/nn.2599
Durrant SJ, Taylor C, Cairney S, Lewis PA (2011) Sleep-dependent consolidation of statistical learning. Neuropsychologia 49(5):1322–1331. doi:10.1016/j.neuropsychologia.2011.02.015
Ebbinghaus H (1885) Memory: a contribution to experimental psychology. Columbia University Press, New York
Ego-Stengel V, Wilson MA (2009) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20(1):1–10. doi:10.1002/hipo.20707
Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL (2006) Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. Curr Biol 16(13):1290–1294. doi:10.1016/j.cub.2006.05.024
Empson J, Clarke P (1970) Rapid eye movements and remembering. Nature 227:287–288
Eschenko O, Mölle M, Born J, Sara SJ (2006) Elevated sleep spindle density after learning or after retrieval in rats. J Neurosci 26(50):12914–12920
Eschenko O, Ramadan W, Mölle M, Born J, Sara S (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. Learn Mem 15:222–228
Euston DR, Tatsuno M, McNaughton BL (2007) Fast-forward playback of recent memory sequences in prefrontal cortex during sleep. Science 318(5853):1147–1150. doi:10.1126/science.1148979
Feld GB, Besedovsky L, Kaida K, Münte TF, Born J (2014) Dopamine D2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. J Cogn Neurosci 26(10):2310–2320. doi:10.1162/jocn
Fenn KM, Hambrick DZ (2012) Individual differences in working memory capacity predict sleep-dependent memory consolidation. J Exp Psychol Gen 141(3):404–410. doi:10.1037/a0025268

Fenn KM, Hambrick DZ (2015) General intelligence predicts memory change across sleep. Psychon Bull Rev 22(3):791–799. doi:10.3758/s13423-014-0731-1
Fenn KM, Nusbaum HC, Margoliash D (2003) Consolidation during sleep of perceptual learning of spoken language. Nature 425:614–616. doi:10.1038/nature01971.1
Fischer S, Born J (2009) Anticipated reward enhances offline learning during sleep. J Exp Psychol Learn Mem Cogn 35(6):1586–1593. doi:10.1037/a0017256
Fischer S, Hallschmid M, Elsner AL, Born J (2002) Sleep forms memory for finger skills. Proc Natl Acad Sci USA 99(18):11987–11991
Fischer S, Diekelmann S, Born J (2011) Sleep's role in the processing of unwanted memories. J Sleep Res 20(2):267–274. doi:10.1111/j.1365-2869.2010.00881.x
Fishbein W (1971) Disruptive effects of rapid eye movement sleep deprivation on long-term memory. Physiol Behav 6(1):279–282
Fogel SM, Smith CT (2006) Learning-dependent changes in sleep spindles and Stage 2 sleep. J Sleep Res 15:250–255
Fosse R, Stickgold R, Hobson JA (2001) The mind in REM sleep: reports of emotional experience. Sleep 24(8):947–955 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11766165
Frank MG, Issa NP, Stryker MP (2001) Sleep enhances plasticity in the developing visual cortex. Neuron 30:275–287
Freud S (1913) The interpretation of dreams. Macmillan, New York, NY
Fuentemilla L, Miró J, Ripollés P, Vilà-Balló A, Juncadella M, Castañer S et al (2013) Hippocampus-dependent strengthening of targeted memories via reactivation during sleep in humans. Curr Biol 23(18):1769–1775. doi:10.1016/j.cub.2013.07.006
Gaab N, Paetzold M, Becker M, Walker MP, Schlaug G (2004) The influence of sleep on auditory learning: a behavioral study. NeuroReport 15(4):731–734. doi:10.1097/01.wnr.0000113532.32218.d6
Gais S, Born J (2004) Declarative memory consolidation: mechanisms acting during human sleep. Learn Mem 11(6):679–685. doi:10.1101/lm.80504
Gais S, Plihal W, Wagner U, Born J (2000) Early sleep triggers memory for early visual discrimination skills. Nat Neurosci 3(12):1335–1339
Gais S, Mo M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22(15):6830–6834
Gais S, Lucas B, Born J (2006) Sleep after learning aids memory recall. Learn Mem 13(3):259–262. doi:10.1101/lm.132106
Gelbard-Sagiv H, Mukamel R, Harel M, Malach R, Fried I (2008) Internally generated reactivation of single neurons in human hippocampus during free recall. Science 322(5898):96–101. doi:10.1126/science.1164685
Genzel L, Kroes MCW, Dresler M, Battaglia FP (2013) Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends Neurosci 37(1):1–10. doi:10.1016/j.tins.2013.10.002
Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB (2009) Selective suppression of hippocampal ripples impairs spatial memory. Nat Neurosci 12(10):1222–1223. doi:10.1038/nn.2384
Godden D, Baddeley A (1975) Context-dependent memory in two natural environments: on land and underwater. Br J Psychol 66(3):325–331
Gómez RL, Bootzin RR, Nadel L (2006) Naps promote abstraction in language-learning infants. Psychol Sci 17(8):670–674. doi:10.1111/j.1467-9280.2006.01764.x
Guerrien A, Dujardin K, Mandai O, Sockeel P, Leconte P (1989) Enhancement of memory by auditory stimulation during postlearning REM sleep in humans. Physiol Behav 45:947–950
Gulati T, Ramanathan DS, Wong CC, Ganguly K (2014) Reactivation of emergent task-related ensembles during slow-wave sleep after neuroprosthetic learning. Nat Neurosci 17(8):1107–1113. doi:10.1038/nn.3759
Hars B, Hennevin E (1990) Reactivation of an old memory during sleep and wakefulness. Anim Learn Behav 18(4):365–376

