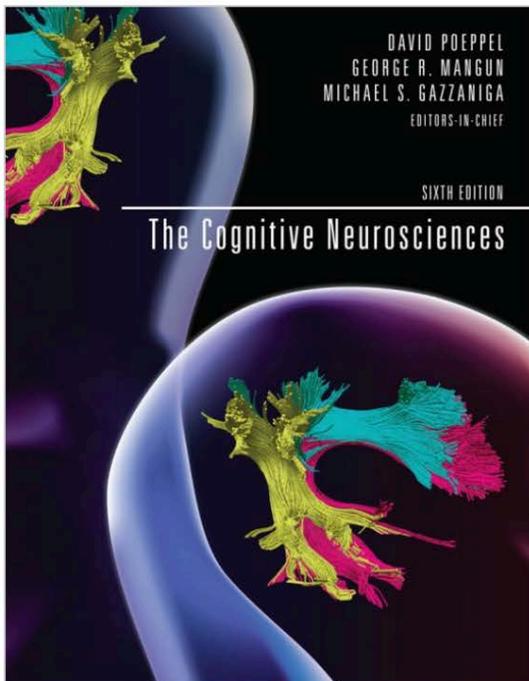


Replay-Based Consolidation Governs Enduring Memory Storage

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ABSTRACT The human ability to remember unique experiences from many years ago comes so naturally that we often take it for granted. It depends on three stages: (1) encoding, when new information is initially registered, (2) storage, when encoded information is held in the brain, and (3) retrieval, when stored information is used. Historically, cognitive neuroscience studies of memory have emphasized encoding and retrieval. Yet the intervening stage may hold the most intrigue and has become a major research focus in the years since the last edition of this book. Here we describe recent investigations of postacquisition memory processing in relation to enduring storage. This evidence of memory processing belies the notion that memories stored in the brain are held in stasis, without changing. Various methods for influencing and monitoring brain activity have been applied to study off-line memory processing. In particular, memories can be reactivated during sleep and during resting periods, with distinctive physiological correlates. These neural signals shed light on the contribution of hippocampal-neocortical interactions to memory consolidation. Overall, results converge on a framework whereby memory reactivation is a critical determinant of systems-level consolidation, and thus of future remembering, which in turn facilitates future planning and problem solving.

How do we acquire new knowledge? Not easily! We often fail to retain important information, even when we try to forestall forgetting by rehearsing what we wish to keep. Indeed, repeated retrieval may be the key to enduring memory storage. Yet a deep conundrum remains in that intentional retrieval alone cannot explain the seemingly unpredictable way that some memories drift away while others are retained.

This chapter explores the idea that memory storage also depends on rehearsal that occurs unintentionally and implicitly, including while we sleep. A key driving force behind consolidation, according to our view, is the regular reactivation of memories without our awareness. This view goes beyond the first-person sense of rehearse-to-remember. When rehearsal is hidden, the consequences may go unnoticed. Whereas speculations about consolidation have largely been derived from behavioral and neural studies of memory change over time, particularly in retrograde amnesia, the incremental improvements in storage due to consolidation have

been difficult to observe. The additional consideration that we emphasize here, with implications for making such observations, is that memories change in fundamental ways in conjunction with unconscious rehearsal.

The journey of a memory, such as the memory of a unique life event like reading this sentence, begins with encoding and concurrent neural plasticity. The journey may be a long one; a single event may be remembered many years later. If so, one might say that such a memory existed for the duration of that multiyear period, like a file secured away in a file drawer. This commonplace notion—that “the memory” per se lasts from encoding until retrieval—reifies it as existing in a static manner, independently, set apart from other memories. This view is misleading.

Somehow, neural substrates of memory storage must traverse the entire storage interval for a memory to ultimately be retrieved. However, if memories are not static entities, how should we characterize memory storage during this interval? Changes in storage are not a simple matter of the memory transitioning from a labile state to a stable one, such as when a newly created ceramic object is heated. A progression of neural restructuring seems more likely, particularly for an episode from long ago.

Such progressive changes are widely acknowledged as fundamental to the neurobiology of consolidation, now being intensively investigated on many fronts. Through neural restructuring, the informational content of memories can also change. Memories are subject to gradual integration with other stored knowledge; emergence of a theme or interpretation; stabilization of certain features; stripping away of details; gist formation; generalization; forming novel associations among features; producing creative new ideas; and, ultimately, the crystallization of a set of memories that form the fabric of one’s life story.

Whereas our thesis is that memory reactivation is a critical determinant of memory storage, one classic memory phenomenon—the *flashbulb memory*—seems in direct opposition. A classical flashbulb memory is found when a person can recount, in detail, learning of some momentous public event, such as an assassination. The metaphorical flashbulb would illuminate

everything in view at that instant; that singular moment would be frozen in time, preserved in a permastore to remain forever available. Livingston (1967) proposed that the emotional impact engaged a “now-print” mechanism that permanently preserved the event and all concurrent details. However, flashbulb memories become distorted just like ordinary episodic memories (Schmolck, Buffalo, & Squire, 2000). Repeatedly retelling a story is a common way to introduce distortions. So our view is that these momentous events are not immediately etched into memory. In place of the classic view of flashbulb memories, we attribute their dramatic persistence to repeated memory reactivation.

