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Sleep's role in memory reconsolidation

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Processes occurring during sleep contribute critically to the stabilization of new learning for long-term retention. Previously consolidated memory traces can be reactivated rendering memories labile again, and vulnerable to disruption or alteration. Across the phases of reactivation, modification, and re-consolidation, processing during sleep may play an essential role in restabilizing the transformed memory. We discuss recent research assessing the impact of sleep on reactivated memories potentially undergoing reconsolidation. We further evaluate targeted memory reactivation, an intervention that can directly engineer reconsolidation during sleep. Although sleep may play a role in restabilizing newly-modified memories, much remains to be explored before we fully understand the supporting mechanisms.

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Introduction

Recent decades bring two facts about memory to the fore: first, sleep plays an important role in consolidation; and second, reactivating consolidated memories renders them labile again, subject to change, and in need of reconsolidation if they are to be preserved, albeit transformed. One can now pose the question: does sleep also affect reconsolidation and, if so, how? In this review, we start by sketching the background to the two pillars of this paper: sleep and memory, and memory reactivation and reconsolidation. We then review findings directly assessing the impact of sleep on reactivated, and potentially reconsolidating, memories. We consider memories reactivated during wake and during sleep.

In the early 1920's, Jenkins and Dallenbach [1] demonstrated that retention of nonsense syllables benefited from a night of sleep compared to wakefulness, showing that sleep played a special role in preserving new memories. In the decades since, repeated demonstrations show that sleep compared to wakefulness preferentially benefits certain memories [2–5]. The discovery that hippocampal place cells replay the same experience-specific neuronal firing patterns during subsequent periods of sleep suggests that sleep plays more than a passive role in memory consolidation [6–8]. Hippocampal replay is a candidate mechanism for stabilizing memory connections with the neocortex via a coordinated dialogue between slow waves (>4 Hz), sleep spindles (bursts of activation in the 9–16 HZ range), and hippocampal ripples (~80 Hz) [see Ref. [2] for review [9]]. More recent research reveals causal links between memory performance and specific electrophysiological markers, such as slow wave activity and spindles [10–12].

At the same time, memories are dynamic. During initial encoding, synaptic changes in hippocampal and cortical circuits serve to represent the details of an event, its context, and its substance. The resulting memory trace must be quickly stabilized or else become susceptible to forgetting [13–15]. The hippocampus appears particularly important for continued access to specific details. Previously consolidated memories can be reactivated, returning them to a labile state [16,17], one that again tilts the balance to hippocampal engagement [18], resulting in memory trace vulnerability and susceptibility to disruption or alteration. Furthermore, once reactivated, a memory trace must undergo a restabilization process, termed re-consolidation [13,19,20].

Sleep and reconsolidation

Does sleep also play a crucial role for memory reconsolidation? In what follows, we discuss the role sleep plays for subsequent restabilization during reconsolidation. We propose that sleep's role need not be limited to memories formed solely during wake, but instead can include processing and reconsolidation of memories reactivated during sleep itself.