Hars B, Hennevin E, Pasques P (1985) Improvement of learning by cueing during postlearning paradoxical sleep. Behav Brain Res 18:241–250

Hartse KM, Eisenhart SF, Bergmann BM, Rechtschaffen A (1979) Ventral hippocampus spikes during sleep, wakefulness, and arousal in the cat. Sleep 1(3):231–246

Hasselmo ME, McGaughy J (2004) High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. Prog Brain Res 145:207–231. doi:10.1016/S0079-6123(03)45015-2

Hauner KK, Howard JD, Zelano C, Gottfried JA (2013) Stimulus-specific enhancement of fear extinction during slow-wave sleep. Nat Neurosci 16(11):1553–1555. doi:10.1038/nn.3527

Heib DPJ, Hoedlmoser K, Anderer P, Gruber G, Zeitlhofer J, Schabus M (2015) Oscillatory theta activity during memory formation and its impact on overnight consolidation: a missing link? J Cogn Neurosci 27(8):1648–1658. doi:10.1162/jocn

Hennevin E, Hars B (1987) Is increase in post-learning paradoxical sleep modified by cueing? Behav Brain Res 24(3):243–249

Hoffman K, McNaughton B (2002) Coordinated reactivation of distributed memory traces in primate neocortex. Science 297:2070–2073

Hu P, Stylos-Allan M, Walker MP (2006) Sleep facilitates consolidation of emotional declarative memory. Psychol Sci 17(10):891–898

Hu X, Antony JW, Creery JD, Vargas IM, Bodenhausen GV, Paller KA (2015) Unlearning implicit social biases during sleep. Science 348(6238):1013–1015

Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning. Nature 430: 78–81

Jadhav SP, Kemere C, German PW, Frank LM (2012) Awake hippocampal sharp-wave ripples support spatial memory. Science 336(6087):1454–1458. doi:10.1126/science.1217230

Jenkins J, Dallenbach K (1924) Obliviscence during sleep and waking. Am J Psychol 35(4): 605–612

Jensen LC, Harris K, Anderson DC (1971) Retention following a change in ambient contextual stimuli for six age groups. Dev Psychol 4(3):394–399. doi:10.1037/h0030957

Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10(1):100–107. doi:10.1038/nn1825

Johnson JD, Rugg MD (2007) Recollection and the reinstatement of encoding-related cortical activity. Cereb Cortex 17(11):2507–2515. doi:10.1093/cercor/bhl156

Johnson JD, McDuff SGR, Rugg MD, Norman KA (2009) Recollection, familiarity, and cortical reinstatement: a multivoxel pattern analysis. Neuron 63(5):697–708. doi:10.1016/j.neuron.2009.08.011

Johnson L, Blakely T, Hermes D, Hakimian S, Ramsey N, Ojemann J (2012) Sleep spindles are locally modulated by training on a brain-computer interface. Proc Natl Acad Sci USA 109(45): 18583–18588

Kaestner EJ, Wixted JT, Mednick SC (2013) Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. J Cogn Neurosci 25(10): 1597–1610

Karlsson MP, Frank LM (2009) Awake replay of remote experiences in the hippocampus. Nat Neurosci 12(7):913–918. doi:10.1038/nn.2344