Likewise, we may carry some memories with us throughout our lives, thanks to consolidation rather than to superior encoding. The most decisive memory process could be repeated reactivation, some of which occurs implicitly. Off-line reactivation and concomitant plasticity may even be a necessity for enduring memory storage, ultimately determining which memories we keep. In this account of memory preservation, how should we now conceptualize the “replay” of a memory?

Defining “Replay” in the Context of Memory Categories

The prime directive of a *Star Trek* expedition to an alien planet is to avoid undue interference with another culture. The prime directive of an expedition in memory research is to acknowledge that different types of memory depend on distinct mechanisms.

What type of memory are we talking about? William James’ (1890) classic distinction between *primary memory* and *secondary memory* is an appropriate starting point. The former comprises the content of our moment-to-moment train of thought, whereas the latter concerns information brought back to mind after departing from awareness. James’ terms were supplanted by the contrast between *short- and long-term memory* (STM and LTM), but this distinction is problematic because it emphasizes time span. As long as active rehearsal continues, information can be kept alive. In place of STM, with time span as the defining feature, *immediate memory* and *working memory* adequately designate information kept in mind.

Time span is nevertheless essential to consider. Memory research typically emphasizes acquisition-to-retrieval delays not longer than a few minutes. In contrast, here we strive to explain *enduring memory storage*—memories that somehow last days, weeks, even years in the face of the daily trudge of new learning, wherein forgetting seems to be the rule.

Declarative memory is defined as the type of memory used in recalling and recognizing episodes and facts.

Patients with circumscribed amnesia have difficulty with recent episodic and factual knowledge. Their capabilities on tests designed to assess other types of memory—such as skills, procedures, priming, conditioning, and habits—can be entirely preserved. These other types of memory have been categorized collectively as *nondeclarative memory*. Although replay is certainly relevant for nondeclarative memory, here we focus on declarative memory.

The fundamental distinctiveness of declarative memory likely arises in relation to (1) storage across multiple neocortical regions and (2) the potential for conscious recollection. For example, the components of a specific event, including relevant causes and repercussions, are represented in multiple neocortical regions specialized for processing different informational features. Recollecting an enduring declarative memory relies on combining such assorted elements. Because the cortical fragments are spatially separated in the brain, they must be linked to form a cohesive unit, requiring what at a neural level can be called cross-cortical storage (Paller, 1997, 2002) or, at a cognitive level, relational representations (Eichenbaum & Cohen, 2001; Shimamura, 2002).

Another fundamental characteristic of enduring declarative memories is that storage is altered gradually via consolidation (Squire, Cohen, & Nadel, 1984). Which pathway will a newly formed memory take—stabilization, integration, corruption, forgetting? Optimally, an initial stage of rapid plasticity involving the formation of new hippocampal connections with various cortical representations is followed by a gradual process involving further hippocampal-neocortical interaction (McClelland, McNaughton, & O’Reilly, 1995). Postacquisition processing may promote cross-cortical storage by gradually and thoroughly binding together a memory’s distinct representational components. Synaptic consolidation involves molecular changes at individual synapses shortly after learning; systems consolidation concerns changes in storage that take place over a prolonged period of time and that involve multiple brain regions. Systems consolidation can include restructuring, and this restructuring may continue indefinitely (Dudai, 2012).

A pivotal physiological bond between consolidation and the hippocampus comes from reports of *hippocampal replay* in rodent place cells (reviewed by Foster, 2017). Firing patterns during sleep mirrored those previously exhibited during exploratory behavior in a new environment (Pavlidis & Winson, 1989; Wilson & McNaughton, 1994). Replay is also found during wake, in cortical regions, in the striatum, and in various forms in multiple species. Although the term *replay* is sometimes restricted to repeated firing sequences in hippocampal place cells,

here we use the term *replay* to encompass the notion of any neural recapitulation of stored information and *hippocampal replay* to denote this specific example.

If replay is at the heart of declarative memory consolidation, the opportunity may arise each and every time a memory is reactivated, online or off-line. Online reactivation would be when one knowingly recalls a memory, intentionally or otherwise. The canonical example of an off-line period is when we sleep.

Memory Processing during Sleep

The notion that memories change during sleep has not always been on the radar of memory researchers. Our view is that declarative memories change both during waking and during sleep and that such changes contribute to the gradual process of consolidation (Paller, 1997; Paller & Voss, 2004). Substantial empirical support has accrued for sleep-based memory processing (Rasch & Born, 2013). According to this view, memories do not just lie dormant during sleep but instead receive regular exercise that changes what is stored.

