An opportunistic theory of cellular and systems consolidation

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Abstract

Memories are often classified as hippocampus-dependent or –independent, and sleep has been found to facilitate both, but in different ways. In this Opinion article, we explore the optimal neural state for cellular and systems consolidation of hippocampus-dependent memories that benefit from sleep. We suggest that these two kinds of consolidation, which are ordinarily treated separately, may overlap in time and jointly benefit from a period of reduced interference (during which no new memories are formed). Conditions that result in reduced interference include slow wave sleep (SWS), NMDA receptor antagonists, benzodiazepines, alcohol, and acetylcholine antagonists. We hypothesize that the consolidation of hippocampal-dependent memories may not depend on SWS per se. Instead, the brain opportunistically consolidates previously encoded memories whenever the hippocampus is not otherwise occupied by the task of encoding new memories.

Introduction

One of the central questions in cognitive neuroscience is: how does the human brain learn new information while not overwriting previously stored memories? Memory models have addressed this so-called stability plasticity dilemma [1] by proposing a post-encoding, offline period that allows the brain to consolidate recent experience into long-term storage [2–4]. Recent models propose that this offline period takes place during sleep [5]. In general agreement with this idea, a large number of behavioral studies have demonstrated that sleep facilitates both non-declarative memories (i.e., non-conscious memories such as sensorimotor skills, perceptual skills, habits, priming, etc.) [6–11], which are not dependent on the hippocampus, and declarative memories (i.e., conscious memories of events, places, and general knowledge), which are dependent on the hippocampus. Although both kinds of memory benefit from sleep, they benefit in different ways. Non-declarative memories are often *enhanced* after a period of rapid eye movement (REM) sleep (Glossary) such that performance increases from the end of training [6, 8, 12–15]. In contrast, the sleep-related

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facilitation of declarative memories usually consists of *decreased forgetting* after a post-encoding period of non-REM (nREM) sleep composed of Stage Two and Slow Wave Sleep (SWS)[10, 16–19].

These opposing performance outcomes (i.e. enhanced memory performance versus decreased forgetting; Figure 1), raise the possibility that the consolidation of declarative and non-declarative memories rely on distinct mechanisms. With regard to declarative memory, which is the main focus of our Opinion article, we ask the question: What are the essential conditions for consolidation to occur? It has previously been proposed that SWS is critical for declarative memory consolidation [20, 21]. The viewpoint that we advance here suggests that the critical condition is a period of reduced interference, during which consolidation renders the memory trace less vulnerable to the negative effects of new encoding. In addition, we argue that this process occurs as a result of both cellular consolidation and systems consolidation.

SWS facilitates declarative memory

A long history of research has consistently shown that a period of SWS yields less forgetting than a comparable period of REM sleep or waking activity [9, 10, 17, 22]. In humans, the first half of the night is rich in SWS, while the second half of the night is rich in REM sleep. Previous studies have shown that 4 hours of mostly SWS resulted in less forgetting of a declarative verbal memory task performed earlier in the day than a comparable period of REM sleep or waking, which did not differ from each other in terms of performance [9, 22]. Similar results were found in a study that controlled for time-of-day and circadian confounds[9]. Subsequent studies replicated the effect [10, 17]. Similarly, compared with wake, daytime sleep (naps) (consisting of only nREM) showed less forgetting on a declarative paired word associates task, but not on a non-declarative procedural memory task. Furthermore, better performance in this task was positively correlated with minutes of SWS during the nap [23].

Why is SWS good for declarative memory? A number of different hypotheses to explain this have been put forward over the years. In the following section, we will briefly outline two hypotheses, namely the Unique-to-sleep consolidation hypothesis and the Passive Interference Reduction hypothesis, that have been previously put forth in the sleep field, as well as outlining the rationale behind our Opportunistic consolidation hypothesis.

Unique-to-sleep consolidation hypothesis

One possibility is that the consolidation of declarative memories depends on neural mechanisms that are unique to SWS [21, 24], a view that we refer to as the Unique-to-Sleep Consolidation hypothesis (see Table 1). This view is sometimes called the "active" hypothesis [24] because sleep is assumed to play an active role in consolidation, but its key feature is the assumption that SWS is an "essential" [21] or, at least, "crucial" [25] trigger for systems consolidation. Such a viewpoint generally does not emphasize an important role for interference reduction, and it generally does not consider the role of cellular consolidation during SWS. However, the Unique-to-Sleep Consolidation hypothesis is an umbrella term for a variety of specific accounts, some of which include considerations similar to the Opportunistic Consolidation Hypothesis (e.g., one of the aforementioned studies [21] , recently proposed that REM is critical for the cellular consolidation of declarative memory and another recent paper [24] included provisions for increased resistance to interference associated with sleep).

