Comparing Models of Sleep-dependent Memory Consolidation

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The enhancement of normal cognition and breakthrough treatments in cognitive disorders require an improved understanding of memory consolidation. Insights into the mechanisms of memory consolidation have been advanced by the incorporation of a quantifiable variable: sleep. Over the past 20 years, a substantial number of studies have shown that memory performance is facilitated after a bout of sleep, compared with the same period of waking, implicating a slow, offline process during sleep that transforms the memory trace into a more robust form through a consolidation process. Until recently, the majority of these studies have examined cognitive tasks that utilize non-declarative, procedural memory (e.g., knowing “how”, learning actions, habits, perceptual and motor skills, and implicit learning) to show enhanced performance above baseline. Recent attention has turned to studying the relationship between sleep and declarative memory, which refers to consciously accessible memories of fact-based information (i.e., knowing “what”, in terms of events, places, and general knowledge) that are dependent on the hippocampus. Although the exact nature of the relationship between sleep and declarative memory consolidation is hotly debated, there is strong emerging evidence for the importance of slow wave sleep. In contrast with the “enhancement” model of procedural memory, there are two declarative memory models; first, the active model, in which memory depends on sleep specifically; and second, the permissive model, which posits a time-dependent, interference-sensitive process that opportunistically seizes any period of dampened hippocampal input to further process prior, learned information. We review the evidence for the active and permissive models and discuss areas of research that would benefit from future studies. Bridging these scientific fields will impact fundamental research in memory, sleep and pharmacology, as well as have relevance for treatment of memory impairments affecting people with mental illness and age-related cognitive decline.

1. Introduction

Research over the last half century has demonstrated that memory is not unified but is instead composed of anatomically and mechanistically distinct processes. The greatest dissociation is between memories that depend on the hippocampus versus those that do not. Hippocampal-dependent memories, also called declarative or explicit memories, are memories for people, places, or things; memories that we can consciously manipulate. In contrast, hippocampal-independent memories, also called non-declarative or implicit memories, are memories to which we do not have conscious access, such as procedural and perceptual learning, habits, priming and conditioning. One strategy for gaining insight into this wide range of memory processes is to...
Models of sleep-dependent memory consolidation

Two forms of consolidation have been suggested: 

1. Synaptic consolidation
2. Systems consolidation

## 3. Mechanisms of Memory

With regard to declarative memory, two forms of consolidation have been suggested: 

- **Synaptic consolidation** refers to the stabilization of information storage at local nodes in the neuronal circuit that encodes the memory. For example, long-term potentiation (LTP) spreads in the hippocampus, the major cellular model for synaptic plasticity that is thought to be associated with memory consolidation, in the hours (and perhaps, days) following the induction of LTP. LTP induction in hippocampal neurons involves the influx of calcium via postsynaptic N-methyl-D-aspartate (NMDA) receptors. When these receptors are blocked by an NMDA antagonist, high-frequency stimulation fails to induce LTP. Consistent with these findings, NMDA antagonists have often been shown to impair the learning of hippocampal-dependent tasks in animals, suggesting that LTP processes play an important role in the formation of new episodic memories. A second form of consolidation associated with declarative memory is systems consolidation, which refers to the time-limited role of the hippocampus in explicit memory storage where learning-related changes occur first in the hippocampus followed by the gradual development of a more distributed memory trace in the neocortex. The mechanism that underlies systems consolidation is not known, but a leading candidate is neural replay, in which cells that are activated in sequence together during a learning episode while awake are more likely to fire in a similar sequence during sleep and rest. For declarative memory consolidation, we hypothesize that both short-term synaptic consolidation (perhaps involving the stabilization of LTP in the hippocampus) and long-term systems consolidation (perhaps involving neural replay or reactivation) preferentially occur when the hippocampus is not encoding new information (i.e., when LTP or LTP-like processes are not being induced).
An important consideration for understanding the time-related effects of synaptic consolidation is that LTP is thought to have at least two stages: early-stage LTP, which does not involve protein synthesis (and during which time LTP is vulnerable to interference); and late-stage LTP, which does involve protein synthesis associated with morphological changes in dendritic spines and synapses (and after which LTP is less vulnerable to interference). Late-stage LTP, which begins approximately 4–5 hours after the induction of LTP, can be prevented by protein synthesis inhibitors. Upon reaching the late stage, evidence suggests that LTP is less vulnerable to interference. For example, in experimental animals, memories formed in the hippocampus and LTP induced in the hippocampus both exhibit a similar temporal gradient with respect to retroactive interference (vulnerability to having memory traces corrupted by new memories). In humans, a similar timeline of vulnerability to interference has been shown for sleep-related memory. That is, sleep immediately after learning results in less forgetting than when sleep is delayed for 10 or more hours post-learning.