Sleep has a complex physiological architecture. The classic staging of sleep into just four stages is deceptive in its apparent simplicity. Electroencephalographic (EEG) signals differ markedly between *slow-wave sleep* (SWS, also known as N3) and *rapid eye movement sleep* (REM). Non-REM sleep includes three stages—N1, N2, and N3—going from light sleep to deep sleep. Current thinking is that SWS and REM have complementary memory functions.

In prior decades before the recent waves of empirical support, many theories on memory and sleep were entertained (e.g., Cartwright, 1977; Marr, 1971; Winson, 1985). An intuitively reasonable idea was that sleep supports adaptive mechanisms for evaluating recent experiences and relating them to current goals. Hippocampal replay connects with these ideas, although early studies of hippocampal replay lacked suitable behavioral measures that might show improved spatial memory following sleep, so hippocampal replay could not be directly linked with consolidation.

A good case can now be made to link consolidation with both hippocampal replay and hippocampal *sharp-wave ripples* (SWRs; ripples are high-frequency bursts in field-potential recordings, 100–250 Hz, lasting approximately 50 ms). For example, hippocampal replay can occur during SWRs, which increase as a function of learning (Dupret, O'Neill, Pleydell-Bouverie, & Csicsvari, 2010; O'Neill, Senior, Allen, Huxter, & Csicsvari, 2008; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009). More telling, hippocampal replay is specific to learning-related ensembles and correlates with retention (Dupret et al., 2010). Furthermore, manipulating SWRs alters memory

(Barnes & Wilson, 2014; Ego-Stengel & Wilson, 2009; Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009).

Additional evidence brings in cortical activity, as neocortical SWRs and hippocampal SWRs can be observed together with thalamocortical *sleep spindles* (Khodagholy, Gelinas, & Buzsáki, 2017; Siapas & Wilson, 1998). Spindles are brief (0.5–3 s) oscillations at approximately 11–16 Hz. Spindles may both be temporally guided by cortical slow waves and help to synchronize hippocampal SWRs with cortical activity.

In humans, ample results demonstrate superior memory after a period of sleep compared to a period of wake (Rasch & Born, 2013). In an extreme way, sleep deprivation can produce such a result, but this can be problematic because of memory difficulties arising from excessive sleepiness or nonspecific effects of deprivation, such as stress. In any such sleep/wake comparison, wakefulness can entail more memory interference than sleep, calling into question whether sleep necessarily made a specific contribution. Thus, this sort of evidence provides only tentative support for the notion that sleep after learning improves memory.

To get a better handle on how the physiology of sleep might map onto processing pertaining to consolidation, we will need to better specify connections between specific signals in sleep EEG and specific aspects of memory processing. One way to reach for this goal, while also avoiding the problem of differential memory interference that plagues sleep/wake comparisons, is to use subtle but systematic sensory stimulation during sleep.

Manipulating memory during sleep The literature on presenting a sleeper with cues to information recently learned while awake has grown considerably in the last few years (Cellini & Capuozzo, 2018; Oudiette & Paller, 2013; Schouten, Pereira, Tops, & Louzada, 2017). Note that gaining new knowledge presented only during sleep was ostensibly ruled out by Emmons and Simon (1956), who investigated presenting spoken facts during sleep. Their subjects showed no evidence of learning as long as no signs of arousal were present in EEG recordings. Many studies on this topic up to that point did not include physiological verification of sleep state, which came to be deemed essential. The work of Emmons and Simon led to widespread skepticism in the scientific community about the validity of so-called sleep learning, impeding workers from pursuing many adjacent research directions (Paller & Oudiette, 2018). However, recent findings show that some implicit learning during sleep may indeed be possible (Arzi et al., 2012; Andrillon et al., 2017).

Here we focus instead on the use of sensory stimulation to study brain mechanisms, whereby memories

formed while awake can be consolidated during sleep. Among the early studies on this topic were classical-conditioning studies in rats trained to fear a tone repeatedly paired with a shock during wakefulness; conditioning was enhanced by a mild shock during sleep (Hars, Hennevin, & Pasques, 1985; Hennevin, Hars, Maho, & Bloch, 1995). Smith and Weeden (1990) trained people in a complex finger-tapping task while listening to a ticking sound, and performance was improved by playing the sound during sleep. In the landmark study of Rasch and colleagues (2007), a rose odor was presented while subjects learned spatial locations of objects. Presenting the rose odor again during SWS improved cued recall of all the learned locations (relative to several control conditions in other subjects) and functional magnetic resonance imaging (fMRI) showed hippocampal activation, a putative correlate of the memory reactivation.

In 2009 we took the further step of showing that specific memories could be strengthened using sounds during sleep (Rudoy, Voss, Westerberg, & Paller, 2009; figure 23.1). *Targeted memory reactivation* (TMR) refers to this method for selectively manipulating memory during sleep. Whereas memory comparisons following a period of sleep versus wake can be confounded by indirect effects of alertness or interference, TMR studies are immune from this problem. TMR studies generally rely on within-subject contrasts of postsleep performance for cued versus uncued material. Selectively improved recall performance after TMR during sleep thus demonstrated that specific memories were changed, an effect replicated in subsequent studies (e.g., Creery, Oudiette, Antony, & Paller, 2014; Vargas, Schechtman, & Paller, 2019).

