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# Memory consolidation and reconsolidation: what is the role of sleep?

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**Memory consolidation and reconsolidation reflect molecular, cellular and systems-level processes that convert labile memory representations into more permanent ones, available for continued reactivation and recall over extended periods of time. Here, we discuss the complexities of consolidation and reconsolidation, and suggest they should be viewed not as all-or-none phenomena, but as a continuing series of biological adjustments that enhance both the efficiency and the utility of stored memories over time and in response to changing needs of the organism. As such, consolidation and reconsolidation might be better thought of as memory organization and reorganization. A rapidly growing body of evidence suggests that many of these processes are optimally engaged during sleep.**

## Introduction

The original concept of memory 'consolidation' described the conversion, over a period of minutes to hours, of an unstable memory trace into a stable form that is resistant to degradation over subsequent days to years [1–3]. As such, consolidation is triggered by memory encoding (acquisition). But this notion of a single, relatively rapid process of memory consolidation has yielded to one that includes phases of stabilization, enhancement and integration, extending over hours to years. In addition, the idea of these processes occurring inexorably over specific time intervals has given way to one that acknowledges important roles for specific wake–sleep states in these consolidation processes.

In contrast to the concept of consolidation is the suggestion that later recall returns the consolidated memory representation back into an unstable form, once more requiring consolidation, or 'reconsolidation'. Therefore, reconsolidation is triggered by memory recall (reactivation). Our understanding of memory reconsolidation is at an earlier stage than that of consolidation. Its component processes, and their time courses and functions, are not well defined, and almost no attention has been paid to their possible dependence on brain states. As a result, there has been little discussion of the significance or possible functions of these processes. Recent evidence that reconsolidation can be blocked by ACh-reuptake inhibitors and β-adrenoceptor blockers, which mimic normal sleep-dependent changes, and by classic interference training suggests that reconsolidation processes could be part of an essential mechanism involved in the offline reprocessing of existing memories.

Here, we review literature supporting the hypothesis that the multiple stages of memory consolidation and reconsolidation form a coherent whole, which functions to integrate initially encoded memories optimally into the existing informational networks of an organism, and which continues to refine and remodel these memories following reactivation, during waking and sleep.

## Memory systems and brain states

Before we consider the different stages involved in memory processing, two important points must be made. First, although often used as a unitary term, 'memory' is not a single entity. For example, human memories are normally divided into declarative and non-declarative memory systems [4] (Figure 1a), although most cognitive operations utilize multiple memory systems in concert or even in opposition to one another [5].

Second, it is important to keep in mind that the brain does not reside in one single physiological state across the day, but instead cycles through periods of differing neural and metabolic activity, associated with distinct biological states, most obviously those of waking and sleep. Sleep itself has been broadly divided into rapid eye movement (REM) sleep and non-REM (NREM) sleep, which alternate across the night, in a 90-min cycle in humans (Figure 1b). Thus, like memory, sleep must be treated as a range of stages distinct in physiology and neurochemistry that can contribute independently to memory processing [6].

## Memory stages: consolidation and reconsolidation

Stable, long-term memories evolve over time in several distinct stages (Figure 2). The initial encoding of a memory is a rapid process (taking from milliseconds to seconds). But after this initial acquisition, the memory remains susceptible to change or loss. Thus, long-term maintenance (continuing for hours to years) requires a second process, or set of processes, termed memory consolidation [7].

When originally proposed in 1900 [7], consolidation was defined as resistance to interference from competing