Karlsson Wirebring L, Wiklund-Hornqvist C, Eriksson J, Andersson M, Jonsson B, Nyberg L (2015) Lesser neural pattern similarity across repeated tests is associated with better long-term memory retention. J Neurosci 35(26):9595–9602. doi:10.1523/JNEUROSCI.3550-14.2015

Karni A, Tanne D, Rubenstein B, Askenasy J, Sagi D (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. Science 265:679–682

Korman M, Doyon J, Doljansky J, Carrier J, Dagan Y, Karni A (2007) Daytime sleep condenses the time course of motor memory consolidation. Nat Neurosci 10(9):1206–1213. doi:10.1038/nn1959

Kudrimoti HS, Barnes CA, Mcnaughton BL (1999) Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. J Neurosci 19(10):4090–4101

Kuhl BA, Shah AT, DuBrow S, Wagner AD (2010) Resistance to forgetting associated with hippocampus-mediated reactivation during new learning. Nat Neurosci 13(4):501–506. doi:10.1038/nn.2498

Kuhl BA, Bainbridge WA, Chun MM (2012a) Neural reactivation reveals mechanisms for updating memory. J Neurosci 32(10):3453–3461. doi:10.1523/JNEUROSCI.5846-11.2012

Kuhl BA, Rissman J, Wagner AD (2012b) Multi-voxel patterns of visual category representation during episodic encoding are predictive of subsequent memory. Neuropsychologia 50(4):458–469. doi:10.1016/j.neuropsychologia.2011.09.002

Kurdziel L, Duclos K, Spencer RMC (2013) Sleep spindles in midday naps enhance learning in preschool children. Proc Natl Acad Sci USA 110(43):17267–17272. doi:10.1073/pnas.1306418110

Kuriyama K, Stickgold R, Walker MP (2004) Sleep-dependent learning and motor-skill complexity. Learn Mem 11:705–713. doi:10.1101/lm.76304.appears

LaBar KS, Cabeza R (2006) Cognitive neuroscience of emotional memory. Nat Rev Neurosci 7(1):54–64. doi:10.1038/nrn1825

Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H et al (2009) Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. Sleep 32(10):1273–1284

Lansink CS, Goltstein PM, Lankelma JV, Joosten RNJMA, McNaughton BL, Pennartz CMA (2008) Preferential reactivation of motivationally relevant information in the ventral striatum. J Neurosci 28(25):6372–6382. doi:10.1523/JNEUROSCI.1054-08.2008

Lansink CS, Goltstein PM, Lankelma JV, McNaughton BL, Pennartz CMA (2009) Hippocampus leads ventral striatum in replay of place-reward information. PLoS Biol 7(8):e1000173. doi:10.1371/journal.pbio.1000173

Lany J, Gómez RL (2008) Twelve-month-old infants benefit from prior experience in statistical learning. Psychol Sci 19(12):1247–1252. doi:10.1111/j.1467-9280.2008.02233.x

Lechner H, Squire L, Byrne J (1999) 100 years of consolidation—remembering Müller and Pilzecker. Learn Mem 6:77–88

Lehmann H, McNamara KC (2011) Repeatedly reactivated memories become more resistant to hippocampal damage. Learn Mem 18(3):132–135. doi:10.1101/lm.2000811

Lehmann H, Sparks FT, Spanswick SC, Hadikin C, McDonald RJ, Sutherland RJ (2009) Making context memories independent of the hippocampus. Learn Mem 16(7):417–420. doi:10.1101/lm.1385409

Lesburguères E, Gobbo OL, Alaux-Cantin S, Hambucken A, Trifilieff P, Bontempi B (2011) Early tagging of cortical networks is required for the formation of enduring associative memory. Science 331(6019):924–928. doi:10.1126/science.1196164

Lewis PA, Cairney S, Manning L, Critchley HD (2011) The impact of overnight consolidation upon memory for emotional and neutral encoding contexts. Neuropsychologia 49:2619–2629. doi:10.1016/j.neuropsychologia.2011.05.009

Lisman JE, Grace AA (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46(5):703–713. doi:10.1016/j.neuron.2005.05.002

Louie K, Wilson MA (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. Neuron 29(1):145–156. doi:10.1016/S0896-6273(01)00186-6

Mandai O, Guerrien A, Sockeel P, Dujardin K, Leconte P (1989) REM sleep modifications following a Morse code learning session in humans. Physiol Behav 46(4):639–642. doi:10.1016/0031-9384(89)90344-2