Auditory processing may be reduced during sleep, but it is not eliminated. Van Dongen and colleagues (2012) examined TMR while subjects slept during fMRI scanning. Subjects were motivated to suppress auditory processing, given the exceedingly loud scanning noise. Supporting the idea of sensory gating operative at the level of the thalamus, the degree of memory benefit, which was not reliable overall, was correlated with brain activation in the thalamus across subjects. The degree of memory benefit was also correlated with activity in the medial temporal lobe and the cerebellum, as well as with parahippocampal-precuneus connectivity, thus identifying several measures of brain activity associated with sound-cued memory reactivation (see also Berkers, Ekman, van Dongen, Takashima, Paller, & Fernandez, 2018; Shanahan, Gjorgieva, Paller, Kahnt, & Gottfried, 2018). In another study with the same spatial recall task, we showed that sleep without sounds favored high-value information (Oudiette, Antony, Creery, & Paller, 2013) recall for low-value items was brought up to the level of

high-value items when low-value sound cues were presented during SWS. In a variation on these procedures with rodents, Bendor and Wilson (2012) used TMR to link reactivation with hippocampal replay. Tones previously associated with spatial learning were played during sleep, and a systematic bias in hippocampal place cell firing was found as a function of which tone was presented.

With TMR during sleep, memory can be manipulated by surreptitiously presenting part of what has been learned prior to sleep. In addition to influencing learning of spatial locations, TMR can influence a variety of other types of learning, including learning complex skills (Antony, Gobel, O'Hare, Reber, & Paller, 2012), foreign vocabulary (Schreiner & Rasch, 2014), conditioning (Hauner, Howard, Zelano, & Gottfried, 2013), body-ownership changes (Honma et al., 2016), and words in locations (Fuentemilla et al., 2013). In this last study, the degree of word recall benefit after TMR was inversely correlated with the degree of medial temporal damage in epileptic patients.

Another way to manipulate sleep that can provide clues about the relevant physiology is to entrain brain oscillations. Slow waves and sleep spindles have been linked with memory consolidation on the basis of correlative findings, along with direct manipulations, that strongly suggest a causal link. Disrupting SWS can produce memory difficulties (e.g., Landsness et al., 2009), but the disruption could affect memory either directly or indirectly. Therefore, sleep-memory connections can more convincingly be derived by facilitating SWS. Marshall and colleagues (2006) were the first to show that transcranial stimulation with slow oscillatory electrical currents can enhance slow waves and thereby benefit word-pair learning. Precisely timed auditory stimulation can have similar effects (e.g., Ngo, Martinetz, Born, & Mölle, 2013). Thus, there is convincing evidence that slow waves play a causal role in sleep-based memory consolidation.

Slow-wave entrainment often produces a concomitant increase in spindles as well. Spindles can also be entrained electrically (Lustenberger et al., 2016) or with auditory stimulation (Antony & Paller, 2017). A pharmacological approach, using Ambien, produced both an increase in spindles and an improvement in memory (Mednick et al., 2013). Spindle timing relative to slow-wave phase may be critical (Helfrich, Mander, Jagust, Knight, & Walker, 2018; Niknazar, Krishnan, Bazhenov, & Mednick, 2015). Although the precise role of sleep spindles in memory consolidation remains to be elucidated, recent studies have made significant headway (Antony et al., 2018; Cairney, Guttesen, El Marj, & Staresina, 2018; Schreiner, Lehmann, & Rasch, 2015; figure 23.2).