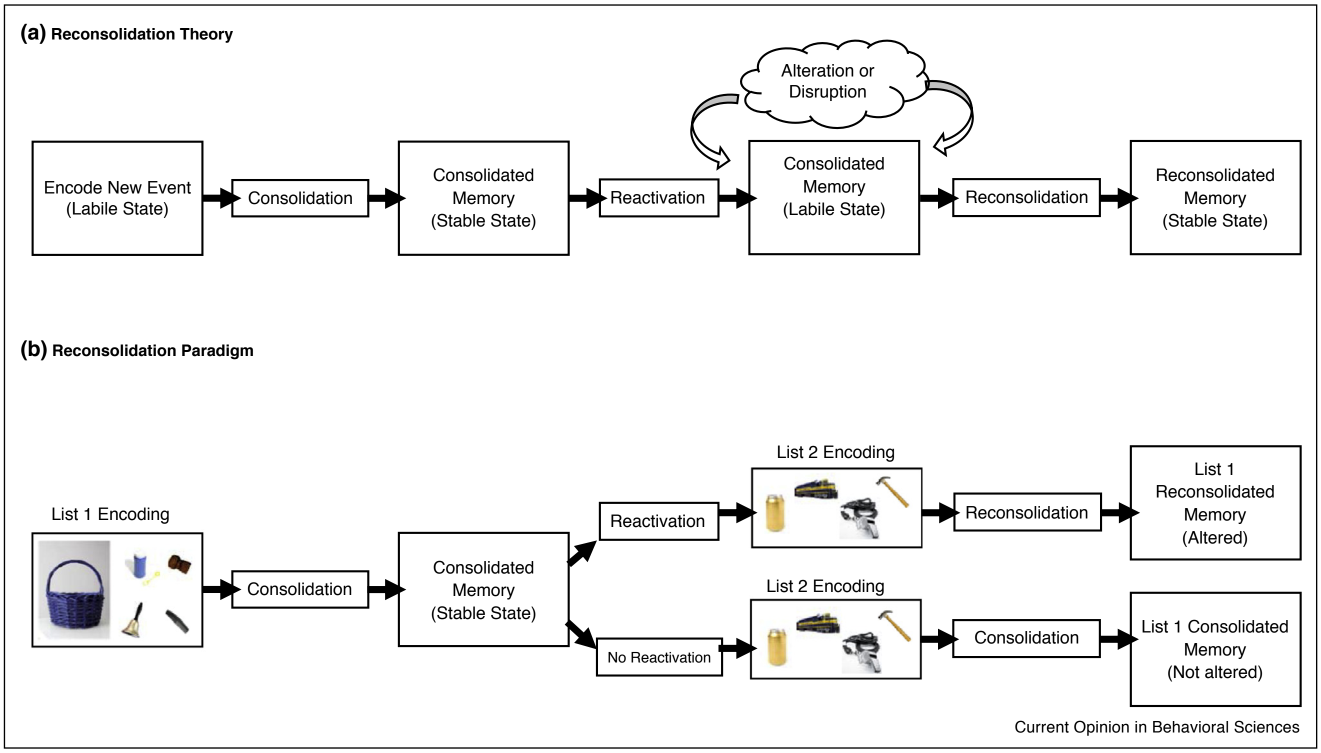
That reconsolidation starts with the reactivation of a previously formed memory distinguishes reconsolidation from consolidation, and reactivation itself is not a simple matter. A number of factors influence successful reactivation including type of reactivation cue, contextual similarities between the initial and reactivated events, timing between the formation and reactivation of a memory, and strength of the old memory [20–26]. Furthermore, reactivated memories are vulnerable to disruption [27,28] or modification [20,29–31]. Experiences that follow reactivation, and the neural processes those experiences initiate, could erase the reactivated memory trace, or modify it in a way that leads either to a loss of detail, or retention of many original details with inclusion of newly acquired details [20,29]. Whether weakened or modified, the memory trace must then be restabilized through the cellular/molecular processes supporting reconsolidation [31] (Figure 1).

The foregoing provides background to our main question: does sleep play a role in reconsolidation that differs from its role in consolidation? To address this question, we must first consider an important fact about memory reconsolidation: updating (or disruption) of a reactivated memory requires a delay for that updating (or disruption) to be evident in behavior [20,29]. That is, neither alteration nor disruption of the memory is immediately observable [27,28]. Instead, changes are only evident after a period of time, *typically filled with sleep*. Two early studies suggested that the absence, or disruption, of sleep impairs reconsolidation [32,33], but neither established a unique role for sleep.