Mander BA, Santhanam S, Saletin JM, Walker MP (2011) Wake deterioration and sleep restoration of human learning. Curr Biol 21(5):R183–R184. doi:10.1016/j.cub.2011.01.019

Manning JR, Sperling MR, Sharan A, Rosenberg EA, Kahana MJ (2012) Spontaneously reactivated patterns in frontal and temporal lobe predict semantic clustering during memory search. J Neurosci 32(26):8871–8878. doi:10.1523/JNEUROSCI.5321-11.2012

Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E et al (2009) Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia

is related to specific sleep stages. J Psychiatr Res 44(2):112–120. doi:10.1016/j.jpsychires.2009.06.011

Maquet P, Péters J, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G (1996) Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 383(6596):163–166. doi:10.1038/383163a0

Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C et al (2000) Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci 3(8):831–836

Marshall L, Helgadóttir H, Mölle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444(7119):610–613

Mather M, Sutherland MR (2011) Arousal-biased competition in -perception and memory. Perspect Psychol Sci 6:114–133. doi:10.1177/1745691611400234

Maviel T, Durkin TP, Menzaghi F, Bontempi B (2004) Sites of neocortical reorganization critical for remote spatial memory. Science 305(5680):96–99. doi:10.1126/science.1098180

McGaugh JL (2000) Memory—a century of consolidation. Science 287(5451):248–251. doi:10.1126/science.287.5451.248

McNamara CG, Tejero-Cantero Á, Trouche S, Campo-Urriza N, Dupret D (2014) Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. Nat Neurosci 17:1658–1660. doi:10.1038/nn.3843

Mednick SC, Nakayama K, Cantero JL, Atienza M, Levin AA, Pathak N, Stickgold R (2002) The restorative effect of naps on perceptual deterioration. Nat Neurosci 5(7):677–681

Mednick S, Nakayama K, Stickgold R (2003) Sleep-dependent learning: a nap is as good as a night. Nat Neurosci 6(7):697–698

Mednick SC, Drummond SPA, Arman AC, Boynton GM (2008) Perceptual deterioration is reflected in the neural response: fMRI study of nappers and non-nappers. Perception 37(7):1086–1097. doi:10.1068/p5998

Mednick S, McDevitt E, Walsh J, Wamsley E, Paulus M, Kanady J, Drummond S (2013) The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J Neurosci 33(10):4494–4504

Mölle M, Born J (2011) Slow oscillations orchestrating fast oscillations and memory consolidation. Prog Brain Res 193:93–110

Mölle M, Yeshenko O, Marshall L, Sara S, Born J (2006) Hippocampal sharp wave-ripples linked to slow oscillations in rat slow-wave sleep. J Neurophysiol 96(1):62–70

Mölle M, Bergmann T, Marshall L, Born J (2011) Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep 34(10):1411–1421

Morin A, Doyon J, Dostie V, Barakat M, Tahar AH, Korman M et al (2008) Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. Sleep 31(8):1149–1156

Morison R, Bassett D (1945) Electrical activity of the thalamus and basal ganglia in decorticate cats. J Neurophysiol 8(5):309–314

Morris RGM (2006) Elements of a neurobiological theory of hippocampal function: the role of synaptic plasticity, synaptic tagging and schemas. Eur J Neurosci 23(11):2829–2846. doi:10.1111/j.1460-9568.2006.04888.x

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C et al (2005) Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 207(1):35–66. doi:10.1111/j.1469-7580.2005.00421.x

Müller G, Pilzecker A (1900) Experimental contributions to the theory of memory. Z Psychol Ergänzungsband 1:1–300

Newman EL, Norman KA (2010) Moderate excitation leads to weakening of perceptual representations. Cereb Cortex 20(11):2760–2770. doi:10.1093/cercor/bhq021

Ngo HV, Martinetz T, Born J, Mölle M (2013) Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78(3):545–553

Ngo H, Miedema A, Faude I, Martinetz T, Molle M, Born J (2015) Driving sleep slow oscillations by auditory closed-loop stimulation—a self-limiting process. J Neurosci 35(17):6630–6638. doi:10.1523/JNEUROSCI.3133-14.2015

Nir Y, Tononi G (2010) Dreaming and the brain: from phenomenology to neurophysiology. Trends Cogn Sci 14(2):88–100. doi:10.1016/j.tics.2009.12.001

Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, Tononi G (2011) Regional slow waves and spindles in human sleep. Neuron 70(1):153–169

Nishida M, Walker MP (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. PLoS One 2(4):e341