4. Sleep-dependent Memory Consolidation

4.1. Sleep structure

Sleep is a highly structured set of processes separated into five stages, each demonstrating: (1) stereotypic electrical activity; (2) neurochemical bases; (3) and both enhancement and depression of activities in specific brain regions. The five stages [Stages 1, 2, SWS (Stages 3 and 4) and REM (Stage 5)] progress in a 90–110-minute cycle from Stage 1 through SWS and then to REM sleep (Figure 1). Stages 3 and 4 are often collapsed and referred to as SWS. Adults spend 60% of sleep in Stage 2, about 20% in REM, and the remaining 20% in the other stages, primarily SWS. Stage 1 is briefly observed at sleep onset. Stage 2 sleep is characterized by fast 12–14-Hz EEG (termed spindles) and slower K-complex signals. Early SWS consists of 0.5–3.0-Hz EEG (delta) and higher frequency signals, whereas later SWS has higher delta content. REM sleep, in contrast to SWS, is a lighter sleep accompanied by rapid irregular shallow breathing, rapid eye movements, increased heart rate, increased cortical blood flow, muscle paralysis, and a predominance of 4–7-Hz EEG theta waves. Perhaps due to the focus of research on REM sleep, researchers commonly divide sleep into REM and non-REM (NREM), as illustrated in Figure 1. Sleep structure is circadian and, across nocturnal sleep, the amount of SWS progresses from high to low and REM from low to high.

A significant difference between REM and SWS is the relationship to LTP. Generally, REM sleep has relatively normal synaptic plasticity (e.g., LTP can be induced), whereas SWS has reduced plasticity in that LTP is more difficult to induce. Diekelmann and Born suggest that SWS and REM sleep support systems consolidation and synaptic consolidation, respectively. During SWS, slow oscillations, spindles and ripples (at minimum cholinergic activity) coordinate the reactivation and redistribution of hippocampus-dependent memories to neocortical sites, whereas during REM sleep, local increases in plasticity-related immediate-early gene activity (at high cholinergic and theta activity) might favor the subsequent synaptic consolidation of memories in the cortex.

4.2. Procedural memory and sleep

Several studies have demonstrated that REM sleep contributes to perceptual learning. Karni and Sagi developed a texture discrimination task with clear learning results in regards to sleep. Specifically, they showed that post-training improvement is only evident several hours after training, and improvement can develop overnight that is REM-dependent. Extending these findings, Stickgold and colleagues demonstrated that firstly, improvement in performance on the texture discrimination task can only be achieved after 6 hours of nocturnal sleep; and secondly, additional nights of sleep appear to produce additional, incremental improvements in performance. These improvements occurred without additional training and were SWS- and REM-dependent. Specifically, improvement was correlated with the product of the number of minutes in SWS in the first part of the night and the number of minutes in REM in the last part of the night. No correlation was seen between SWS and REM, indicating that each contributed independently to the improved performance. Other laboratories have corroborated these findings. Anatomically, a functional magnetic resonance imaging study showed that, along with improved performance, training could lead to enlarged regions of activation in the primary and secondary visual cortex. These results have been corroborated in subsequent studies.

Stage 2 sleep has been shown to contribute to procedural learning of motor skills. Walker and colleagues...
studied performance on a motor task (finger-tapping, in which subjects are asked to enter a specific sequence of keys on a keypad as quickly and accurately as possible) and found improvement after an episode of sleep relative to being awake.\textsuperscript{40} Overnight improvement was specific to both the motor sequence learned and the hand used to perform the task.\textsuperscript{41,42} While perceptual learning correlated with the product of SWS and REM, motor learning improvement correlated with the amount of Stage 2 sleep.\textsuperscript{40,43} Rickard and colleagues, however, have argued that some of this sleep effect may be due to a release from motor fatigue.\textsuperscript{44} Fogel and Smith reported that following an intense period of simple motor procedural learning, the duration of Stage 2 sleep and spindle density increased. There were no changes observed in the duration of any other sleep stage.\textsuperscript{45} Similarly, improvement on a visuomotor pursuit task (in which optimal performance required developing an implicit model of the motion of the learned trajectory) was dependent on a post-training night of sleep.\textsuperscript{46} In one sleep-deprivation study, half of the subjects were sleep-deprived on the night after training. After all subjects slept on night 2, only the sleep-deprived group demonstrated a lack of improvement.\textsuperscript{47} Although making comparisons between well-rested and sleep-deprived subjects has been criticized, these results indicate that, first, sleep may also improve visuomotor learning, and second, there is a critical window for sleep to occur, without which information can be lost.