Opportunistic consolidation hypothesis

While there is ample evidence to support the importance of SWS in some form of memory consolidation, an alternative hypothesis suggests that SWS may not be the only crucial neural state that triggers consolidation. In this hypothesis, which we refer to as the Opportunistic consolidation hypothesis, we argue that the core condition favoring both cellular and systems consolidation may not be sleep per se, but may instead be reduced retroactive interference. More specifically, the Opportunistic consolidation hypothesis posits that declarative memory consolidation processes associated with recently encoded memories are facilitated by a subsequent period of reduced interference (i.e., a post-encoding period during which new memories are not encoded) (Table 1). Importantly, this period of reduced interference must occur within a limited temporal window after a memory is encoded in order to initiate cellular and systems consolidation. Furthermore, this view holds that anything that induces a period of reduced interference (ie. not only SWS) will benefit the consolidation of recently encoded memories. Along with SWS, quiet wake, and anterograde amnesia-inducing drugs (e.g., NMDAR antagonists, alcohol, and benzodiazepines) should all facilitate declarative memory by creating favorable conditions (i.e., reduced interference) for both cellular and systems consolidation. We propose that by virtue of these consolidation processes, the memory trace is rendered more resistant to retroactive interference because of: (i) the stabilization of the representation at local synapses and their cell bodies associated with cellular consolidation, and (ii) the distributed encoding of the representation across different association cortices that occurs as a result of systems consolidation. Importantly, this proposal differs in a critical way from the older Passive Interference Reduction Hypothesis, which we briefly outline below.

Passive interference reduction hypothesis

The Passive Interference reduction hypothesis posits that sleep has beneficial effects merely because it eliminates interference that would otherwise occur (Table 1) [26]. According to this view, the benefit of sleep results only from a period of reduced retroactive interference, not because reduced interference allows consolidation processes to proceed. The prediction is that sleep (and drugs that produce anterograde amnesia) after learning will lead to less forgetting. However, because consolidation is not a relevant consideration, this account makes no distinction about the timing of the interference period (i.e. a period of reduced interference will have the same effect if it occurs immediately after new encoding or 8 hrs later).

Phases of declarative memory consolidation

The encoding of a memory trace begins with activation of primary and associative cortical areas. The hippocampus integrates information from these distributed cortical structures and rapidly fuses these features into a coherent memory trace. At least two phases of consolidation have been identified, which together trace the process of consolidation from the hippocampus to cortex: cellular and systems consolidation. A review of the phases of consolidation is necessary to understand the effect of SWS and other brain states on memory for previously learned information.

Cellular consolidation

Cellular (or molecular) consolidation refers to the molecular and cellular processes that stabilize information by strengthening synaptic connections within the hippocampus and elsewhere [27–30]. Long term potentiation (LTP), a form of synaptic plasticity, is the leading physiological model for the initial encoding and subsequent stabilization of memory [31] (Figure 2). Indeed memory acquisition and the induction of LTP share many common features including the requirement of Ca^{2+} to enter through postsynaptic NMDA receptors

(NMDARs) [32]. Following high levels of glutamate transmission and consequent depolarization, Ca^{2+} enters the cell and acts as an intracellular messenger activating numerous signaling pathways that lead to LTP. These changes ultimately lead to the insertion of additional AMPA receptors into dendritic membranes [33] and morphological changes in dendritic spines [34]. In addition, other factors such as monoamines play a key role in modulating LTP, and may play a role in activating the cellular cascade leading to stable LTP [35]. When NMDARs, calcium signaling, or other early aspects of this process are disrupted, LTP induction and memory acquisition fail [27, 36]. When transcription factors, new protein synthesis, or other late aspects of this process are disrupted, LTP forms but is unstable; likewise, memory is acquired but quickly forgotten [37] (Figure 3). This process of molecular consolidation is thought to take up to one day, with much emphasis on the first six hours [38, 39].