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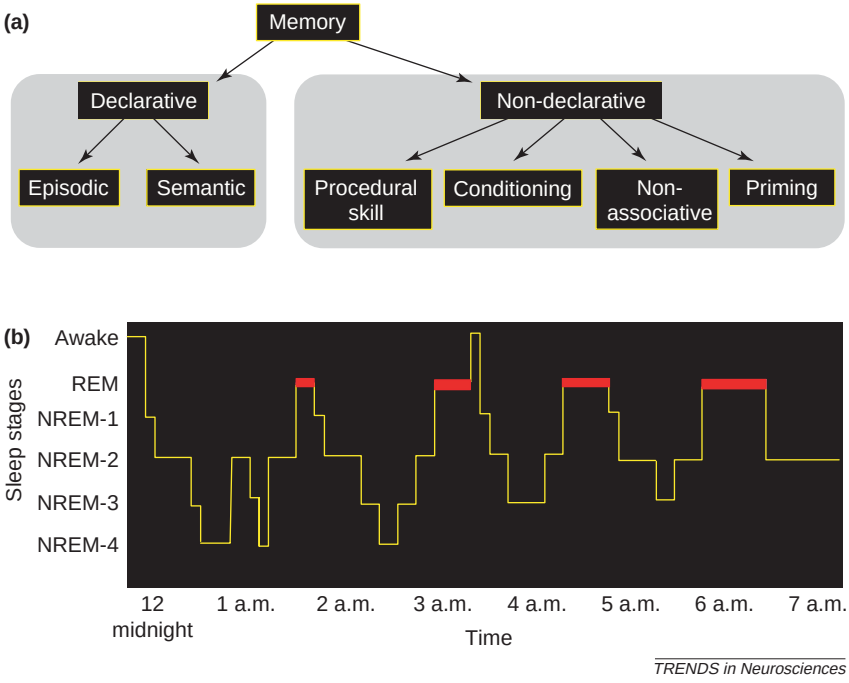


**Figure 1.** Forms of memory and stages of sleep. Neither memory (a) nor sleep (b) represents a homogeneous phenomenon. **(a)** Declarative memory includes consciously accessible memories of fact-based information (i.e. knowing 'what'), and contains several subcategories, including episodic memory (memory for events in one's past) and semantic memory (memory for general knowledge) [4]. By contrast, non-declarative memory includes all non-conscious memories, and has subcategories such as conditioning, implicit memory and procedural memory (i.e. knowing 'how'). **(b)** In humans, sleep follows a 90-min cycle of alternating REM (in red) and NREM sleep. In primates and felines, NREM sleep has been divided into sub-stages 1 to 4, corresponding to increasingly deeper states of sleep [67]. The deepest NREM stages, stages 3 and 4, are collectively referred to as 'slow-wave sleep' (SWS), based on a prevalence of low-frequency (0.5–4.0 Hz) cortical oscillations. Dramatic changes in brain electrophysiology, neurochemistry and functional anatomy occur across these sleep stages (shown here for a typical night), making them biologically distinct from the waking brain, and dissociable from one another. For example, SWS is characterized by diminution in cholinergic neuron activity; REM sleep is characterized by suppression both of noradrenaline release from the locus coeruleus and of serotonin release from the Raphe nucleus.

memories. Animal studies in the middle of the 20th century demonstrated that such consolidation was also required for resistance to the more drastic actions of electroconvulsive shock (ECS) [8] and protein-synthesis inhibitors [9]. More recently, human motor-skill memories were reported to be disrupted by training on an alternate task within the first several hours after training, suggesting that such learning also requires a process of consolidation [10,11], although others have failed to reproduce this effect [12]. In any case, it is likely that these memories remain sensitive to ECS and protein-synthesis inhibitors for several hours [13], reflecting a required process of consolidation. Indeed, there is little objection to the view that conversion of initial memory traces into long-term memories requires protein synthesis [3]. Whether consolidation is observed thus depends on how interference is attempted. But it also depends on how learning is measured. In one case, interference of sleep-dependent consolidation was seen when consolidation was measured as improved performance accuracy, but not when measured as improved speed [11].

There is little clarity on what other forms of post-encoding memory processing should be included under the rubric of consolidation. In general, processes that are automatic and occur without intent or awareness are included, and those that require either conscious or behavioral rehearsal are not. Thus, the development of hippocampal independence as described by McClelland and colleagues [14] would be included, but improvement through physical or mental rehearsal would not.

Consolidation can also enhance memories, improving behavioral performance, independent of further practice [6]. There are several reasons to believe that stabilization and enhancement reflect distinct processes [6]. First, the consolidation processes leading to enhancement of a motor sequence learning task continue for up to ten times the initial period of stabilization [11,15] (Figure 2), and those for a visual discrimination task continue for at least two days [16]. Second, although stabilization of the motor sequence task occurs over six hours of waking, the enhancement phases both for this task and for a visual discrimination task occur only during sleep [16,17]. Finally, patterns of regional brain activation during performance of these tasks change following sleep and, for the motor sequence task, are different after sleep compared with patterns after an equivalent time awake [18,19]. Thus, stabilization *per se* is not sufficient to produce this shift in activation patterns.