Interestingly, daytime sleep is equivalent to nocturnal sleep for procedural learning. Mednick et al showed that: (1) perceptual learning occurred only after naps containing REM sleep;\textsuperscript{4} (2) naps of either 60 or 90 minutes produced the same levels of learning as a full night’s sleep; (3) naps promoted the same levels of learning on a motor learning task as nocturnal sleep;\textsuperscript{47} (4) sleep spindles and sigma power increases were correlated with improved motor memory in habitual nappers compared with non-habitual nappers;\textsuperscript{48} and (5) REM sleep during naps, compared with NREM and being awake, enhances access to implicitly primed information for solutions in a creative problem-solving task (Figure 2).\textsuperscript{5} These studies suggest that nocturnal sleep and naps enhance procedural memories during an offline process in a sleep-stage-dependent manner.

4.3. Declarative memory and sleep

Until recently, the relationship between sleep and declarative memory had not been well examined. Neural models of declarative memory formation emphasize the critical importance of structures in the medial temporal lobe.\textsuperscript{49} In contrast with “enhancement” models of procedural memory, traditional declarative memory models involve stabilization and protection of memories from interference and decay. A newer hypothesis put forward by Wixted combines the psychological concept of interference with the physiological concept of consolidation.\textsuperscript{50} He proposes that memories are formed and maintained by LTP in the hippocampus, but are also temporarily vulnerable to interference which occurs by subsequent induction of additional LTP associated with the formation of newer memories.\textsuperscript{50} Importantly, the Wixted hypothesis has never been experimentally studied. We next summarize the competing theories for the role of sleep in declarative memory.

In their review, Ellenbogen and colleagues\textsuperscript{51} summarized the major findings of sleep and declarative memory and categorized four theoretical relationships for the role of sleep: (1) no relationship; (2) passive; (3) permissive; and (4) active.

(1) \textit{No relationship}: This argument is countered by a multitude of findings showing that performance is usually better with sleep than without, and while this is a formal possibility that must be experimentally controlled for, we spend no more time on this category.

(2) \textit{Passive}: Classical memory research by Jenkins and Dallenbach in 1924 consisted of presenting a set of nonsense syllables before a sleep or wake episode and found better retention after the sleep episode.\textsuperscript{52} The authors concluded, “The results of our study as a whole indicate that forgetting is not so much a matter of the decay of old impressions and associations as it is a matter of interference, inhibition, or obliteration of the old by the new.” Thus, memory traces are not enhanced by processes occurring during sleep, per se, but rather sleep may be a period of reduced interference.

(3) \textit{Permissive}: This hypothesis considers declarative memory consolidation to be a time-dependent, interference-sensitive process that utilizes any
permissive brain state of reduced LTP to consolidate memory.\textsuperscript{50} This model predicts that permissive states of reduced LTP, such as SWS\textsuperscript{28} or pharmacologically-reduced LTP, will improve declarative memory for information studied within a time before sleep or drugs: the phenomenon of retrograde facilitation. Retrograde facilitation is the observation that a post-learning intervention (e.g., a period of sleep or the administration of a benzodiazepine or ethanol after learning) can improve performance relative to a control intervention (e.g., no sleep or placebo post-learning).

(4) **Active:** This theory is similar to the permissive theory except that it specifies that sleep is a critical component of consolidation, and no other brain state will serve the same function.

### 4.3.1. Passive vs. permissive hypothesis

An important difference between passive and permissive hypotheses is that the passive hypothesis does not incorporate a critical period for consolidation. For example, if one considers a 6-hour training-to-test interval, both models agree that interference will occur. With an intervention, such as 2 hours of sleep, improvement would occur by reducing interference to 4 hours, compared to 6 hours in awake controls. The passive theory would predict that it does not matter when in the subsequent 6 hours the sleep occurs (ignoring fatigue effects for the moment), only that total time of interference is reduced. Consolidation plays no part in the passive hypothesis. In contrast, the permissive hypothesis predicts that memories need time to consolidate in order to become resilient to the interference of new memory formation, and sleep provides a window of time for such consolidation to unfold in the absence of interference. Thus, sleep soon after learning should confer more protection than sleep that is delayed.

