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The role of sleep in declarative memory consolidation: passive, permissive, active or none?

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Those inclined to relish in scientific controversy will not be disappointed by the literature on the effects of sleep on memory. Opinions abound. Yet refinements in the experimental study of these complex processes of sleep and memory are bringing this fascinating relationship into sharper focus. A longstanding position contends that sleep passively protects memories by temporarily sheltering them from interference, thus providing precious little benefit for memory. But recent evidence is unmasking a more substantial and long-lasting benefit of sleep for declarative memories. Although the precise causal mechanisms within sleep that result in memory consolidation remain elusive, recent evidence leads us to conclude that unique neurobiological processes within sleep actively enhance declarative memories.

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Introduction

There is near consensus that periods of sleep, compared with those of wakefulness, actively improve human performance of recently acquired nondeclarative skills [1–4]. Examples include the learning of motor sequences [5–7], of visual texture discriminations [8], of the serial-reaction-time task [9–13], and of auditory discrimination of a synthetic language [14]. In contrast to nondeclarative learning, relatively few studies (e.g. [15•,16]) clearly demonstrate beneficial effects of sleep on declarative memories. The limited evidence that sleep benefits declarative memory has led some researchers to contend that sleep provides no benefit for such memories [17].

Distinct views are embedded within the complex and controversial literature addressing the role of sleep in declarative memory consolidation: a framework is needed in order to clarify the discussion.

In this review, we divide the debate regarding sleep and declarative memory into four, readily distinguishable, competing hypotheses: first, that sleep offers nothing for memory; second, that sleep temporarily shields memory from the negative effects of interference, a passive and transient benefit; third, that, as in the second hypothesis, sleep leads to passive protection from interference, but that this protection enables consolidation to take place more efficiently than in wakefulness; and fourth, that unique biological properties of sleep lead to the active consolidation of declarative memories. Below, we discuss distinctions between, assumptions within, and strengths and weaknesses of each of these four perspectives (Table 1). (And although there are many uses of the term 'consolidation', in this paper we restrict ourselves to the definition provided by Dudai: the ''progressive post-acquisition stabilization of memory'' [18]).

Hypothesis one — no benefit

Sleep contributes nothing to memory

Several lines of reasoning support the view that sleep plays no role in declarative memory consolidation. First, some have pointed out that those with diminished amounts of rapid eye movement sleep (REM; from either REM-suppressing agents, such as certain types of antidepressants, or rare cases of patients sustaining brainstem damage) have continued to lead normal productive lives [17,19–21]. Certainly, if sleep were crucial for memory, then those with such impairments in REM sleep would have apparent deficits in memory. Yet, the same authors acknowledge that the cognitive capacities of those individuals with diminished REM have never been systematically examined. Furthermore, no study of tasks on which performance reportedly depends on sleep has ever been conducted in these individuals. And such studies, even if they were done, could only clarify our understanding of the role of REM in sleep-enhanced memory consolidation, rather than generalize to all of sleep. In fact, it is also worth noting that some authors predict, in contrast to proponents of hypothesis one, that NREM sleep (non-REM sleep, referring to sleep stages 1–4) is more important for memory consolidation than REM sleep, and, therefore, that impaired REM sleep might even enhance sleep-dependent memory consolidation [22]. But, to date, no empirical studies have tested either of these hypotheses.

Another argument among proponents of hypothesis one is that improvements of memory overnight can be explained by the mere passage of time, rather than attributed to a function of sleep [17]. But studies that

Table 1

Predictions based on hypothesis: the four main hypotheses and their various predictions.