Other post-encoding stages of memory processing include the integration of recently consolidated memories into existing memory networks [20,21], the development of hippocampal independence for declarative memories [14,22], and even the active weakening of memories [23], all of which have been hypothesized to occur during sleep.

Finally, following its initial stabilization, a memory can be retained for weeks to years, during which time it can be

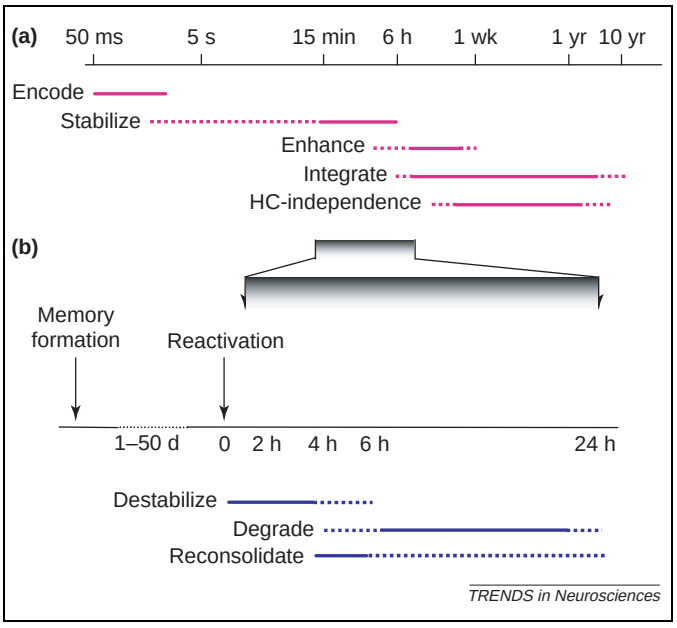


**Figure 2.** Time course of memory processes. **(a)** Memory formation and consolidation. After the initial rapid encoding of a sensory experience, the neural representation of the memory can go through several automatic processes, independent of rehearsal, intent or awareness. These can stabilize and enhance a memory, so it is resistant to interference and more effective to guiding behavior, and can also integrate the memory into larger associative networks. The latter process is thought to permit episodic memories to be recalled without hippocampal (HC) involvement. The extent to which such processes affect different memory systems is unclear. Note the logarithmic time scale. **(b)** Memory reactivation and reconsolidation (featuring an enlargement of (a), as indicated by the gray shading). After stabilization is complete, reactivation of a memory can lead to its return to an unstable form. Normally, such memories appear to be reconsolidated following this destabilization but, if such reconsolidation is blocked, degradation of the memory can ensue (see also Figure 4). Solid bars represent periods of known processing; dotted bars reflect hypothesized or variable periods of processing.

effectively recalled. But the act of memory recall itself can destabilize the memory, making it again labile and subject to subsequent degradation. Reconsolidation – the transformation of the now destabilized memory into a restabilized form – has therefore been proposed [24]. When a destabilized memory is not reconsolidated, it can degrade (Figure 2), although it is unclear whether the memory trace is actually weakened or simply made inaccessible to recall processes.

Why this plethora of slow, state-dependent processes? Memory consolidation and reconsolidation could serve at least three conceptually distinct functions. Some components appear necessary simply to cope with the constraints of the brain. Thus, the molecular mechanisms that support rapid memory encoding (e.g. $Ca^{2+}$ influxes) are inadequate for long-term maintenance of synaptic changes, whereas processes that support long-term maintenance (e.g. protein synthesis) cannot be accomplished quickly enough to support rapid encoding [25]. Similarly, network structures that can capture an episodic memory might likewise be incapable of supporting dense network storage of memories [14].

But processes of consolidation over time can also facilitate behavior, often through offline memory reorganization [26]. For example, they could: (i) automate behaviors, shifting representations from declarative to procedural systems and reducing frontal demands, (ii) extract valuable details from complex episodic memories, and (iii) integrate this information into associative networks. Finally, continued plasticity over time is crucial if old memories are to become integrated with newly acquired information [27]. For all of these memory processes, sleep can have an important role in meeting the demands of the organism.

## Sleep and memory consolidation

Over the past ten years, a large body of evidence has supported a role for sleep in the offline (re)processing of memories. We have recently reviewed evidence for the crucial role of sleep in memory consolidation [28], and here summarize only briefly this extensive literature (for an opposing viewpoint, see [29]).