Nishida M, Pearsall J, Buckner RL, Walker MP (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. Cereb Cortex 19:1158–1166. doi:10.1093/cercor/bhn155

Nyberg L, Habib R, McIntosh AR, Tulving E (2000) Reactivation of encoding-related brain activity during memory retrieval. Proc Natl Acad Sci USA 97(20):11120–11124. doi:10.1073/pnas.97.20.11120

O'Neill J, Senior T, Csicsvari J (2006) Place-selective firing of CA1 pyramidal cells during sharp wave/ripple network patterns in exploratory behavior. Neuron 49(1):143–155. doi:10.1016/j.neuron.2005.10.037

O'Neill J, Senior TJ, Allen K, Huxter JR, Csicsvari J (2008) Reactivation of experience-dependent cell assembly patterns in the hippocampus. Nat Neurosci 11(2):209–215. doi:10.1038/nn2037

Ong JL, Lo JC, Chee NIYN, Santostasi G, Paller KA, Zee PC, Chee MWL (2016) Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. Sleep Med 20:88–97

Oswald I, Taylor A, Treisman M (1960) Discriminative responses to stimuli during human sleep. Brain 83(3):440–453. doi:10.1093/brain/83.3.440

Oudiette D, Antony JW, Creery JD, Paller KA (2013) The role of memory reactivation during wakefulness and sleep in determining which memories endure. J Neurosci 33(15):6672–6678. doi:10.1523/JNEUROSCI.5497-12.2013

Pavlides C, Winson J (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. J Neurosci 9(8):2907–2918

Payne JD, Kensinger EA (2011) Sleep leads to changes in the emotional memory trace: evidence from fMRI. J Cogn Neurosci 23(6):1285–1297. doi:10.1162/jocn.2010.21526

Payne JD, Stickgold R, Swanberg K, Kensinger EA (2008) Sleep preferentially enhances memory for emotional components of scenes. Psychol Sci 19(8):781–788. doi:10.1111/j.1467-9280.2008.02157.x

Payne JD, Chambers AM, Kensinger EA (2012) Sleep promotes lasting changes in selective memory for emotional scenes. Front Integr Neurosci 6:108. doi:10.3389/fnint.2012.00108

Payne JD, Kensinger EA, Wamsley EJ, Spreng RN, Alger SE, Gibler K et al (2015) Napping and the selective consolidation of negative aspects of scenes. Emotion 15(2):176–186. doi:10.1037/a0038683

Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J et al (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron 44:535–545

Peigneux P, Orban P, Balteau E, Degueldre C, Luxen A, Laureys S, Maquet P (2006) Offline persistence of memory-related cerebral activity during active wakefulness. PLoS Biol 4(4):e100. doi:10.1371/journal.pbio.0040100

Pennartz CMA, Lee E, Verheul J, Lipa P, Barnes CA, McNaughton BL (2004) The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. J Neurosci 24(29):6446–6456. doi:10.1523/JNEUROSCI.0575-04.2004

Peyrache A, Khamassi M, Benchenane K, Wiener SI, Battaglia FP (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat Neurosci 12(7):919–926. doi:10.1038/nn.2337

Plihal W, Born J (1997) Effects of early and late nocturnal sleep on declarative and procedural memory. J Cogn Neurosci 9(4):534–547

Polyn SM, Natu VS, Cohen JD, Norman KA (2005) Category-specific cortical activity precedes retrieval during memory search. Science 310(5756):1963–1966. doi:10.1126/science.1117645

Ramadan W, Eschenko O, Sara SJ (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. PLoS One 4(8):1–9. doi:10.1371/journal.pone.0006697

Rasch B, Büchel C, Gais S, Born J (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. Science:1426–1429

Rasch B, Pommer J, Diekelmann S, Born J (2009) Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat Neurosci 12(4):396–397. doi:10.1038/nn.2206

Rauchs G, Feyers D, Landeau B, Bastin C, Luxen A, Maquet P, Collette F (2011) Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. J Neurosci 31(7):2563–2568. doi:10.1523/JNEUROSCI.3972-10.2011

Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system of sleep stages in human subjects. University of California, Los Angele

Redondo RL, Morris RGM (2011) Making memories last: the synaptic tagging and capture hypothesis. Nat Rev Neurosci 12(1):17–30. doi:10.1038/nrn2963

Richter-Levin G, Akirav I (2003) Emotional tagging of memory formation—in the search for neural mechanisms. Brain Res Rev 43:247–256. doi:10.1016/j.brainresrev.2003.08.005