Prediction	Hypothesis			
	No benefit	Passive protection	Permissive consolidation	Active consolidation
Recall performance is better after sleep than after wake	No	Yes	Yes	Yes
Superior recall performance after sleep is sustained	No	No	Yes	Yes
Consolidation occurs during sleep (retrograde facilitation)	No	No	Yes	Yes
Unique properties of sleep directly contribute to consolidation	No	No	No	Yes
All memory consolidation depends on sleep	No	No	No	No

The four competing hypotheses — that each describe how sleep might impact memory — can be differentiated by their various predictions. For example, the main distinction between 'permissive consolidation' and 'active consolidation' rests on the fact that the active consolidation hypothesis predicts that neurobiological properties of sleep directly contribute to memory consolidation, whereas the permissive consolidation hypothesis does not. ('Yes' means that the hypothesis does assert the prediction, and 'No' means the hypothesis rejects the prediction.) Of note, no hypothesis predicts that *all* memory is dependent on sleep.

employ waking control groups (e.g. [23••,24••,25]) make this argument unsustainable, as the wake and sleep groups have equal amounts of time, yet the participants in the sleep group perform better. Certainly there are memory consolidation processes that occur across periods of wakefulness, some of which neither depend on nor are enhanced by sleep when sleep is compared with wakefulness, and performance is better after sleep, then some benefit of sleep for memory must be acknowledged.

In summary, the arguments that sleep contributes nothing to declarative memory lack empirical support. Moreover, existing experimental data strongly argue against their assumptions. Thus, we turn to the three remaining alternatives.

Hypothesis two — passive protection

Sleep transiently shelters memories from interference

According to the second hypothesis, sleep only transiently sustains memories, by protecting them from interference during sleep, but does not consolidate them. Thus, recall is better in the morning immediately after sleep, compared with that after a day awake, but only until exposure to interference in the subsequent day. Because sleep does not consolidate memories, they will be, once again, rendered vulnerable to interference in the waking day to come — as vulnerable as they would be had the person not slept at all.

These assumptions are nearly 100 years old. The legacy of Jenkins and Dallenbach [26] is so ingrained in scientific thinking about the relationship between sleep and memory that their conclusion in 1924 — that sleep protects memory from interference — remains a prominent hypothesis on how sleep affects memory. Their seminal work demonstrated that recall of nonsense syllables was superior immediately after sleep, compared with that after similar amounts of time awake. But in their discussion, Jenkins and Dallenbach afforded sleep no active role in memory consolidation. Rather, they concluded that sleep transiently protects memory from interference: ''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'' [26]. Hardly a single manuscript addressing sleep and memory fails to cite this work.

Viewed from this passive-protection perspective, any study that demonstrates superior recall performance immediately after periods of sleep, compared with that after periods of wakefulness, is not showing that sleep improves memory; rather, it demonstrates the negative effects of waking mental experience on memory. Therefore, sleep is a temporary shelter — a respite for memory — from the inevitable negative effects of interfering mental activity during wakefulness. Much like a document that cannot be edited or deleted while the computer is in sleep mode, memories remain unchanged across a night of sleep; neither for better nor worse. In short, sleep adds nothing to declarative memories.

But two recent studies that examine verbal recall, interference and sleep call this hypothesis into question. In the first of these two studies [15•], when time of training, time of testing and time of sleep were manipulated, sleep was found to improve declarative memory recall independent of the amount of time awake, providing evidence that sleep does more than passively protect the previously formed declarative memories.

In the second study, which promotes the benefit of sleep for declarative memory and argues against hypotheses one and two, interference was controlled and experimentally manipulated [23••]. Rather than simply test subjects on memory performance after sleep, the authors unmasked the extent of the benefit of sleep for declarative memory by experimentally introducing interference after periods of wakefulness or sleep. Using a classic AB–AC interference paradigm [27], subjects first learned unrelated paired associates, designated A_iB_i. After sleep at night, or wakefulness during the day, half of the

subjects in each group learned new paired associates, A_iC_i, before being tested for recall of the original (A_iB_i) list. Results demonstrated two main findings: first, that sleep provides a modest protection against memory deterioration, as evident by slightly better recall after sleep than after wake conditions (Figure 1a); and, second, that sleep protected remembered words from future interference, as evident by the resistance to interference after sleep but not after wake alone (Figure 1b). An additional separate group of subjects trained in the evening, slept and stayed awake the entire next day before being tested in the evening (24 h after initial training). This last group showed that the benefit of sleep for memory was sustained throughout the subsequent waking day (Figure 1c). Thus, memories tested after a night of sleep were highly resistant to interference, and remained resistant across the subsequent day. These findings demonstrate that sleep strengthened the memory above and beyond that which could be accounted for by a passive protection hypothesis alone.