Significantly, the induction and maintenance of LTP can be dissociated, as drugs that inhibit induction do not necessarily interfere with the maintenance of prior LTP [40, 41]. In particular, the application of an NMDAR antagonist prior to induction blocks the formation of new LTP, but has little or no effect when applied after induction [42]. However, a critical consideration for our theory is that new hippocampal LTP induction (and the formation of new memories) can interfere with the maintenance of older LTP (and with the retention of older memories). For example, memories formed in the hippocampus and LTP induced in the hippocampus both exhibit a similar temporal gradient with respect to interference from new learning (i.e., retroactive interference) [43, 44]. Specifically, subsequent learning interferes with original learning if the time between them is relatively short (e.g., 1 hr), but less interference is observed when the time between them is relatively long (e.g.,≥6 hrs) (Figure 2)[43, 44]. When the time between learning and interference is long, the processes associated with LTP are given time to occur, and the trace becomes less vulnerable to the interfering effects of new learning (i.e., it becomes stabilized). These findings suggest that the neural representation of an experience encoded in the hippocampus is vulnerable to the interfering effects of new learning but may become less so after cellular consolidation has had a chance to run its course[45, 46]. One key assumption of the Opportunistic consolidation hypothesis is that behavioral states or drugs that minimize new learning should facilitate cellular consolidation.

Systems consolidation

Systems consolidation refers to the time-limited role of the hippocampus in declarative memory storage [47, 48]. Through successive reactivation of the hippocampal–cortical network new memories are presumed to be gradually integrated with pre-existing memories and become independent of the hippocampus [2, 47, 49]. Although this form of consolidation is thought to occur over a time-course lasting weeks, months, or even years, systems consolidation is initiated within the first days after encoding [50].

One of the leading candidate mechanisms underlying systems consolidation is neural replay (Figure 2), a process that has been observed in studies of rodent spatial memory. Specifically, place cells that are activated in sequence together during a learning episode tend to fire in a similar sequence during sleep [51]. Studies have shown: 1) hippocampal replay during SWS in rats is coordinated with firing patterns in the visual cortex[52]; 2) the hippocampus and cortex appear to communicate during sleep by means of hippocampal sharp waves or ripples[53] during which place cells are reactivated[54]; and 3) these events are temporally correlated with spindles in the medial prefrontal cortex (PFC) during SWS[55].

Systems consolidation has the effect of rendering the memory trace independent of the hippocampus. By encoding the memory trace in a distributed fashion in the cortex[56],

systems consolidation (like cellular consolidation) may also have the effect of rendering the trace more resistant to interference (Figure 3). In this case, however, the increased resistance to interference results from the fact that subsequently encoded memories are less likely to compete for the same neural pathways that were used to consolidate previously encoded memories.

Consistent with this idea, the cue-dependent reactivation of memories during SWS was recently found to increase the resistance of those memories to subsequent interference [57]. In contrast, during the awake state, the same manipulation had the opposite effect [58]. Reconsolidation theory holds that cuing memories destabilizes them until they can again be consolidated. Conceivably, a reactivated memory is destabilized in the sense that it again becomes vulnerable to interference caused by the encoding of subsequent memories. During SWS, however, reactivated memories would not suffer the effects of interference as they are encoded in cortical areas, rendering them less vulnerable to interference [57]. Although not tested in this experiment, we would predict that the cue-dependent reactivation of memories during an awake state that did not involve the encoding of other memories would have the same beneficial effect that was seen when memories were activated during SWS.

Cellular consolidation and systems consolidation are usually discussed separately, but they may be coupled processes. For example, in hippocampal slices, the induction of LTP (normally discussed in terms of cellular consolidation) leads to spontaneous sharp wave activity (a process ordinarily associated with systems consolidation) [58]. If cellular and systems consolidation are coupled processes, then one might expect to find that the conditions that favor cellular consolidation would also be found to favor systems consolidation. We suggest that those conditions involve reduced interference, and SWS appears to be one such condition.