Discrete stages of sleep appear to be crucial for specific steps in the development of various forms of memory; for other steps, periods of being awake appear to be sufficient [6]. For example, stabilization of some forms of procedural motor memory can develop across 3–6 waking hours [10,11,13]. By contrast, the enhancement phase of procedural sensory and motor memory consolidation has almost always been found to depend on overnight sleep, and equivalent time periods awake result in no performance gains [11,15–17,30–41] (Figure 3). Interestingly, although these overnight enhancements are seen across a range of memory tasks, they appear to rely on different sleep-stages or sleep characteristics. NREM sleep [both its stage-2 and slow-wave sleep (SWS) components] and specific physiological characteristics of NREM have been related to the consolidation of motor skill tasks [17,30,33,34,42], and both SWS and REM sleep have been associated with the consolidation of visual skill memory [16,35,36]. Thus, different forms of procedural memory require uniquely different sleep-stage-dependent brain states for consolidation enhancement. In addition, selective deprivation of specific sleep stages, and even specific sleep-stage time windows, can inhibit memory consolidation [43,44], suggesting that there might be more than a single phase of sleep-dependent consolidation [16,45].

Exceptions exist. Post-training improvement of a serial reaction time task (SRTT) was sleep dependent when subjects were explicitly aware that there was a sequence to be learned, but occurred across both wake and sleep states when subjects were not so informed [33]. In addition, an auditory task showed time-dependent enhancement even in the absence of sleep [39] (although see [38]). An important unanswered question is why only some procedural tasks show this sleep-dependent enhancement.

The situation is less clear with regard to declarative memory formation, with some early studies supporting a role for sleep-dependent memory consolidation, and others reporting little effect [46]. Using a declarative word-pair-associates task, Born and colleagues have more recently shown that daytime training can trigger changes in characteristics of early-night SWS, with modifications reported both in the number of sleep spindles [47] and in the coherence of NREM low-frequency electroencephalogram (EEG) oscillations [48]. Furthermore, periods of early-night sleep, rich in SWS, were particularly beneficial for this consolidation [49]. This effect is seen only during SWS-rich periods early in the night, and not in REM-rich periods later in the night, suggesting that physiological