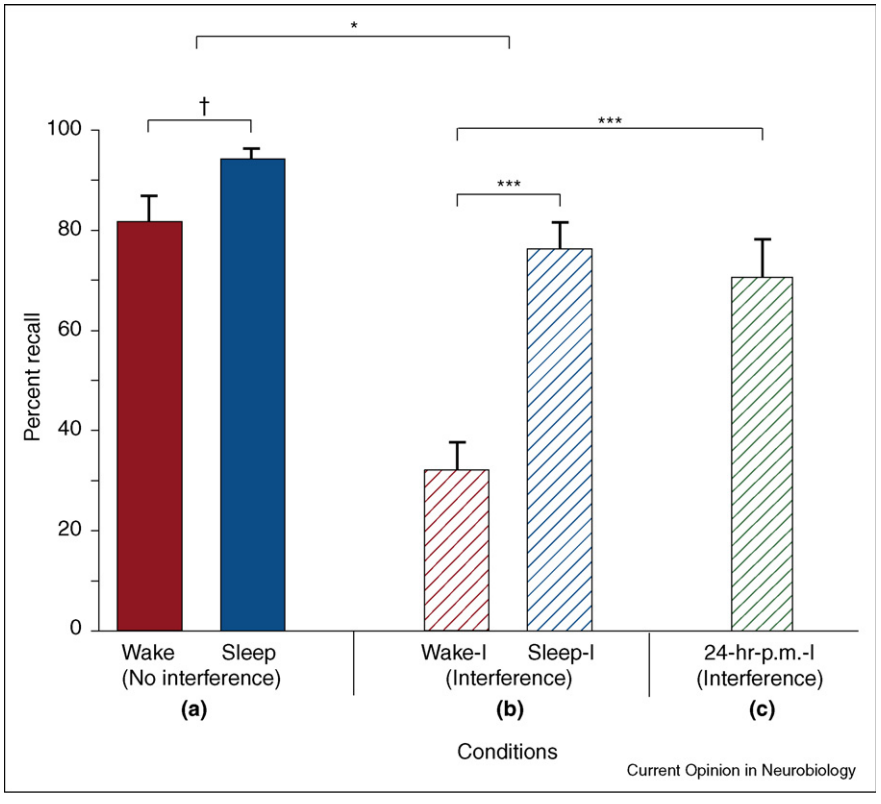
Thus, although sleep might passively protect declarative memories from interference, consolidation must also occur during sleep for the memories to become resistant to interference the following day. We therefore turn to hypothesis three and four, which both assert that consolidation takes place during sleep.

Hypothesis three — permissive consolidation

Sleep creates conditions conducive to memory consolidation, but plays no other unique role in the consolidation process

This hypothesis states that sleep can indirectly contribute to consolidation. Similar to hypothesis two, it incorporates the notion that sleep leads to reduced interference. But extending further, the third hypothesis states that reduced interference during sleep facilitates consolidation. Despite this acknowledgement to sleep-dependent consolidation, the essence of this hypothesis is that there is nothing special about the biological state of sleep that enhances consolidation. Rather, sleep merely reduces

Figure 1



The data from a study of memory for word pairs [23••]. All subjects were asked to learn a list of 20 word pairs and recall them after periods of sleep, wakefulness or both. **(a)** In the no-interference conditions, subjects were asked to recall the learned words after 12-h periods: the performance of sleep group was marginally better — a finding predicted by hypotheses two, three and four. **(b and c)** In the interference conditions, subjects learned another list immediately before being asked to recall the old list. This new list was meant to disrupt the memory of the original list. The sleep group was highly resistant to the negative effects of interference presented in the subsequent day, implying that sleep stabilized the memory (consolidation) — a finding predicted only by hypotheses three and four. In the 24-h group (c), learning took place at night and was tested the following night. The results from this group show that the benefit of sleep persists throughout the subsequent waking day. (Note that no portion of this study involved sleep deprivation — wake groups were awake during the daytime.) Error bars are standard error of the mean. $^{\dagger}p = .06$; $^{*}p < 0.05$; $^{***}p < 0.001$.

interference and this enables an already available consolidation mechanism to function more effectively [22]. Thus, during the day, recently encoded memories are bombarded by interference from waking mental activity, which not only weakens them but also impedes their effective consolidation. By contrast, memories have an enhanced opportunity to consolidate during sleep — unbridled by waking interference.