Recent research

Klinzing *et al.* [34••] directly assessed sleep's role in reconsolidation. Participants learned the locations of card pairs, similar to the game Concentration, in the presence of an odor (Task A). A day later, some participants returned to the same learning context and received a reminder cue that consisted of initiating but immediately stopping a 'test' of the initial card pairs as if by accident. Other participants returned to a separate building and received no reminder cue (the control condition). Participants then slept or remained awake for 40 min. All participants then learned new, altered card pairs—designed to assess retroactive interference. For example, in Task A, participants learned pair A–B whereas in interference Task B, participants learned A–C (B and C represented different locations). After a short delay, all participants recalled card B's location in response to its paired A-card. In line with previous animal research suggesting faster restabilization after reactivation [35,36], Klinzing *et al.* found rapid Task A restabilization in the sleep-reactivation (but not the sleep-control) group that correlated significantly with time in slow wave sleep, a notable finding given that a 40-min sleep episode does not result in consolidation of Task A learning [37].

Figure 1



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(a) Memory reconsolidation theory schematic. Here we present the progression from new encoding through consolidation, reactivation, and final reconsolidation. **(b)** Our standard reconsolidation paradigm. Subjects learn two lists of objects spaced 48 hours apart. If reactivated before learning List 2, newly learned objects are likely to be attributed to the old, reactivated List 1 memory. If List 1 memory is not reactivated, List 2 object memory remains independent and separate.

Moyano *et al.* [38•] recently found that a 90-min nap restabilized a memory, protecting it against alteration from newly learned and potentially interfering information. Participants first learned a list of nonsense-syllable pairs (List 1), each presented in a specific context (e.g. overlaid on an image with music playing). The following day, subjects returned for a reminder cue of List 1. After reactivation, subjects slept or remained awake for 90 min, or remained awake for 10 hours. After the delay periods, all subjects learned a second, interfering list of nonsense syllables (List 2). Forcato *et al.* [39] previously demonstrated List 1 disruption up to 10 hours after reactivation, after which the syllable-pair memory showed restabilization. On Day 3, Moyano *et al.*, tested if wakefulness or sleep limited List 1 memory disruption by having participants recall both nonsense-word lists and measuring the degree of List-1 memory-trace disruption using the retrieval induced forgetting (RIF) measure. In RIF, a stable memory (List 1) causes the reduction in the recall of a second, separate memory (List 2). In contrast, if the original memory is disrupted or unstable, there is no reduction in List 2 recall. In the current study, both the 90-minute nap and 10 hr wakefulness conditions showed equivalent stable List 1 memories as evidenced by reduced List 2 recall. Whereas, the 90-min wakefulness group showed greater List 2 recall, suggesting a disrupted List-1 memory. These findings, along with Klinzing *et al.*, suggest that sleep contributes to rapidly restabilizing reactivated memory traces, reducing their susceptibility to disruption or alteration.

Brawn *et al.* [40••] further investigated the time course of stabilization and restabilization of reconsolidated memories by training song birds on two separate songs. The first song (S1) became the 'original' memory to be reactivated. Song 2 (S2) provided potentially interfering information. Across several studies, reactivation of S1 followed by training on S2, resulted in destabilization and reduced S1 performance across wakefulness. However, the more destabilized S1 became (tested before sleep), the greater the benefit of sleep on subsequent performance, restabilizing S1 song. Brawn *et al.* then repeatedly trained, reactivated, destabilized, and restabilized S1 and S2. Over the cyclic reactivations and interference learning sleep restabilized the S1 memory trace, improving its performance. Although this study clearly demonstrates the role of sleep in re-stabilizing reactivated memories, it does not address the processes happening during sleep that advance restabilization and limit memory distortion.