The role of SWS in cellular and systems consolidation

SWS has been shown to reduce experience-dependent hippocampal plasticity, thereby inhibiting the formation of new memories. For example, in sleeping rats, LTP can be readily induced during REM sleep, but is much less readily induced during SWS [59]. Similar to NMDAR antagonists, SWS inhibits the induction of LTP, but does not disrupt the maintenance or persistence of previously induced LTP [60]. In contrast, regarding synaptic plasticity in the hippocampus, REM sleep is similar to the awake state, as LTP can be readily induced [60]. Similarly, associative learning is impaired during SWS, and not during REM. For example, in a classical conditioning paradigm using brain stimulation as the conditioned stimulus (CS) and unconditioned stimulus (US), with multiunit firing of hippocampal neurons as a measure of associative learning, paired CS-US brain stimulation resulted in increased hippocampal firing in response to the CS during REM and wake, but not during SWS[61]. Thus, in rodents, it appears that SWS is a period of reduced hippocampal plasticity. As a consequence, few memories should be formed during SWS, compared with REM or wake, even though considerable mental activity occurs during SWS[62].

If memories are not encoded during SWS, then post-training SWS should be conducive to the cellular consolidation of both LTP and memories formed during training, just as post-training NMDAR antagonists are often conducive to both. LTP induced during wakefulness is later fully expressed during SWS [60], which is consistent with our proposed view. However, it is not known if SWS is more protective of previously induced LTP than a corresponding period of wakefulness or if a temporal gradient of interference reduction (with SWS being more protective of LTP soon after induction) is observed, as our hypothesis predicts. With regard to its effect on declarative memory, SWS has in fact been

shown to have such effects. Sleep studies with humans have reported a temporal gradient of interference that is similar to the gradient obtained in studies of the effect of NMDAR antagonists in rats discussed earlier. Using a 24-hr retention interval between initial learning and a subsequent memory test, these studies showed that sleep soon after learning is more beneficial than sleep that is delayed[63], even after controlling for circadian confounds [64, 65]. The temporal gradient associated with sleep is consistent with the notion that reduced hippocampal plasticity protects recently formed and still-fragile memories, giving them a chance to become hardened against the forces of retroactive interference as cellular consolidation unfolds.

In addition to benefiting cellular consolidation, the absence of encoding during SWS may also be conducive to neural replay and systems consolidation of memories formed prior to sleep. Indeed, in rodents, the coordinated replay of place cell activity has often been reported during SWS [52, 54, 55]. Analogously, in a positron emission tomography (PET) study with humans, hippocampal areas that were activated during a route learning task were reactivated during subsequent SWS [66]. Interventions designed to enhance reactivation during SWS have also been shown to affect consolidation. In a functional magnetic resonance imaging (fMRI) study with humans, cuing recently formed odor-associated memories by odor re-exposure during SWS (but not during REM sleep) prompted hippocampal activation during sleep resulting in less forgetting after sleep, compared to a control group [67]. Overnight sleep increased the integration of newly learned words into the mental lexicon (i.e. lexical competition effect), a measure of systems consolidation, and the degree of lexical competition correlated with sleep spindles during NREM sleep [68]. Similarly, transcranial direct current stimulation of delta activity (<3Hz) during SWS significantly decreased forgetting in declarative memory but not procedural memory performance[69]. Thus, these results do not show that systems consolidation improves the fidelity of the memory trace (i.e. increased retention from baseline was not observed). Instead, SWS appears to protect new memories by consolidating them in a low-interference storage site (such as the cortex).

Computational models of the role of the hippocampus in declarative memory posit that the degree to which new encoding interferes with recently learning material is related to the amount of overlap in the synaptic representations of successive experiences, with greater overlap leading to greater interference [70–73]. It is therefore possible that the mechanism by which SWS improves retention during reactivation involves facilitating the consolidation of multiple memories in a more distributed, non-overlapping fashion in the cortex. If so, then the reduced interference associated with SWS may render memory traces more resistant to interference in two (related) ways: (1) by allowing the molecular processes associated with cellular consolidation to proceed undisrupted, and (2) by facilitating the activation (and reactivation) of the distributed network between hippocampus and various cortical areas through the processes associated with systems consolidation (Figure 3).

Quiet Wake: the resting mind at replay

Much of the earlier work on neural replay documented its occurrence during SWS, which was consistent with the idea that this form of consolidation may have been sleep-specific. However, recent evidence suggests that replay of recent experiences[54, 74, 75], and future experiences [76], as well as remote replay (i.e., replay of sequential place cell firing that occurred earlier in a different environment) can occur during the awake resting state as well[77–79]. These findings suggest that the hippocampus may take advantage of any down time (including, but not limited to, SWS) to consolidate memory. That is to say, the processes that underlie systems consolidation may unfold whenever the hippocampus is not encoding new memories (e.g., [53]).