Rihm JS, Diekelmann S, Born J, Rasch B (2014) Reactivating memories during sleep by odors: odor specificity and associated changes in sleep oscillations. J Cogn Neurosci 26(8): 1806–1818. doi:10.1162/jocn_a_00579

Ritter SM, Strick M, Bos MW, van Baaren RB, Dijksterhuis A (2012) Good morning creativity: task reactivation during sleep enhances beneficial effect of sleep on creative performance. J Sleep Res 21(6):643–647. doi:10.1111/j.1365-2869.2012.01006.x

Robertson EM, Pascual-Leone A, Press DZ (2004) Awareness modifies the skill-learning benefits of sleep. Curr Biol 14(3):208–212. doi:10.1016/j.cub.2004.01.027

Roediger HL, Karpicke JD (2006) The power of testing memory: basic research and implications for educational practice. Perspect Psychol Sci 1(3):181–210

Rolls A, Makam M, Kroeger D, Colas D, de Lecea L, Heller HC (2013) Sleep to forget: interference of fear memories during sleep. Mol Psychiatry 18(11):1166–1170. doi:10.1038/mp.2013.121

Rosanova M, Ulrich D (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25(41):9398–9405

Routtenberg A, Rekart JL (2005) Post-translational protein modification as the substrate for long-lasting memory. Trends Neurosci 28(1):12–19. doi:10.1016/j.tins.2004.11.006

Rudoy J, Voss J, Westerberg C, Paller K (2009) Strengthening individual memories by reactivating them during sleep. Science 326:1079

Saletin JM, Goldstein AN, Walker MP (2011) The role of sleep in directed forgetting and remembering of human memories. Cereb Cortex 21(11):2534–2541

Sato Y, Fukuoka Y, Minamitani H, Honda K (2007) Sensory stimulation triggers spindles during sleep Stage 2. Sleep 30(4):511–518

Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P et al (2004) Sleep spindles and their significance for declarative memory consolidation. Sleep 27(8):1479–1485

Schabus M, Hödlmoser K, Gruber G, Sauter C, Anderer P, Klösch G et al (2006) Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. Eur J Neurosci 23(7):1738–1746

Schabus M, Kerstin H, Thomas P, Anderer P, Gruber G, Parapatics S et al (2008) Interindividual sleep spindle differences and their relation to learning-related enhancements. Brain Res 29: 127–135

Schabus M, Dang-Vu T, Heib D, Boly M, Desseilles M, Vandewalle G et al (2012) The fate of incoming stimuli during NREM sleep is determined by spindles and the phase of the slow oscillation. Front Neurol 3:40

Schmidt C, Peigneux P, Muto V, Schenkel M, Knoblauch V, Münch M et al (2006) Encoding difficulty promotes postlearning changes in sleep spindle activity during napping. J Neurosci 26(35):8976–8982. doi:10.1523/JNEUROSCI.2464-06.2006

Schönauer M, Geisler T, Gais S (2014) Strengthening procedural memories by reactivation in sleep. J Cogn Neurosci 26(1):143–153. doi:10.1162/jocn_a_00471

Schreiner T, Rasch B (2014) Boosting vocabulary learning by verbal cueing during sleep. Cereb Cortex 25(11):4169–4179. doi:10.1093/cercor/bhu139

Schreiner T, Göldi M, Rasch B (2015) Cueing vocabulary during sleep increases theta activity during later recognition testing. Psychophysiology 52(11):1538–1543. doi:10.1111/psyp.12505

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21

Scrima L (1982) Isolated REM sleep facilitates recall of complex associative information. Psychophysiology 19(3):252–259. doi:10.1111/j.1469-8986.1982.tb02556.x

Shank SS, Margoliash D (2009) Sleep and sensorimotor integration during early vocal learning in a songbird. Nature 458(7234):73–77. doi:10.1038/nature07615

Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21:1123–1128

Silva RH, Abílio VC, Takatsu AL, Kameda SR, Grassl C, Chehin AB et al (2004) Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice. Neuropharmacol 46(6):895–903

Skaggs WE, McNaughton BL (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. Science 271(5257):1870–1873. doi:10.1126/science.271.5257.1870

Smith C (1995) Sleep states and memory processes. Behav Brain Res 69:137–145

Smith C (2001) Sleep states and memory processes in humans: procedural versus declarative memory systems. Sleep Med Rev 5(6):491–506. doi:10.1053/smrv.2001.0164