Our recent work investigated the role of sleep during both consolidation and reconsolidation, looking for sleep markers that could link to memory updating [41••]. First, less sleep after learning List 1 (consolidation), combined with more sleep after learning List 2 (reconsolidation) measured with actigraphy, generated higher rates of memory updating reflected in List-2 object attribution to List 1. In a second, complementary experiment using polysomnography, participants with lower rates of sleep spindles after consolidation and higher rates of sleep spindles after reconsolidation also showed greater rates of memory updating. In contrast to other studies, we did not find a correlation between spindles during consolidation and subsequent updating, which may suggest differing roles of sleep during the restabilization of the reconsolidated trace. Bryant *et al.*'s findings suggest that sleep helps restabilize a reactivated trace, potentially protecting it from interference. Furthermore, spindles might reflect processes unique to memory reconsolidation.

So far, our discussion focuses on the impact of sleep on memories reactivated during wakefulness. A handful of recent studies investigate the impact of reactivating memories during sleep, using techniques collectively referred to as 'targeted memory reactivation (TMR; see Ref. [42] for review). Born and Rasch [43] proposed that during sleep, memories could be reactivated and made labile, paralleling waking reconsolidation and supporting the integration of new information into pre-existing knowledge networks and the subsequent stabilization of this modified memory trace. However, in contrast to the situation during wakefulness, during sleep there is limited ongoing interference. This might remove the possibility of disruption or alteration leading to a default restabilization of sleep-reactivated memories, resulting in stronger and more integrated traces.

TMR provides an opportunity to engineer sleep; specifically cueing certain memory details for alteration [42]. In these paradigms, participants learn information paired with a sound or odor during wake (e.g. participants encoded the location of a train on a grid while hearing a train whistle). During sleep, the associated sound or odor is cued, potentially triggering the reactivation of a specific memory detail. Participants subsequently remember cued details at greater rates than non-cued details, suggesting that memories are indeed activated and modified (here strengthened) during sleep. Thus, one could test whether reconsolidation can be engineered during sleep by reactivating a memory with a cue (sound or odor), which should momentarily return it to a labile state, before providing new learning, and later assessing the extent of memory updating.

Siebold *et al.* [44] attempted to directly engineer reconsolidation in this way during sleep. They trained participants on two lists of 2D-object-location pairings across two days. Participants learned the first list in the presence of an odor on Day 1. During a nap after learning List 2 on Day 2, the List 1 odor was re-presented, presumably cueing the first memory during a period of sleep when List 2 memory might be spontaneously reactivated and consolidated. In particular, the presentation of the List 1 odor cue during the nap on Day 2, after List 2 learning, might activate the List 1 memory, inducing interference with List 2 consolidation, resulting in a weakening of one or both of the memory traces. Prior literature typically shows alteration or modification of the List 1 memory after reactivating it during wakefulness and before List 2 learning [20,29–31]. However, the authors found improved memory performance for both lists. Given that strengthening of a memory can result from both consolidation and reconsolidation, it is possible both lists were reactivated or perhaps List 2 was strengthened through typical consolidation processes whereas reactivation strengthened List 1 independently (see also Ref. [44–46]).

In contrast to Siebold *et al.*'s [44] failure to observe strong evidence of TMR-engineered memory alteration during sleep, we recently demonstrated simultaneous reactivation of two different memories during sleep, and subsequent memory-performance disruption from combining cues during TMR [47••]. Although we did not test reconsolidation in the standard sense, what we accomplished shows that it is possible to reactivate and alter memories during sleep. During wakefulness, we trained participants on a forget-cue (a tone) using a modified directed forgetting paradigm. Every time participants heard the cue they were to forget the word they had just read. In the absence of the cue they were to remember the word. We then trained participants on visually presented object-location pairings while hearing an appropriate sound with each object, for example, participants saw a train and heard a train whistle. That night, during sleep we reactivated some of the objects with their sounds and a few seconds later presented the previously established forget cue — the tone from the modified directed-forgetting paradigm. One week later, we tested participants' memory for all the objects. Participants forgot more TMR-cued objects (objects paired with the forget cue) than uncued objects suggesting that during sleep one can reactivate a consolidating memory (the one being formed about objects and their locations) and alter it by presenting additional, destabilizing information (the forget cue).