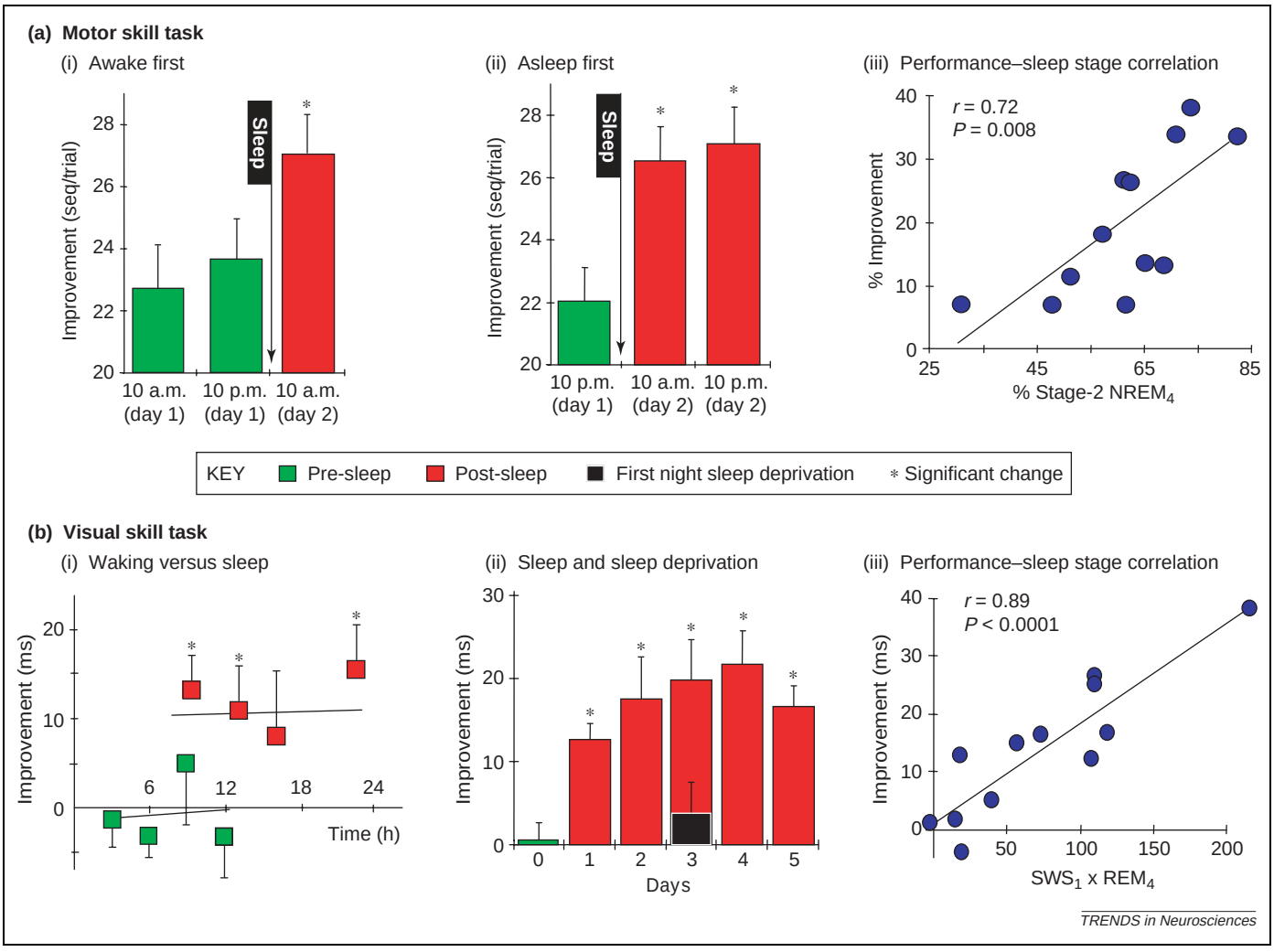


**Figure 3.** Sleep-dependent visual and motor skill learning in the human brain. **(a)** Motor skill task. (i) Awake first. Subjects ($n$=15) trained at 10 a.m. on day 1 (green bar) showed no significant change in performance (in sequences per trial) at retest following 12 h of being awake (10 p.m. on day 1, green bar). However, by the second retest, following a night of sleep (10 a.m. on day 2, red bar), performance improved significantly. (ii) Asleep first. Following evening training (10 p.m. on day 1, green bar), subjects ($n$=15) showed significant improvements in speed just 12 h after training following a night of sleep (10 a.m. on day 2, red bar) but expressed no further significant change following an additional 12 h of being awake (10 p.m. on day 2, red bar). (iii) The percentage of overnight improvement on the motor skill task correlated with the percentage of stage-2 NREM sleep in the last quarter of the night ($NREM_4$). Using data from [17]. **(b)** Visual skill task. Subjects were trained and then retested at a later time, with improvement (ms) in performance illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects. (i) Waking versus sleep states. Subjects ($n$=33) trained and then retested 3, 6, 9 or 12 h later the same day (green squares), showed no significant improvement as a consequence of the passage of waking time for any of the four time intervals. By contrast, subjects ($n$=39) trained and then retested 8, 12, 15 or 23 h later, after a night's sleep (red squares), showed significant improvement. (ii) Sleep and sleep deprivation. Subjects ($n$=89) trained and retested 1–7 d later (red bars) continued to improve after the first night, without additional practice. Subjects ($n$=11) sleep-deprived on the first night after training showed no improvement, even after two nights of recovery sleep (black bar). (iii) Overnight improvement was correlated with the product of the percentages of SWS in the first quarter of the night ($SWS_1$) and REM sleep in the last quarter of the night ($REM_4$). Using data from [16,37]. Asterisks indicate $P<0.05$; error bars indicate SEM.

processes unique to particular stages of sleep are crucial for this consolidation [28]. Arguing against this position, Wixted [50] has suggested that SWS sleep merely provides a time of minimal memory interference that protects word-pair memories from disruption. But Peigneux and colleagues [51] found that overnight improvement in a hippocampally-mediated spatial memory task was positively correlated with increased hippocampal activation during SWS – a finding that would seem to argue for active processing during sleep.

## Sleep-dependent plasticity

The evidence for sleep-dependent consolidation is not limited to behavioral data. Evidence of sleep-dependent plasticity at both local and systems levels suggests that sleep has a crucial role in consolidation processes leading to memory enhancement. At the systems level, functional neuroimaging studies have demonstrated reactivation of patterns of brain activity seen during task training across subsequent sleep [51], matching similar patterns of post-training reactivation in rat hippocampal neurons (e.g. [52]). Furthermore, recent brain-imaging investigations have reported an overnight, systems-level reorganization of memory in association with sleep-dependent learning [18,19].