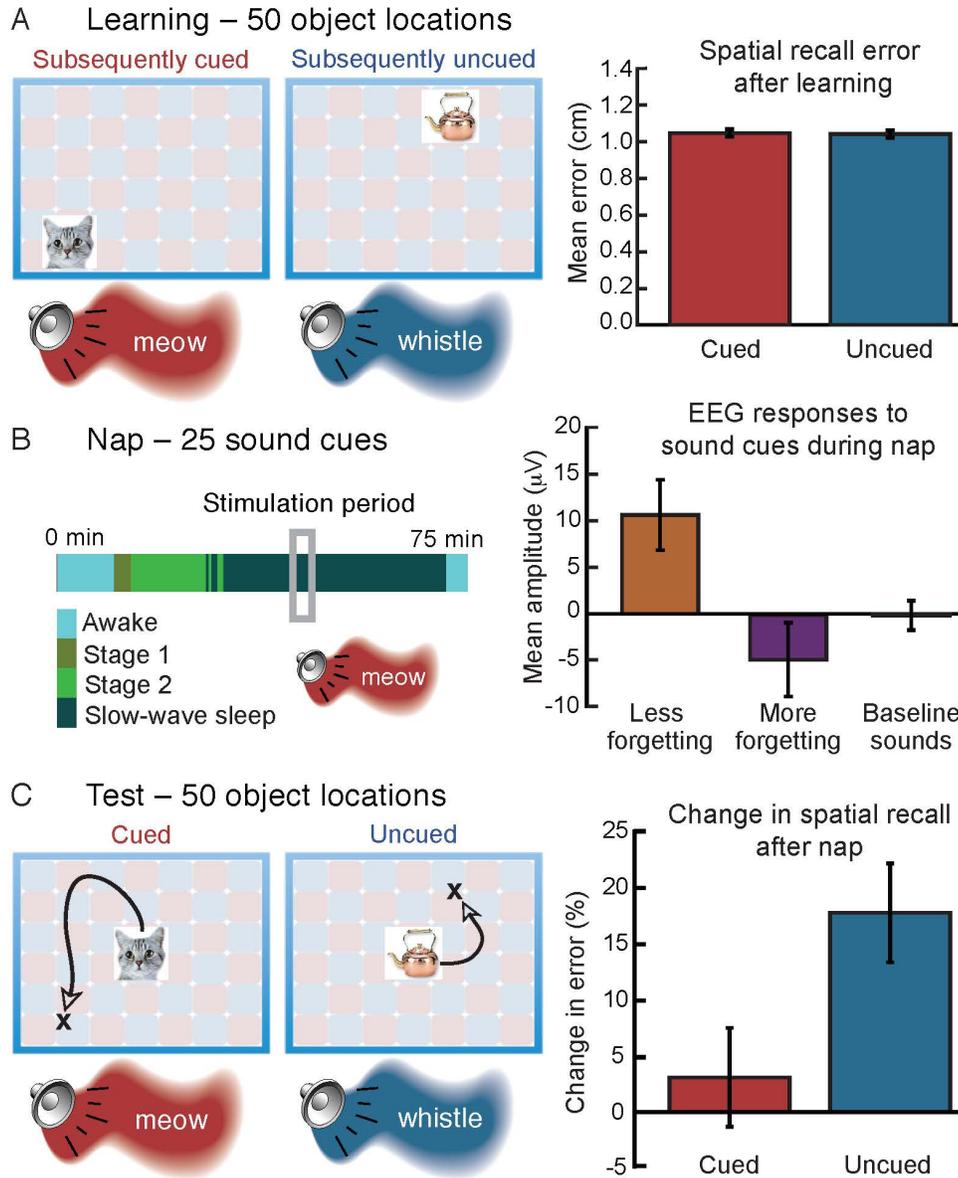


FIGURE 23.1 Targeted memory reactivation (TMR). *A*, Subjects in the study by Rudoy and colleagues (2009) first learned 50 object-location associations. Each object was presented with its characteristic sound. Following an interactive learning procedure, location recall was tested. Half of the objects were assigned to be cued during sleep such that recall accuracy was matched for cued and uncued objects. *B*, Next, subjects slept with EEG monitoring. When signs of SWS were evident, 25 of the sounds were presented at a low intensity. These sounds influenced memory storage without waking people up. *C*, Recall of locations was tested again after the nap. Subjects moved each object from the center to where

they thought it belonged (*arrows*). Recall was more accurate for cued versus uncued objects. Mean EEG responses from 400–800 ms following the onset of each sound presented during sleep were found to be more positive for those objects with less decline in recall (*Less forgetting* in *B*) compared to the remaining objects or to baseline sounds. These responses resembled typical event-related potentials predictive of later memory (Dm effects; Paller et al., 1987), suggesting that spatial memory reactivation occurred as a consequence of cue presentation, leading to improved spatial recall after awakening. Reprinted from Rudoy et al. (2009). (See color plate 24.)