The permissive account hypothesizes that memorization involves a period of LTP induction and maintenance directly following learning, without which the memory would be lost. This initial “critical period” produces experimentally tractable hypotheses about the temporal gradient of declarative memory consolidation. Specifically, sleep, or a similar pharmacologically-induced brain state, needs to occur within a temporal window soon after learning in order to protect LTP when it is vulnerable to interference. SWS (or other period of LTP inhibition) shortly after training allows a cascade of gene expression, protein synthesis and synaptic changes associated with LTP formation for memory consolidation. A period of new LTP formation, such as occurs during waking or REM sleep, would interfere with the fragile memory trace. This model predicts that studies comparing periods of SWS to equivalent periods of wake or REM (both periods of high LTP-like activity in the brain) will find retrograde facilitation of prior experiences.\textsuperscript{50} In other words, SWS sleep may produce improved performance compared to an active wake or REM group due to an absence of LTP-induced interference. Although sleep and pharmacology researchers do not use the same nomenclature (e.g., retroactive facilitation), their results show the same pattern. These results are described in more detail below. This theoretical framework comparing the memory benefits of sleep and pharmacologically-induced LTP inhibition has never been tested.

### 4.3.2. Active hypothesis

In the spirit of findings in procedural learning of absolute performance enhancement (not merely less forgetting), proponents of the active role hypothesis argue that declarative memory consolidation crucially depends on a brain property unique to sleep. Research cited as support for this model includes studies that show that NREM sleep facilitates declarative memory compared with being awake and REM sleep.\textsuperscript{53–58} We argue that these results essentially show retrograde facilitation, in that memory for information learned prior to sleep exhibits less forgetting relative to awake controls. Moreover, a temporal gradient is observed (i.e., sleep soon after learning is more protective than sleep after a delay), implicating a critical period for consolidation to occur after training. Whereas these findings are consistent with the permissive theory, other findings support the active theory for sleep-related consolidation. For example, changes in memory consolidation due to pharmacologic manipulations have been cited as evidence for the essential role of sleep in consolidation.\textsuperscript{59,60} Gais and Born increased cholinergic tone (via physostigmine) during early sleep, a period rich in SWS activity, which blocked declarative memory in a paired word association task, but did not alter performance in a procedural memory task. Thus, low cholinergic tone is necessary for SWS-dependent declarative memory to occur. These studies show that specific pharmacological alterations during SWS can have discrete effects on specific memory processes.

### 4.3.3. Reactivation and consolidation

Recent neurophysiology data show intriguing possibilities for what might be the active neural mechanism of sleep-dependent memory processing. Specifically, strong evidence for a relationship between spatial memory and sleep comes from animal studies reporting post-acquisition neuronal reactivation during sleep that recapitulates the firing pattern of neurons in the hippocampus during alert exploratory behavior in a memory task.\textsuperscript{62–64} These data and others suggest that hippocampal and neocortical parietal regions cooperatively participate in the processing of spatial memories,\textsuperscript{65} and perform off-line activity during NREM sleep.
involved in consolidation of these memories into long-term memory stores.69 This is thought by some to be the mechanism that underlies systems consolidation (i.e., the process that results in a declarative memory trace eventually becoming independent of the hippocampus).

One recent study linked reactivation processes during sleep with performance improvement in humans.57 Peigneux and colleagues showed that following training on a virtual spatial maze task, activation of hippocampal and parahippocampal navigation-related neural populations occurs during SWS sleep.67 They used positron emission tomography to show that the amount of post-training reactivation of hippocampal formation during SWS correlates with the amount of next-day learning on the task. Another functional magnetic resonance imaging study showed that odor could be associated with declarative memory on a spatial task, and that if the odor was presented during SWS, but not REM sleep, subjects would perform better at the test the following day.68 Interestingly, they found that odor cues that were previously associated with learning stimuli were capable of activating the hippocampus during post-learning SWS. Direct comparisons between awake and sleep conditions revealed an even stronger activation in response to odor presentation during SWS than during wakefulness in both the anterior and posterior part of the left hippocampus. Beyond showing that memory-associated odors have access to the hippocampus during SWS, this observation points to a particular sensitivity of hippocampal networks during SWS to stimuli that are capable of reactivation. Returning to our active/permissive distinction, would a pattern of reactivation of previously learned material be reflected similarly in SWS sleep and pharmacologically-induced brain states? Because no other brain state (except being awake) has been compared with sleep, it is impossible to be certain as to whether or not sleep is essential for this process, or simply convenient. More generally, it is important to note that all of the abovementioned results are consistent with both the permissive and active models.