This view likens sleep to benzodiazepine consumption, which also leads to retrograde facilitation (consolidation of memories acquired immediately before medication) [28]. This effect is possibly a result of anterograde amnesia — this class of drug causes a failure to encode new information, thereby limiting interference upon memories encoded immediately before drug consumption, thus providing encoded memories a chance to consolidate without interference. Accordingly, sleep — like benzodiazepines — has no unique property that contributes to memory consolidation other than enabling the hippocampus to conduct its normal consolidation process in its ideal circumstance: without interference.

With behavioral measures alone, it is difficult to distinguish whether sleep is enabling consolidation to occur, as in hypothesis three, or whether sleep activates unique neurobiological processes that play a direct role in consolidation, as predicted by hypothesis four (below). The distinction rests on knowledge of the precise physiologic markers of consolidation, interference and their relationship to sleep.

Hypothesis four — active consolidation

Unique properties of sleep are directly involved in the memory consolidation process

The search for mechanisms underlying sleep-dependent consolidation of declarative memories in humans must rely on examination of specific properties of sleep physiology. By showing that a specific form of memory consolidation crucially depends on a brain property unique to sleep, one can conclusively validate this hypothesis; the boldest of the four.

Recent attempts have been made to address the biological plausibility of sleep physiology leading to memory consolidation. For example, two recent studies extended the works of Barrett and Ekstrand [29] and Fowler *et al.* [30], and emphasized the role of slow wave sleep (SWS) in declarative memory consolidation [25,31]. They showed superior memory recall among subjects that slept across the first half of the night (so called 'early sleep', a portion of sleep with relatively large amounts of SWS) compared with that of subjects that spent the same period awake. The same benefit was not seen when sleep was in the second half of the night, a portion of sleep containing relatively little SWS. In an additional group, the investigators experimentally elevated levels of acetylcholine by administering the drug physostigmine to subjects, and found a reduced benefit of sleep for declarative memory during this period of early sleep. The authors conclude that the naturally occurring nadir of acetylcholine in sleep during the first half of the night interacts with SWS to consolidate memories.

Other studies also emphasize aspects of SWS physiology as important for declarative memory consolidation during sleep [32•]. For example, intracellular *in vivo* studies demonstrate that neocortical neurons spontaneously reactivate during SWS [33]; it is conceivable that this observable phenomenon leads to strengthening of memory traces.

Several animal studies demonstrate that recently acquired, hippocampus-based memories are 'replayed' during sleep (e.g. [34–36,37••]). Interestingly, replay of hippocampal memories after spatial navigation has also been seen in wakefulness; but during wakefulness, these memories are chronologically replayed backward (reverse replay [38••]), whereas during sleep the patterns are replayed forward. It has been suggested that these distinct patterns reflect different roles: whereas initial learning relies on reverse replay, consolidation relies on forward replay [39••]. Recent neuroimaging findings in humans further demonstrate increased hippocampal activity during sleep following spatial learning, an increase that was proportional to the degree of overnight behavioral improvement [16]. Collectively, these studies suggest that hippocampus-dependent memories are reactivated during sleep, and that this reactivation leads to strengthened memory traces.

Although SWS might consolidate memories independent of other sleep stages, an alternative model states that all stages of sleep are important for memory consolidation. This different perspective highlights the fact that each stage of normal human sleep (including SWS and REM) occurs in succession several times throughout the night. (Each of these so-called ultradian cycles lasts a little more than an hour.) Perhaps the interplay of sleep stages within an ultradian cycle — occurring in several iterations throughout the night — orchestrates a complex process of feed-forward and feed-back mechanisms between the hippocampus and the neocortex that enhance memory consolidation by repeatedly shuffling information back and forth. This theoretical hippocampal–neocortical dialog [40] was examined in humans by disrupting the ultradian cycle [41]. The authors demonstrate that ultradian cycles throughout the night are essential for declarative memory consolidation, arguing for a combined role of NREM and REM.