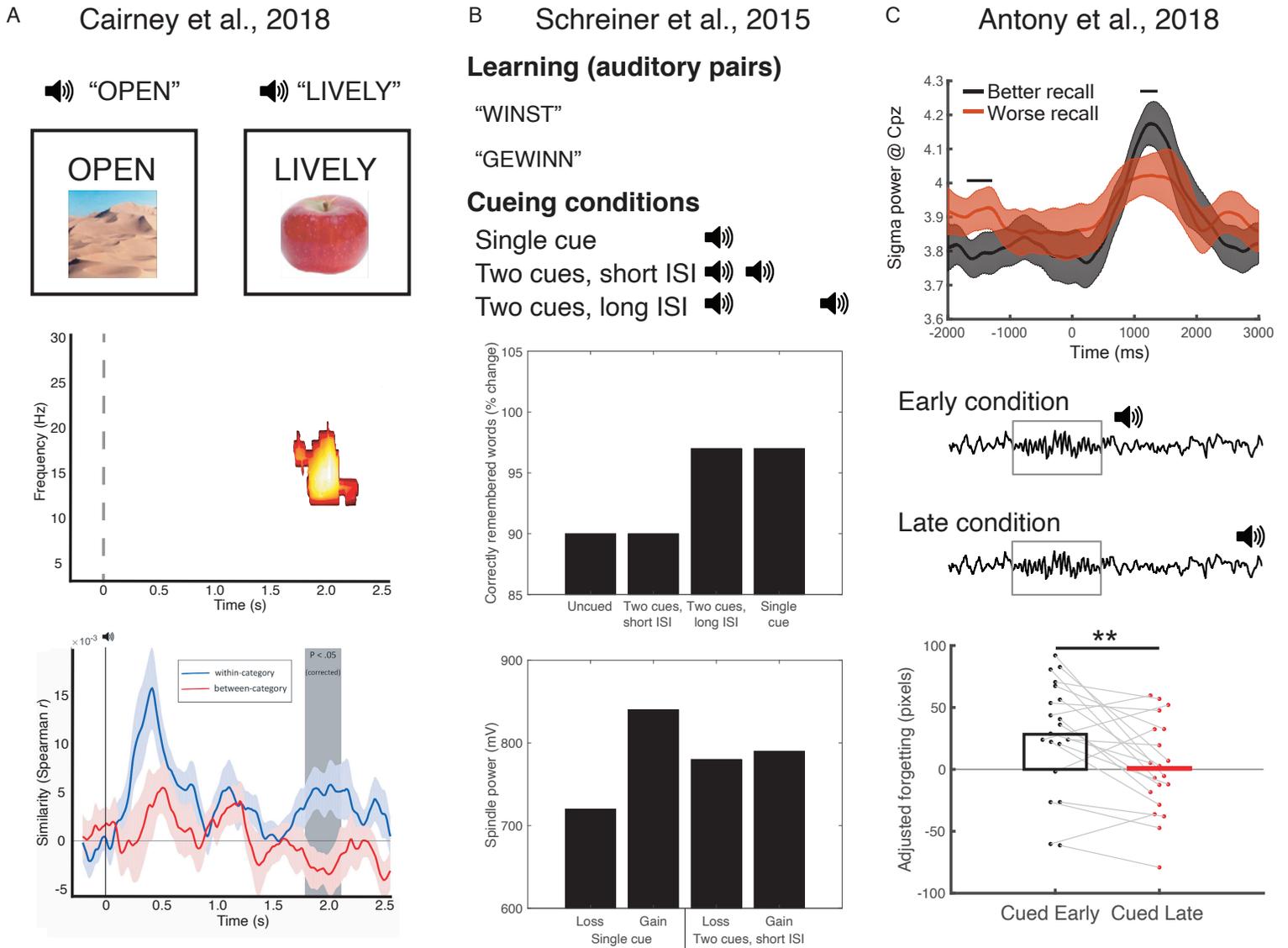


FIGURE 23.2 Sleep spindles and memory as studied in three experiments. *A*, Subjects in Cairney et al. (2018) learned adjective-scene and adjective-object associations. A subset of spoken adjectives were then presented during postlearning sleep. These cues elicited higher EEG power in the spindle band (sigma, ~15 Hz) for learned than for nonlearned words (1.7–2.3 s after cue onset). Additionally, within-category neural similarity (object vs. scene) exceeded between-category similarity at roughly the same time, suggesting that spindles mediate relevant memory reactivation. *B*, Subjects in Schreiner, Lehmann, & Rasch (2015) learned auditory word pairs. Cues presented during sleep included single words, two words separated by 200 ms, or two words separated by 1,500 ms (i.e., a long or short interstimulus interval [ISI]). Subsequent recall was best with single cues or two

cues (long ISI), and spindle power within the immediate postcue period predicted memory change with single cues only. *C*, Antony et al. (2018) similarly found that postcue sigma power predicted memory improvement for spatial recall. Additionally, precue sigma power negatively predicted memory, suggesting that precue spindles impede reactivation in that a well-timed postcue spindle is unlikely in these cases. Spindles were found to be most likely to reoccur after about 4–6 s. Using software to track spindles in real time, TMR benefits were better for sounds presented late (long ISI after prior spindle) versus early (short ISI after prior spindle). These results suggest that memory reactivation is linked with spindles, which also means that there may be pauses in reactivation corresponding with the normal

In sum, evidence from TMR and from direct manipulation of neural oscillations strongly favors the view that memory storage can be enhanced during sleep. Slow waves may set the stage for the drama of intricate interactions manifested by neural oscillations and their cross-frequency coupling. Furthermore, spindles can be taken as a prime example of neural sleep signals that have a causal impact in enhancing specific memories due to replay-based consolidation. A neuropsychological perspective may have intriguing relevance, given the literature on diencephalic amnesia (e.g., Aggleton & Saunders, 1997). That is, we speculate that the central role of the thalamus in generating spindles and corresponding replay events may be at the heart of *both* sleep-based consolidation and the classic symptoms of amnesia after diencephalic damage.