At the molecular level, although several immediate-early genes (IEGs) are specifically downregulated, ~100 genes are preferentially upregulated during sleep [53]. For example, during REM sleep following exposure to a rich sensorimotor environment, the plasticity-associated IEG *zif-268* is upregulated in granule cells of the hippocampal dentate gyrus, and in the piriform and frontal

cortices. However, *zif-268* is downregulated in the absence of such exposure [54]. Taken together, behavioral, brain, cellular and molecular studies across species indicate that distinct components of memory consolidation take place across a range of memory systems, and a range of wake–sleep states. To date, all stages of sleep except sleep onset (stage-1 NREM sleep) have been implicated in these consolidation processes.

## Reconsolidation

Although originally reported in the 1960s [1,2], memory reconsolidation has more recently come under renewed investigation [24]. Most recent studies have focused on the conditions under which reconsolidation can be observed, and the degree to which it differs from the initial processes of encoding and consolidation [55]. Several additional questions have not been as widely addressed. Specifically, there are at least four processes that a consolidated memory can undergo: (i) reactivation, leading to (ii) destabilization, which in turn leads to either (iii) degradation or (iv) reconsolidation (Figure 2b); the time courses of these individual steps, the mechanisms and brain states that produce them, and even their biological functions, have only begun to be investigated.

### *Time course of reconsolidation*

Although memory reactivation can presumably occur in a fraction of a second, the destabilizing effects of such reactivation appear to require longer periods of reactivation, and the extent of subsequent destabilization (defined as the extent of memory degradation seen following prevention of reconsolidation) is correlated with the time spent in a previously learned environment. Nader *et al.* [56] re-exposed rats to a fear-conditioned tone for just 30 s and produced significant destabilization. By contrast, Suzuki *et al*. [57] re-exposed rats to a fear-conditioned environment, and found destabilization after 3 min of exposure, but not after 1 min. After more intense training (three footshocks per trial rather than one), 10 min of re-exposure was required [57]. Thus, as the characteristics (e.g. strength) of a memory change, longer periods of reactivation might be required. This parallels findings that the susceptibility of initial consolidation to interference also can depend on the intensity of training [58].

Determining the time course over which destabilization develops is difficult, because neither cellular–molecular nor behavioral correlates have been identified. But its duration has been studied extensively, with the destabilized state ending by definition when reconsolidation is complete. Thus, when reconsolidation of learning on a radial maze task was blocked using propranolol 5 min, 2 h or 5 h after re-exposure, error rates measured 24 h after reactivation increased sixfold, threefold or not at all, respectively [59], suggesting a half-life for the destabilized state of ~2 h. Inhibition of reconsolidation for conditioned taste aversion showed a similar half-life for the destabilized state (~1 h), with reconsolidation again no longer blocked after 6 h [60]. Similarly, protein-synthesis inhibitors injected 6 h after re-exposure had no effect on destabilized fear-conditioned memories [56]. Thus, reconsolidation would appear to be complete (and hence destabilization ended) by 6 h, after which the memory trace is again resistant to interference.

To date, degradation has been defined only behaviorally (as reduced performance of the learned task or response) and there is little data on its time courses. Following reactivation and blockade of reconsolidation, previously learned behaviors are still intact 2 h [57] and 4 h [56,61,62] later. This makes sense, because reconsolidation appears to take at least this long, and it would be counterproductive for memories to begin to degrade before reconsolidation has had time to complete (Figure 4, vertical dashed line). By 24 h after reactivation, any degradation of the memory appears to be complete [62–64] (see also table 1 in [65]). But little if any data are available for intervals between 4 h and 24 h.

### *Sleep and reconsolidation*

The extreme experimental techniques classically used to prevent reconsolidation (e.g. ECS) might suggest that reconsolidation serves no practical purpose other than preventing inadvertent memory degradation. However, we view destabilization and reconsolidation as sophisticated modulating mechanisms. Hints of their complexity come from studies showing that inhibitors of ACh-mediated [63] and noradrenaline-mediated [59] neuromodulation can prevent reconsolidation, and that NMDA receptor antagonists can block destabilization [66]. But perhaps the most direct evidence comes from studies of sleep-dependent memory processing.