Indeed, prior studies have suggested that hippocampal plasticity is reduced during quiet wake just as it is during SWS [80, 81]. Thus, we argue that reduced experience-dependent hippocampal plasticity is what allows cellular consolidation mechanisms to evolve without interference and simultaneously sets the stage for systems consolidation mechanisms to become operative. Several recent human studies have indicated that quiet wake, a non-sleep resting state with reduced encoding and interference, can induce a similar behavioral enhancement as sleep. In a study using a hippocampus-dependent visual search task [82, 83], similar learning profiles were reported for the nap and quiet wake group, but the active wake group showed less learning [8]. The authors hypothesized that quiet wake mimicked the dampened encoding found in SWS, which facilitated consolidation. Importantly, most sleep studies compare sleep with an active wake period as the control, which does not control for waking experiences that could potentially cause interference with recently encoding memories. The few studies that have compared quiet wake with sleep have reported similar memory gains in both groups [84, 85]. In a similar vein, hippocampal-cortical connectivity in humans, as measured by blood-oxygen-level-dependent (BOLD) fMRI, during quiet wake immediately following a learning task was enhanced compared to a pre-task resting baseline[86]. Further, individual differences in the magnitude of post-task functional connectivity was predictive of later associative memory performance [85]. Thus, data from both rodent and human studies are consistent with our hypothesis that hippocampal-based memory consolidation utilizes optimal brain states to process prior learning, and is not specific to sleep per se.

Pharmacologically induced SWS-like neural states

According to the Opportunistic Consolidation Hypothesis, neither SWS nor quiet rest uniquely trigger consolidation processes. Instead, they facilitate consolidation because they are both associated with reduced hippocampal plasticity (and, therefore, reduced encoding of new memories). Amnesia-inducing drugs, such as alcohol, benzodiazepines and acetylcholine antagonists, modulate memory performance similarly to sleep, perhaps also due to reduced hippocampal plasticity [87]. That is, these drugs may selectively block the encoding of new memories, which may initiate cellular and systems consolidation of memories that were encoded in the recent past.

With respect to ethanol, multiple studies in rodents and humans have demonstrated that it can impair the acquisition of new information when administered before learning [88–91]. However, when taken after learning, alcohol facilitates memory performance more than placebo, in the sense that less forgetting is observed [92, 93]. Similarly, benzodiazepines (GABA$_A$ receptor allosteric modulators), have been shown to protect memory for information learned prior to drug administration, and hence, only induce anterograde amnesia [94–96]. A combination of scopolamine [a muscarinic acetylcholine receptor (AchR) antagonist] and mecamylamine (a nicotinic AchR antagonist) produced retrograde facilitation of word pairs compared with placebo, as well as decreasing acquisition of new words [97]. Consistent with the interference literature, the enhancement of memory consists of less forgetting in the drug group compared to placebo (not an absolute increase in performance relative to prior performance).

It seems unlikely that amnesia-inducing drugs yield less forgetting of previously encoded memories by directly enhancing the consolidation process. This is because a direct enhancement of consolidation would be expected to also yield anterograde facilitation (i.e., the enhancement of memories learned after the drug is taken), not anterograde amnesia. Instead of these drugs directly augmenting consolidation processes, we hypothesize that the mechanism by which amnesia-inducing drugs retroactively facilitate memory involves reduced experience-dependent hippocampal plasticity. The reduced encoding of new

memories indirectly facilitates cellular and systems consolidation processes by allowing them to opportunistically proceed for memories that were encoded in the recent past. In agreement with these considerations, ethanol produces a dose-dependent suppression on the magnitude of LTP following high frequency stimulation in acute hippocampal rodent slices [98], but it specifically blocks the induction of LTP, and not the expression or maintenance of LTP [89]. Thus, it seems reasonable to propose that ethanol may facilitate cellular consolidation. Benzodiazepines also block the induction of hippocampal LTP [99], as do AchR antagonists [100]. Thus, using LTP as a model, alcohol, benzodiazepines and AchR antagonists would be expected to (and do) induce anterograde amnesia, which would (according to our theory) protect older memories from retroactive interference, thereby giving them a chance to undergo cellular consolidation (Figure 2).