Two recent TMR studies have reactivated multiple, overlapping and competing memory details. In the first, participants learned locations for identical pictures (X1–X2), for example participants saw a dog image in 2 locations [48]. After a short (5 min) or long delay (3 hours), participants learned a new picture location for one of the objects creating a new paired object-location association (X1–X3) while also hearing a sound representative of that object. For example, one of the dog images was moved and the sound 'woof' was heard. Subjects then underwent TMR during a nap with some of the pairs cued. This theoretically reactivated overlapping pair representations, X1–X2 and X1–X3, which would have differing inter-object associations given the delay between learning. For example, there would be a strong association between pairs in the short delay condition and weaker associations across the longer delay. After sleep, in the short-delay condition cued pairs showed improved X2 location accuracy compared to non-cued objects, but disrupted recall was observed in the long-delay condition. This suggests that the proximity between learning of overlapping associated information and reactivating the interfering detail (X1–X3) has critical consequences for subsequent gains or losses. A second study that involved learning associations between sounds, objects, and distinct spatial locations [49••], where the spacing between pairs of objects and individual object reward value was manipulated, showed that TMR provided benefit only during spaced learning. In contrast, TMR induced interference for the best-learned consecutively presented pairs, presumably when cued competition between memory details was greatest. Although these studies engineered TMR to induce competition during sleep, rather than reconsolidation, both instantiate the reactivation of a single memory cue with overlapping, interfering information, resulting in disruption in most but not all cases (the exception being Siebold *et al.* [44]).

Altogether, it continues to remain an open question as to whether the mechanisms supporting reconsolidation are the same during wakefulness and sleep. Klinzing *et al.* [50••], using the methods described above [36], recently provided evidence suggesting these mechanisms may differ. During sleep, they pharmacologically induced a heightened state of acetylcholine—which is typically high during waking encoding and low during consolidation in NREM — while simultaneously administering odor-based TMR. Their results demonstrated that cued memory performance benefitted from odor-based TMR, no matter the acetylcholine level during sleep. This contrasts with Gais and Born [51], who reported the elimination of the sleep-dependent memory benefit with heightened acetylcholine. If TMR is effective irrespective of level, as the authors show, this suggests other mechanisms are at play.

Conclusion

Current evidence provides support for the role of sleep in enhancing reconsolidation of memories formed during wake. In particular, reactivation results in faster [36] and more durable [40••] restabilization during sleep, and sleep contributes more to restabilization for memories that showed greater disruption in wakefulness [42]. However evidence that sleep contributes differentially to consolidation and reconsolidation is currently limited to the finding that sleep spindle activity contributed differentially to consolidation and reconsolidation [43]. Whether memories can be reconsolidated via re-engineering during sleep is also unclear, warranting more research. The absence of interfering activities in the sleep state could alone lead to unexpected outcomes for memories activated and potentially manipulated during sleep. Sleep-based reconsolidation, triggered by TMR or other methods, could provide significant translational opportunities [47••,48,49••]. Furthermore, should sleep be instrumental in restabilizing newly modified memories [36,40••,42], those triggered during sleep may be further impenetrable to future modification. At this time, more research is needed into the basic mechanisms behind the re-stabilization of memories that are cued during sleep and the consequences of these processes for reconsolidated memories.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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This study directly examined sleep's role in reconsolidation. Participants learned paired-object card locations (A–B) in the presence of an odor. One day later, half the subjects participants' memory was reactivated. Participants then slept or remained awake for 40 min. All participants learned a second interfering card pair's (A–C) location, with one card (A) remaining in the position. All participants then recalled the first cards locations. Participants who slept after memory reactivation showed speeded restabilization which also correlated with time in slow wave sleep.