5. Pharmacological Manipulations of Memory Consolidation

Ethanol has been shown to block acquisition of new information and, surprisingly, to enhance memory for previously acquired information.69–72 Parker et al found that when normal subjects ingested alcohol (1 mL/kg) after they had encoded some material, they remembered the material better than subjects who had ingested placebo drinks.73 But they showed no consolidation of material trained post-ethanol ingestion. Further, in a dose-response study,74 subjects ingested 0, 0.25, 0.50, and 1.00 mL/kg ethanol after studying a group of pictures. After 7 hours, retesting showed significant increases in memory in the subjects who had ingested 0.5 and 1.00 mL/kg ethanol. A similar finding has been reported in animals.75

The mechanisms by which ethanol may retroactively facilitate memory while suppressing new learning are hypothesized to involve the suppression of LTP in brain areas required for normal memory processing, i.e., the hippocampus and prefrontal cortex. Ethanol produces a dose-dependent suppression on the magnitude of LTP following high-frequency stimulation. In vitro, low concentrations of ethanol (5 mM) in a hippocampal slice preparation inhibited LTP and correlated with an inhibited NMDA response.76 The NMDA receptor is critical for LTP induction as well as for hippocampus-dependent cognitive functions. The NMDA receptor antagonist aminophosphonovaleric acid blocks the induction but not the expression of LTP, indicating that induction and expression involve different physiological mechanisms.77 This is an important point, as the permissive hypothesis predicts that sleep and drugs should inhibit new LTP formation, not the expression and maintenance of previously induced LTP. Ethanol inhibits NMDA-mediated currents in hippocampal neurons,78 suggesting that the effects of ethanol on LTP may be specific to induction. Indeed, Givens and McMahon demonstrated that ethanol specifically blocked the induction but not expression or maintenance of LTP.79 Thus, no new LTP induction occurs during expression and maintenance of LTP associated with memories formed in the recent past. It is unclear, however, whether the mechanism of action to block LTP is due to a direct interaction with the NMDA receptor or with the γ-aminobutyric acid (GABA) A receptor.80

Similar to ethanol, benzodiazepines have been shown repeatedly to improve memory for material learned prior to drug administration.81–83 Weingartner et al randomized subjects to three drug conditions (placebo, 4.5 μg/kg or 6.0 μg/kg).81 Subjects studied a list of words just prior to oral drug administration and then were given a new list of words while on the drug. Recall was tested for both study lists. Triazolam increased the probability of remembering studied words at both doses compared with placebo (Figure 3).81 Although anterograde amnesia for words studied on the drug was not significant, the trend was in the expected direction. Furthermore, other studies have found both retrograde facilitation and anterograde amnesia for triazolam at equivalent doses.82–84

Similar to other benzodiazepines, triazolam has been reported to disrupt LTP induction via potentiation of GABAergic activity and a concomitant attenuation of excitatory synaptic transmission in the mammalian hippocampus.85,86 It is this property that is thought to underlie the ability to produce anterograde amnesia in humans. We hypothesize that this same suppression of LTP induction underlies the phenomenon of retrograde facilitation.
6. Conclusion

The relatively recent addition of sleep to studies of the neural basis and underlying mechanisms of memory has generated an extensive literature for both procedural and declarative memory. Although behavioral profiles of the effects of sleep on declarative memory appear similar to findings from an older literature on the effects of pharmacological interventions, there is a need for studies to directly compare the effects of sleep and pharmacology on memory consolidation. Importantly, there is evidence to support the hypothesis that learning is similarly benefited by SWS and benzodiazepines. Future studies should focus on understanding the behavioral outcomes, temporal dynamics and neural representations underlying declarative memory consolidation produced by SWS and other pharmacologically-induced, dampened brain states that reduce LTP. In addition to laying groundwork to improve normal cognition, sleep and pharmacology. Furthermore, there is the applied relevance for improving memory impairments associated with psychiatric disorders, neurodegenerative diseases and normal aging.

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References

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