Anterograde amnesia may also disinhibit systems consolidation processes (such as neural replay) by quieting hippocampal encoding activity and allowing for hippocampal-cortical dialog associated with previously encoded memories [53]. The results of a recent study [101], which trained rats to learn three new goal locations in an open field each day, is in agreement with this view. Goal-related place-cell replay activity during rest (sleep was not measured) generally corresponded to the newly learned locations. However, the use of an NMDAR antagonist resulted in rapid forgetting of new locations as well as place-cell replay activity that corresponded to the previous day's goal locations [101]. Consistent with these data, studies of amnesics show that delaying a post-encoding period of interference improves recall of words, compared with no delay [102].

Although parallels can be drawn between SWS, quiet wake and amnesia-inducing drugs with regard to their apparent effect on cellular consolidation, it is not yet known whether amnesia-inducing drugs also liberate processes associated with systems consolidation. For example, it is not known whether benzodiazepines and alcohol facilitate communication between the hippocampus and cortex via hippocampal sharp waves/ripples and cortical spindles. We speculate that, like SWS, amnesia-inducing drugs that selectively block the encoding of new memories may, indeed, trigger the switch between encoding and consolidation. That is, the Opportunistic Consolidation hypothesis holds that a temporary period of anterograde amnesia may be the common denominator that ties together a variety of conditions that are favorable to consolidation. Future studies are needed to test this hypothesis.

Acetylcholine: a modulator of declarative memory consolidation

What is the underlying mechanism that may be supporting the switch between encoding and consolidation? In a 2-stage model [53, 103], ACh signaling functions as a switch between inflow (encoding or write-in) and outflow (consolidating or write-out) modes of the hippocampus. In the encoding state, high cholinergic activation, such as during active awake and REM sleep [104], when theta rhythm is present [105, 106], sets the appropriate hippocampal dynamics for inflow of information by suppressing communication from the hippocampus to the cortex [107]. At low cholinergic activation, such as during quiet wake and SWS when hippocampal sharp waves are present [53], there is a release from cholinergic suppression. This permits outflow of information from the hippocampus to the cortex [103]. Thus, according to this view, the consolidating state is not specific to sleep, but it does occur during sleep. Critically, the encoding and consolidating states are also associated with characteristic rhythmic activity, and a basic assumption of this account is that communication between the hippocampus and cortex is mediated by coordinated oscillatory rhythms across different structures of the brain [108]. A similar suggestion has been made in computational models of consolidation [5].

Lower levels of ACh prevail during quiet wake and SWS [109], and this is thought to shift the hippocampus into the consolidating state [97]. In this state, activity along input pathways (ordinarily facilitated by cholinergic-driven, theta rhythm) is suppressed and hippocampal plasticity is low (i.e. hippocampal LTP is not readily induced). As such, and as indicated earlier, recently induced LTP would be protected from interference and would be given a chance to stabilize as the process of cellular consolidation unfolds. In addition, under these conditions, the cortex is characterized by low frequency spindle (i.e. 7–14 Hz) and delta (i.e. ≤ 4 Hz) oscillations [110], whereas the hippocampus is associated with a more broad-spectrum pattern punctuated by brief, high frequency sharp waves (i.e. 30+ Hz) and very high frequency ripples (~ 200 Hz) [53]. These sharp wave oscillations occur within the hippocampal-entorhinal output network. Synchronized neural discharges tend to occur along this pathway during sharp-wave/ripple events [111, 112]. Thus, once again, rhythmic activity seems to coordinate communication between adjacent brain structures.

Such communication has been found to occur between more distant brain structures as well. For example, ripples observed during hippocampal sharp waves have been found to be correlated with the occurrence of spindles in the PFC [55]. Moreover, the neural replay discussed earlier preferentially takes place during the high-frequency bursts of spindle waves [113]. All of this suggests that rhythmically-based feedback activity from the hippocampus may serve to "train" the cortex and thus facilitate the process of systems consolidation. Importantly, this brain state is not specific to SWS but also generalizes to quiet wake as well. If the cessation of encoding triggers this ACh-modulated switch between encoding and consolidation, then we might predict that this same switch would be triggered by other states of reduced encoding, such as pharmacologically-induced states of anterograde amnesia. Interestingly, the drugs that would be expected to have this effect are those that selectively inhibit the encoding of new memories.