Smith C, MacNeill C (1994) Impaired motor memory for a pursuit rotor task following stage 2 sleep loss in college students. J Sleep Res 3:206–213

Smith CT, Smith D (2003) Ingestion of ethanol just prior to sleep onset impairs memory for procedural but not declarative tasks. Sleep 26(2):185–191

Smith C, Weeden K (1990) Post training REMs coincident auditory stimulation enhances memory in humans. Psychiatr J Univ Ott 15(2):85–90

Smith C, Wong PT (1991) Paradoxical sleep increases predict successful learning in a complex operant task. Behav Neurosci 105(2):282–288. doi:10.1037//0735-7044.105.2.282

Smith C, Young J, Young W (1980) Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. Sleep 3(1):67–81

Smith C, Aubrey J, Peters K (2004) Different roles for REM and Stage-2 sleep in motor learning: a proposed model. Psychol Belg 44:79–102

Song S, Cohen LG (2014) Practice and sleep form different aspects of skill. Nat Commun 5:3407. doi:10.1038/ncomms4407

Squire LR, Bayley PJ (2007) The neuroscience of remote memory. Curr Opin Neurobiol 17(2):185–196. doi:10.1016/j.conb.2007.02.006

Squire LR, Genzel L, Wixted JT, Morris RG (2015) Memory consolidation. Cold Spring Harb Perspect Biol 7(8):a021766

Staresina BP, Alink A, Kriegeskorte N, Henson RN (2013) Awake reactivation predicts memory in humans. Proc Natl Acad Sci USA 110(52):21159–21164. doi:10.1073/pnas.1311989110

Staresina BP, Bergmann TO, Bonnefond M, van der Meij R, Jensen O, Deuker L et al (2015) Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat Neurosci 18:1679–1686. doi:10.1038/nn.4119

Stickgold R, Walker MP (2013) Sleep-dependent memory triage: evolving generalization through selective processing. Nat Neurosci 16(2):139–145. doi:10.1038/nn.3303

Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA (2000) Visual discrimination task improvement: a multi-step process occurring during sleep. J Cogn Neurosci 12(2):246–254

St-Laurent M, Abdi H, Buchsbaum BR (2014) Distributed patterns of reactivation predict vividness of recollection. J Cogn Neurosci 27(10):2000–2018. doi:10.1162/jocn

Studte S, Bridger E, Mecklinger A (2015) Nap sleep preserves associative but not item memory performance. Neurobiol Learn Mem 120:84–93. doi:10.1016/j.nlm.2015.02.012

Takashima A, Nieuwenhuis ILC, Jensen O, Talamini LM, Rijpkema M, Fernández G (2009) Shift from hippocampal to neocortical centered retrieval network with consolidation. J Neurosci 29(32):10087–10093. doi:10.1523/JNEUROSCI.0799-09.2009

Takeuchi T, Duszkiewicz AJ, Morris RGM (2014) The synaptic plasticity and memory hypothesis: encoding, storage and persistence. Philos Trans R Soc Lond B Biol Sci 369(1633):20130288. doi:10.1098/rstb.2013.0288

Talamini LM, Nieuwenhuis ILC, Takashima A, Jensen O (2008) Sleep directly following learning benefits consolidation of spatial associative memory. Learn Mem 15(4):233–237. doi:10.1101/lm.771608

Tamaki M, Matsuoka T, Nittono H, Hori T (2008) Fast sleep spindle (13–15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance. Sleep 31(2):204–211

Tambini A, Ketz N, Davachi L (2010) Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 65(2):280–290. doi:10.1016/j.neuron.2010.01.001

Tilley A, Empson J (1978) REM sleep and memory consolidation. Biol Psychol 6(4):293–300. doi:10.1016/0301-0511(78)90031-5

Tononi G, Cirelli C (2014) Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81(1):12–34. doi:10.1016/j.neuron.2013.12.025

Torres M, Giraldez F (1998) The development of the vertebrate inner ear. Mech Dev 71:5–21

Tse D, Takeuchi T, Kakeyama M, Kajii Y, Okuno H, Tohyama C et al (2011) Schema-dependent gene activation and memory encoding in neocortex. Science 333:891–895