As with initial memory consolidation, it has generally been assumed that reconsolidation processes progress over a specific period of time, independent of brain state. Yet as more and more phases of consolidation are found to be influenced by, and in some cases dependent on, sleep, it is important to ask what role sleep might have in reconsolidation. Although few data directly pertain to this question, we offer the hypothesis that both degradation and reconsolidation processes can, and in some circumstances must, occur during sleep. Indeed, most rodent studies of reconsolidation are carried out during the light (sleep) phase of the circadian cycle, and it is likely that animals in these studies slept between reactivation and subsequent measurements of reconsolidation. Thus

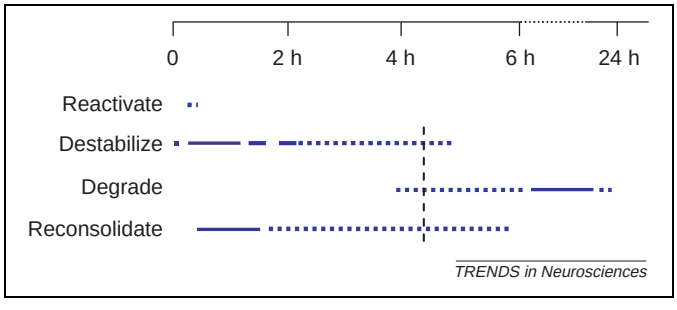


**Figure 4.** Time course of reconsolidation and associated processes. Although reactivation of a memory can occur in milliseconds, destabilization of a memory appears to require more sustained reactivation. Degradation of the destabilized memory presumably does not normally begin until after reconsolidation would normally be complete, thus preventing any deterioration in normal conditions. The vertical dashed line represents the hypothesized border between the end of normal reconsolidation and the start of degradation. Solid horizontal bars represent periods of known processing; dotted bars reflect hypothesized or variable periods of processing.

existing evidence cannot distinguish between time-dependent and sleep-dependent reconsolidation.

Evidence that sleep has a role comes from studies of procedural memory reconsolidation in humans [11], in which subjects learned a short motor sequence. When retested the following day ('day 2'), subjects showed overnight sleep-dependent enhancement of both speed and accuracy (Figure 5a, 'none'). However, if a second, competing sequence was learned 10 min after the first sequence, interference of sleep-dependent consolidation was observed (Figure 5a, '10 min'): the normal delayed overnight improvement in accuracy was completely blocked [17]. If the time between learning the two sequences was increased from 10 min to either 6 h (Figure 5a, '6 h') or 24 h (Figure 5b, 'none'), no significant interference was observed. Thus, a time period between 10 min and 6 h provided the memory with a level of stabilization that was still present 24 h later, following sleep.

By contrast, if the original memory was reactivated (through 90 s of rehearsal) just before interference training on day 2, a 57% decrease in accuracy was seen across the subsequent night of sleep (Figure 5b, 48 h), returning subjects' accuracy to slightly below the level at the end of the original training session. Thus, it is clear that reactivation can lead to destabilization of the sleep-enhanced memory. Presumably, under normal conditions, this memory restabilizes over the next 6 h, becoming once again resistant to interference, although this reconsolidation was not explicitly measured.