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This study showed that a 90-min nap re-stabilized a memory, protecting it against alteration from newly learned and potentially interfering information. Participants learned a set of nonsense-syllable pairs on Day 1. On Day 2 the memory was reactivated after which it was followed by sleep or wake. After the delay, participants learned an interference task. This who slept after the reactivation showed intact, stable memory for the first card list and increased recall errors for the second list. In contrast, those in the reactivation-wake control condition continued to show a reactivated, labile memory.

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The authors showed the time course of reactivating and reconsolidating memories in song birds. In the study, birds were repeatedly trained on a song which was reactivated, destabilized, and restabilized. Sleep, compared to wakefulness, played a unique role in re-stabilizing the memory trace.

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Bryant *et al.* conducted two studies evaluating the sleep across a multi-day object reconsolidation study. In the first study, they found that less total sleep time after consolidation, combined with more sleep after reconsolidation increased rates of memory alteration. In the second study, those with lower rates of sleep spindles after the first object list-learning and higher rates of sleep spindles after the second object list showed greater rates of memory modification. This was the first study to suggest a unique role of specific electrophysiological sleep events in reconsolidation compared to consolidation.

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Siebold *et al.* attempted to use targeted memory reactivation (TMR) to engineer reconsolidation during sleep. They trained participants on two lists of 2-dimensional object-locations across two days, the first being associated with an odor. During the period of sleep after the List 2 learning, they cued List 1 with odor-based TMR which was expected to activate List 1 memory, inducing interference with List 2 consolidation, List 1 reconsolidation, or both. Previous reconsolidation literature typically shows alteration of the older memory. Rather than disruption, they found strengthening of both memories.

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This is the first TMR study to show that two separate memories can be reactivated causing interference to one of the memories. We first trained participants on an auditory forget cue using a modified directed forgetting paradigm. We then trained participants on a series of object-location pairings with associated sounds. During sleep, we reactivated some of the objects sounds and the forget cue. One week later, participants' memory was lower for TMR-cued objects (objects paired with the forget cue) than uncued objects. This demonstrated a reconsolidation like effect: one can reactivate a consolidating memory (objects-locations) and alter it by presenting additional, destabilizing information (the forget cue).

48. Oyarzún JP, Morís J, Luque D, de Diego-Balaguer R, Fuentemilla L: **Targeted memory reactivation during sleep adaptively promotes the strengthening or weakening of overlapping memories**. *J Neurosci* 2017, **37**:7748-7758 http://dx.doi.org/10.1523/JNEUROSCI.3537-16.2017.

49. •• Antony JW, Cheng LY, Brooks PP, Paller KA, Norman KA: **Competitive learning modulates memory consolidation during sleep**. *Neurobiol Learn Mem* 2018, **155**:216-230 http://dx.doi.org/10.1016/j.nlm.2018.08.007

In this study, subjects learned object-location-sound associations. In some cases, a pair of objects were linked to the same sound while others a single sound. Objects linked by sounds were trained using consecutive or spaced learning and had individual reward value increasing the likelihood of object-competition. During sleep, some objects were cued. TMR only provided a benefit for objects paired to a same sound that had spaced learning. Furthermore, those cued that had the greatest competition (best learned consecutively presented pairs) showed the greatest performance disruption. This study suggested that cueing potentially competing information induces interference and disruption of both memories.

50. •• Klinzing JG, Kugler S, Soekadar SR, Rasch B, Born J, Diekelmann S: **Odor cueing during slow-wave sleep benefits memory independently of low cholinergic tone**. *Psychopharmacology* 2018, **235**:291-299

Using the same methods described in [34], the authors pharmacologically administered an acetylcholine-esterase inhibitor to artificially increase the acetylcholine level during odor-based TMR. They found no differences in subsequent memory performance between cued conditions with heightened v. typically low levels of acetylcholine suggesting that mechanisms for reactivation during wakefulness and sleep may differ.

51. Gais S, Born J: **Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation**. *Proce Natl Acad Sci U S A* 2004, **101**:2140-2144 http://dx.doi.org/10.1073/pnas.0305404101.