Tulving E, Thomson D (1973) Encoding specificity and retrieval processes in episodic memory. Psychol Rev 80(5):352–373

van der Helm E, Gujar N, Nishida M, Walker MP (2011) Sleep-dependent facilitation of episodic memory details. PLoS One 6(11):e27421. doi:10.1371/journal.pone.0027421

van Dongen EV, Takashima A, Barth M, Zapp J, Schad LR, Paller KA, Fernández G (2012a) Memory stabilization with targeted reactivation during human slow-wave sleep. Proc Natl Acad Sci USA 109(26):10575–10580. doi:10.1073/pnas.1201072109

van Dongen EV, Thielen J-W, Takashima A, Barth M, Fernández G (2012b) Sleep supports selective retention of associative memories based on relevance for future utilization. PLoS One 7(8):e43426. doi:10.1371/journal.pone.0043426

van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijer JPA, Rombouts SARB (2005) Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. NeuroImage 24:898–909. doi:10.1016/j.neuroimage.2004.09.011

Vilberg KL, Davachi L (2013) Perirhinal-hippocampal connectivity during reactivation is a marker for object-based memory consolidation. Neuron 79(6):1232–1242. doi:10.1016/j.neuron.2013.07.013

Vyazovskiy VV, Harris KD (2013) Sleep and the single neuron: the role of global slow oscillations in individual cell rest. Nat Rev Neurosci 14(6):443–451

Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 11(2):200–208

Vyazovskiy VV, Olcese U, Lazimy YM, Faraguna U, Esser SK, Williams JC et al (2009) Cortical firing and sleep homeostasis. Neuron 63(6):865–878

Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G (2011) Local sleep in awake rats. Nature 472(7344):443–447

Wagner U, Gais S, Born J (2001) Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. Learn Mem 8:112–119. doi:10.1101/lm.36801.sleep

Wagner U, Gais S, Haider H, Verleger R, Born J (2004) Sleep inspires insight. Nature 427(22): 352–355

Wagner U, Hallschmid M, Rasch B, Born J (2006) Brief sleep after learning keeps emotional memories alive for years. Biol Psychiatry 60:788–790. doi:10.1016/j.biopsych.2006.03.061

Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002a) Practice with sleep makes perfect: sleep-dependent motor skill learning. Neuron 35:205–211

Walker MP, Liston C, Hobson JA, Stickgold R (2002b) Cognitive flexibility across the sleep–wake cycle: REM-sleep enhancement of anagram problem solving. Cogn Brain Res 14(3):317–324. doi:10.1016/S0926-6410(02)00134-9

Walker MP, Brakefield T, Hobson JA (2003) Dissociable stages of human memory consolidation and reconsolidation. Nature 425:616–620. doi:10.1038/nature01951.1

Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G (2005) Sleep-dependent motor memory plasticity in the human brain. Neuroscience 133(4):911–917. doi:10.1016/j.neuroscience.2005.04.007

Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV et al (2012) Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? Biol Psychiatry 71(2):154–161. doi:10.1016/j.biopsych.2011.08.008

Wang S-H, Redondo RL, Morris RGM (2010) Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. Proc Natl Acad Sci 107(45):19537–19542

Wiesel TN, Hubel DH (1963) Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. J Neurophysiol 26:978–993 Retrieved from http://hubel.med.harvard.edu/papers/HubelWiesel1963Jneurophysiol3.pdf. http://www.ncbi.nlm.nih.gov/pubmed/14084170

Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Mölle M, Born J (2011) Sleep selectively enhances memory expected to be of future relevance. J Neurosci 31(5):1563–1569. doi:10.1523/JNEUROSCI.3575-10.2011

Wilson M, McNaughton B (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679

Wing EA, Ritchey M, Cabeza R (2015) Reinstatement of individual past events revealed by the similarity of distributed activation patterns during encoding and retrieval. J Cogn Neurosci 27(4):679–691. doi:10.1162/jocn

Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Düzel E (2005) Reward-related fMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron 45:459–467. doi:10.1016/j.neuron.2005.01.010

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M et al (2013) Sleep drives metabolite clearance from the adult brain. Science 342:373–377

Xue G, Dong Q, Chen C, Lu Z, Mumford JA, Poldrack RA (2010) Greater neural pattern similarity across repetitions is associated with better memory. Science 330(6000):97–101. doi:10.1126/science.1193125

Yaroush R, Sullivan MJ, Ekstrand BR (1971) Effect of sleep on memory: II. Differential effect of the first and second half of the night. J Exp Psychol 88(3):361–366. doi:10.1037/h0030914

Yordanova J, Kolev V, Wagner U, Born J, Verleger R (2012) Increased alpha (8–12 Hz) activity during slow wave sleep as a marker for the transition from implicit knowledge to explicit insight. J Cogn Neurosci 24(1):119–132