Memory Processing during Wake

Many electrophysiological and behavioral findings implicate memory reactivation during wake. Rodent hippocampal replay can be observed during or just after learning (Diba & Buzsáki, 2007), as well as more remotely during both wake and sleep (Karlsson & Frank, 2009). Likewise, SWRs occur during waking immobility (Buzsáki, Lai-Wo, & Vanderwolf, 1983) and contain replay content (Davidson, Kloosterman, & Wilson, 2009; Karlsson & Frank, 2009). These wake SWRs correlate with retention (Dupret et al., 2010), and their disruption impairs performance on a working memory task (Jadhav, Kemere, German, & Frank, 2012).

In human studies, fMRI data acquired shortly after learning have shown increases in connectivity between the hippocampus and cortical regions (e.g., Schlichting & Preston, 2014). In addition, specific patterns of hippocampal activity associated with what was just learned can appear spontaneously shortly after learning and can correlate with retention (Gruber, Ritchey, Wang, Doss, & Ranganath, 2016; Schapiro, McDevitt, Rogers, Mednick, & Norman, 2018; Tambini & Davachi, 2013). Moreover, a brief rest after encoding can apparently aid retention (e.g., Craig & Dewar, 2018).

Memory reactivation engaged when relevant information is encountered commonly leads to improved subsequent memory. This observation borders on the territory of standard methods to improve learning. Restudying material strengthens memories, but recall provides a superior benefit (Roediger & Karpicke, 2006). Likewise, cued recall in a spatial task one day after initial learning improves recall accuracy the following day (Bridge & Paller, 2012). Additionally, TMR during wake can improve memory when delivered with subliminal cues (Tambini, Berners-Lee, & Davachi,

2017) or during an engaging task that likely limited rehearsal (Oudiette et al., 2013). Furthermore, reactivation of learning-related neural patterns occurs during restudy (Xue et al., 2010), during successful retrieval (Karlsson Wirebring et al., 2015; Ritchey, Wing, LaBar, & Cabeza, 2013), and even during subliminal wake reactivation (Henke et al., 2003).

Finally, both retrieval (relative to restudy) and sleep (relative to wake) were found to improve consolidation (Antony & Paller, 2018; Bäuml, Holtermann, & Abel, 2014). These similar effects of retrieval during wake and sleep support a recent idea that retrieval may naturally engender online consolidation (Antony, Ferreira, Norman, & Wimber, 2017). In sum, consolidation may proceed during sleep and during wake, in conjunction with reactivation that can be intentional, unintentional, with awareness of retrieval, or without awareness of retrieval.

Consolidation and Interference

Whereas research on sleep and memory has largely focused on memory strengthening via replay, a limitation of this approach is that it typically neglects interactions between memories. These interactions may be crucial for shaping retention. Decades of memory research have established that interference from other similar memories can cause forgetting (Underwood, 1957). To predict whether memories will be retained in the long term, we need to understand both how reactivation can cause interference and how it might mitigate interference.

Numerous studies have found, during wake, that retrieving a memory can lead to forgetting competing memories (e.g., Anderson, Bjork, & Bjork, 2000; Lewis-Peacock & Norman, 2014; Norman, Newman, & Detre, 2007). Recent studies using TMR have found that these forgetting effects can also occur when memories are reactivated during sleep (Antony, Cheng, Brooks, Paller, & Norman, 2018; Oyarzún, Moris, Luque, Diego-Balaguer, & Fuentemilla, 2017). In addition to causing interference, reactivation-related learning might restructure memories in a way that mitigates interference. Generally speaking, there are two ways to reduce interference between two memories while still preserving the retrievability of both memories: integrating them into a single, cohesive memory or differentiating them so one memory does not trigger retrieval of the other. Intuitively, this corresponds to the two main ways to prevent enemies from fighting—you can make them friends (integration) or you can separate them (differentiation). Drawing on prior studies showing that strong activation leads to strengthening of memory

associations but moderate activation leads to weakening of these associations (e.g., Detre, Natarajan, Gershman, & Norman, 2013), Antony and colleagues (2017) describe how retrieval-driven learning could lead to integration and differentiation. If two memories strongly coactivate during retrieval, this will lead to strengthened connections between the memories, integrating them. Conversely, if two memories show a moderate level of coactivation during retrieval (such that one tends to moderately activate when the other is retrieved and vice versa), this will lead to weakened connections between the memories, differentiating them.

Further progress will require studies that link three measures: neural measures of reactivation during sleep (or wake/rest), neural measures of memory restructuring (e.g., from fMRI pattern analysis; Kim, Norman, & Turk-Browne, 2017), and behavioral measures of memory interference. At present, some data speak to pieces of this puzzle, but no extant studies connect all three. For example, a reduction in memory interference has been observed after sleep (Baran, Wilson, & Spencer, 2010; McDevitt, Duggan, & Mednick, 2015), but these studies did not include neural measures of memory restructuring. Other studies have shown memory integration or differentiation effects with fMRI pattern analysis after a delay that includes sleep, but they did not relate this restructuring to neural activity during the intervening sleep period (Favila, Chanales, & Kuhl, 2016; Kim, Norman, & Turk-Browne, 2017; Tomparý & Davachi, 2017).