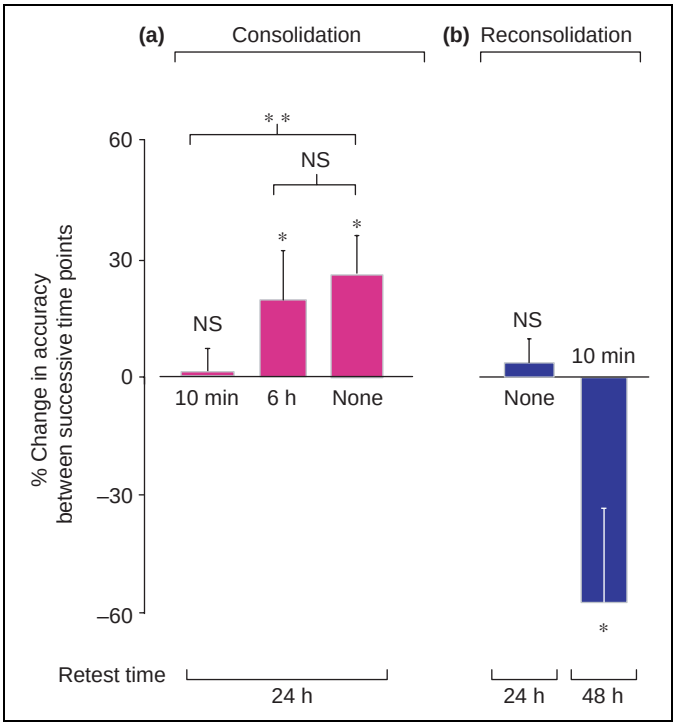


**Figure 5.** Reconsolidation of sleep-dependent learning. **(a)** Consolidation. Interference training (a second competing motor sequence) at 10 min, but not at 6 h, post-training reduced overnight improvement in accuracy relative to that of controls without interference ('none'). **(b)** Reconsolidation. Interference training 10 min after reactivation (retest 24 h after initial training) did not cause an immediate deterioration in the overnight improvement, but 24 h after reactivation and interference training, the initial overnight improvement was abolished (retest 48 h after initial training). Modified from [11]. Abbreviation: NS, not significant. Asterisks indicate significant improvement; error bars indicate SEM. Values are calculated as the percentage change in accuracy between successive test–retest intervals. Using data from [11].

These results lead to two conclusions. First, reconsolidation can be blocked by ecologically relevant stimuli, such as a competing motor sequence, without extreme electrical or chemical interventions [11]. Second, the deterioration in performance seen following blockade of reconsolidation might be limited to the reversal of earlier sleep-dependent consolidation.

## Final comments

Functional synaptic stability requires molecular plasticity [27], so that the encoding of new information necessarily modifies the storage of older memories. The processes of memory consolidation and reconsolidation offer a series of opportunities for such plastic modification to occur, and might be thought of as processes of memory organization, reorganization and refinement. Some of these events, such as initial stabilization, might reflect simple strengthening of the initial memory trace, but sleep-dependent stages of enhancement and possibly reconsolidation are likely to be more complex, integrating memories within neural networks and across memory systems.

In a pilot study, we asked whether non-conscious, non-volitional reactivation of memory traces during sleep was sufficient to destabilize these memories and make them again susceptible to interference and degradation (R. Stickgold and M.P. Walker, unpublished). We trained human subjects on the motor sequence task shortly before bed. Six hours into sleep, when sleep-dependent consolidation is thought to be in progress [17], subjects were awakened and either trained on a new motor sequence or allowed to read a magazine for an equivalent period of time. However, they did not practice, and hence intentionally reactivate, the initial memory as in earlier studies [11]. Following an additional 2 h of sleep, they were again awakened, and retested on the original sequence learned the day before. Control subjects, who did not receive late-night interference training, showed a normal 21% enhancement of speed in the morning. By contrast, subjects who had received late-night interference training showed only 9% improvement, 59% less than the controls ($P=0.03$, R. Stickgold and M.P. Walker, unpublished) – strikingly similar to the 57% deterioration seen after daytime reactivation and interference (Figure 5). The fact that similar training is resistant to interference 6 h after training suggests that reactivation during sleep could have destabilized the memory, allowing subsequent interference. Whether similarly effective interference could occur during sleep (e.g. while dreaming) is unknown, and these are still preliminary findings.

Another strong prediction of our model is that degradation of memories following reactivation necessarily occurs during sleep. Thus, it predicts that rats sleep-deprived for 24 h after reactivation and interference (e.g. using protein-synthesis inhibitors) would show no deterioration in performance at retest. Similarly, in humans, deterioration should be seen 12 h after reactivation and interference if, and only if, the interval includes sleep. Such findings would provide substantial support for the hypothesis that sleep-dependent mechanisms of

consolidation and reconsolidation enable memory organization and reorganization.

One might argue that because stabilization is complete within hours, all consolidation processes occurring after this period must necessarily begin with destabilization, so that the memory can be altered. This would imply that such consolidation processes require reactivation of the memory. But whether 'stabilization' prevents all changes to a memory, or only a class of degradative changes, remains to be clarified.

In summary, memory consolidation and reconsolidation can be viewed as components of a complex system of memory processing that modifies the strength, stability, form and integrative connectivity of memories across their lifespan. For many of these processes, sleep, and often specific stages of sleep, appears to be either permissive or obligatory. Thus, memories must be viewed as constantly evolving – an evolution that is controlled by a series of time-dependent and brain-state-dependent processes occurring during wake and sleep states.

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