Sleep spindles are another candidate mechanism for sleep to directly enhance memory [42]. Animal models demonstrate that these distinct electrophysiological phenomena co-occur with hippocampal activity during sleep [43]. It is suggested that this represents a reorganization mechan-

ism that transfers information between the hippocampus and the neocortex during sleep, thus consolidating memories [44].

Although there is promising work in this area of ongoing investigation, definitive evidence of a role for spindles in memory consolidation remains to be found. Spindle quantity appears to correlate with intelligence [45,46]; thus correlating spindle quantity to performance after sleep could be confounded by intelligence. Therefore, the most effective spindle studies examine within-subject changes between a baseline night and the experimental night, to account for inter-individual differences in spindle quantity secondary to intelligence. Otherwise, it is difficult to discern whether high spindle content correlates with overnight improvement in memory, whether overnight improvement is a function of higher IQ alone, whether it is interaction between the two (i.e. those with higher IQ have more spindles, and those with more spindles have a more pronounced overnight improvement), or whether those with more spindles have a higher IQ because of more pronounced overnight sleep consolidation processes.

Still, a reported 34% within-subject increase in spindle density early in the night following task training [42] and increased spindle density after learning difficult lists of words [47••] argues for a role of sleep spindles in declarative memory processing. Similarly, a second study found a strong correlation between spindle density and overnight verbal memory retention, but no correlation between memory for face recognition and spindles, arguing against a general intelligence effect [48].

Taking a different tack, several researchers examined whether sleep can help repair damaged memories. Fenn *et al.* [14] showed that sleep can restore damaged memories in perceptual learning of a spoken language, albeit in a task that was more procedural than declarative. Norman *et al.* [49••] used a computational, neural network (the complementary learning system model [50,51]) to model the effects of sleep on learning [49••]. Knowing that learning new information can sometimes disrupt existing knowledge (the so-called stability–plasticity problem), they looked at whether pre-existing memories, impaired by recently acquired knowledge, could be restored by REM-like models of sleep. This computational model demonstrates that REM sleep can 'repair' damaged memories. Continued application of these models to declarative memory and sleep is likely to reveal important findings.

Finally, two studies have examined the role of sleep in the consolidation of recently learned emotional memory. One study demonstrated that sleep in the latter half of the night, a period rich in REM sleep physiology, led to improved recall [52]. Another study demonstrated that an entire night of sleep led to enhanced consolidation of arousing emotional stimuli [53••]. Taken together, these studies argue that sleep consolidates emotionally arousing memories and that REM sleep provides the unique mechanism.

In summary, future technological advances in measures of sleep physiology, coupled with refinements in memory tasks employed in these studies, will undoubtedly be instrumental in teasing apart the precise contributions of sleep for a wide range of memory systems. Nonetheless, the available evidence converges on the notion that neurobiological processes within sleep directly facilitate declarative memory consolidation in humans.

Conclusions

A review of the literature concerning the putative role of sleep in declarative memory consolidation reveals divisions among researchers. Embedded within the layers of controversy and multitudes of opinion are four distinct positions regarding how sleep affects declarative memory: no benefit, passive protection, permissive consolidation and active consolidation. Experimental evidence argues strongly for the rejection of the first two hypotheses. The latter two hypotheses both state that declarative memory consolidation occurs preferentially during sleep — one because sleep enables the ideal circumstances for consolidation to take place, the other because unique properties of sleep directly engage consolidation. At this point, there is no evidence that conclusively eliminates one of these options.

Here, we presented the available evidence: that sleep leads to improved performance in memory recall; that sleep renders memories resistant to subsequent interference; that the resistance to interference lasts throughout the subsequent waking period; that certain stages of sleep correlate with performance improvements on certain tasks; that the hippocampus replays information during sleep; and that the behavioral improvements correlate with hippocampal re-activation. Given this evidence, we believe the most parsimonious conclusion is that there are specific, sleep-dependent, neurobiological processes that directly lead to the consolidation of declarative memories.

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