A related challenge is understanding the role of specific sleep stages in restructuring memories. Prior neural network modeling has found that interleaved learning—repeatedly looping through a playlist of memories marked as important, doing incremental learning each time—is the most effective way to force the brain to reconcile competing representations (McClelland, McNaughton, & O'Reilly, 1995). One intriguing hypothesis is that REM sleep provides a focused period of interleaved learning of competing memories, thereby driving representational change that helps the memories coexist, either through integration or differentiation (Norman, Newman, & Perotte, 2005). The idea that REM is especially important for restructuring representations has the potential to explain results from a wide range of studies, including studies showing that REM leads to improved performance when multi-item integration is required (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Schapiro et al., 2017; Stickgold & Walker, 2013); studies showing that REM helps to reduce interference between similar memories, potentially through differentiation

of representations (Baran, Wilson, & Spencer, 2010; McDevitt, Duggan, & Mednick, 2015); and studies showing that REM plays a role in gaining new insights (Cai et al., 2009; Fosse, Stickgold, & Hobson, 2001; Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner, Gais, Haider, Verleger, & Born, 2004).

Future Directions

The results surveyed here convincingly document sleep's relevance for memory storage. Still, many outstanding questions remain about the neurocognitive mechanisms that support sleep-based memory consolidation and offline consolidation generally (figure 23.3).

Whereas memories may be reactivated throughout the sleep-wake cycle, the divergent physiological signals apparent during sleep versus wake suggest different mechanisms of memory change. Future research should seek to elucidate these mechanisms. In particular, deciphering the significance of signals such as slow waves and spindles for memory reactivation could be a big step in advancing our understanding of consolidation.

Various neuroscience techniques will likely provide future insights into these mechanisms. Recent optogenetic work provides a glimpse into how systems-level interactions can be revealed; for example, plasticity in cortical neurons may begin early and then change gradually (e.g., Kitamura et al., 2017; Lesburguères et al., 2011). The hypothetical progression of neural restructuring thought to underlie consolidation may entail a complex set of neural interactions across regions. Prolonged hippocampal-neocortical interactions (e.g., Goshen et al., 2011; Rothschild, 2019) could mediate consolidation in conjunction with memory reactivation. Although few experimental studies have examined long retention delays, there is evidence supporting the importance of repeatedly revising memories (e.g., Cepeda, Vul, Rohrer, Wixted, & Pashler, 2008).

The notion that repeated reactivation is at the core of declarative memory consolidation is consonant with various theories of consolidation. For example, Squire, Cohen, and Nadel (1984) pointed out that “the neural elements participating in memory storage can undergo reorganization with the passage of time after learning” (p. 201). More ideas about the complexities of reorganization were added in subsequent theoretical conceptions (e.g., Moscovitch et al., 2005). Competition has also long been recognized as relevant—“loss of connectivity among elements due to forgetting is accompanied by, causes, or results from a process of reorganization of that which remains” (Squire, Cohen, & Nadel, 1984, p. 201). Whereas concepts of reorganization and

FIGURE 23.3
Outstanding questions for future research.

- **What is the physiology of memory reactivation, and how does reactivation lead to changes in memory storage?**
- **In what ways does consolidation progress differently during wake reactivation and sleep reactivation?**
- **In what ways does consolidation progress differently during reactivation with awareness of retrieval versus reactivation without awareness of retrieval?**
- **How can studies of human memory consolidation best connect with fine-grained neurobiological analyses (e.g., two-photon microscopy and optogenetics)?**
- **Does the principle of expanding retrieval practice hold for sleep reactivation, such that consolidation is best with repeated reactivation after progressively longer delays?**

competition have been acknowledged within theoretical frameworks for consolidation, what happens to engender progressive memory changes over the course of consolidation has usually not been fleshed out. Going back even to Burnham's (1903) early view citing both "a physical process of [re]organization and a psychological process of repetition and association," consolidation theories usually allow for neural changes to progress without necessarily being tied to replay. The current view proposes a shift in emphasis from prior views: repeated memory reactivation is here explicitly conceived as the motive force behind progressive changes in memory storage, which, along with inter-memory competition, ultimately determines what information is available for retrieval.

Memory—what is it good for? This question has become a focal point of the overarching orientation to contemporary memory research and has alerted us to the importance of memory for future planning and problem-solving in particular. In this chapter we have zeroed in on enduring memories of episodes and facts. These long-enduring memories have the greatest potential for influencing our future actions. We have a lot to learn about how all types of memories persevere in the brain and manage to remain operative months and years after they are initially acquired. What we eventually can retrieve after long delays is not a pure record of the initial experience but rather a function of a progression of changes in memory storage resulting from intervening retrieval, an idea that has been evident in memory research since Bartlett (1932). Understanding the progressive changes that underlie consolidation will help us gain a fuller conception of learning, and may also provide insights into the fundamental forces that determine the biographical story line and identity that we each carry with us.

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