Synaptic Tagging and Capture

According to our hypothesis, retroactive interference occurs when newly encoded memories usurp resources that might otherwise be used to consolidate previously encoded memories. Under some conditions, however, a new memory may have the opposite effect of providing consolidation resources to weak memories[114–116]. The synaptic tagging and capture hypothesis posits that early-LTP produced by weak stimulation can be converted into late-LTP when a strong stimulus is delivered either before or after the early-LTP (i.e., the consolidation of weak Event A would be enhanced if preceded or followed by strong Event B)[117]. The analog to this is behavioral tagging and capture, where a short-term memory (e.g. a weak fear conditioning paradigm which lasts a few hours) can be converted into a long-term memory (e.g. 24hrs) if preceded or followed by a long-term memory[118, 119]. The idea is that a weak memory alone is insufficient to induce the molecular cascades leading to cellular memory consolidation. But, when another strong memory elicits such molecular cascades, it allows the weak memory to share resources (i.e. plasticity-related proteins) before it decays, thereby allowing it to consolidate into a long-term memory.

Interestingly, this intriguing result stands in apparent contrast to many other results in animals [43, 44] and humans [102, 120–122] showing that interference is often observed under conditions much like the ones that enhance the durability of weak memory in tagging and capture studies. Thus, considered in that light, the tagging and capture hypothesis may not always readily explain all phenomenon. The time interval between the two tasks may be a critical variable, and thus, will be an important issue to address in future studies.

Conclusion

In summary, we propose that it is not a coincidence that the mechanisms of cellular and systems consolidation are favored during periods of reduced encoding and hippocampal plasticity (including, but not limited to, SWS). According to the Opportunistic Consolidation Hypothesis that we put forth here, both phases of consolidation are compromised when hippocampal encoding mechanisms are engaged (i.e., when new memories are being formed). Furthermore, when hippocampal encoding mechanisms are disengaged without compromising hippocampal consolidation mechanisms, the consolidation mechanisms are released (Figure 3). We hypothesize that cellular and systems consolidation may be closely connected processes that unfold together in the hours after learning (with systems consolidation continuing for an extended period of time thereafter), rather than considering them as processes that unfold independently of each other on vastly different time scales. If so, this might explain why the conditions that favor one form of consolidation also appear to favor the other (Figure 3). According to the Opportunistic Consolidation Hypothesis, these potentially related consolidation processes preferentially unfold in an opportunistic fashion whenever the hippocampus is disengaged from the process of encoding new memories. Moreover, according to this view, the processes of declarative memory consolidation do not strengthen memories such that performance is enhanced from a baseline (Figure 1). Instead, as forgetting occurs (i.e., as memories weaken), both cellular and systems consolidation serve to render those memories more resistant to interference caused by the encoding of subsequent memories. These considerations suggest that for declarative memory, the issues of consolidation and interference are intimately connected, although future studies are needed to directly address this (Box 1).

A reduction in interference may also play a key role in the consolidation of non-declarative memories. However, in that case, the behavioral phenomenon to be explained (i.e., an absolute enhancement in performance, Figure 1) is different, suggesting different consolidation mechanisms as well. We assume that non-declarative memory benefits when the cortex is released from input – input that comes from sensory processing during the awake state or from hippocampus-to-cortex neural replay during SWS. Under these conditions of reduced input, combined with a cortically activated state relative to SWS and in some cases waking[123], cortical circuits may be free to extrapolate, which may account for the absolute enhancement of transitive inference[11], creativity[8], and perceptual learning[6] as a function of REM sleep. However, the story seems quite different for declarative memory. In our view, it is not sleep, per se, that is essential for the systems consolidation of declarative memory. Instead, we suggest that cellular and systems consolidation are interlinked, opportunistic processes that capitalize on periods of reduced encoding to render recently learned memories more resistant to interference.

Box 1. Outstanding questions

- What are the conditions under which subsequent learning interferes with prior learning (ie. retroactive interference) versus the conditions under which subsequent learning enables consolidation of prior learning? Do both of these involve mechanisms of synaptic/behavioral tagging and capture?

- Are the cellular and systems level mechanisms that underlie retrograde facilitation associated with SWS similar to the mechanisms that underlie retrograde facilitation associated with alcohol and benzodiazepines? Do they exhibit a temporal gradient?

- Is reduced encoding or reduced hippocampal plasticity sufficient to trigger hippocampal – neocortical replay?

- Unlike in the hippocampus, can LTP be readily induced in the cortex during SWS? What about under conditions of quiet wake, alcohol, and benzodiazepines?

- Is synaptic downscaling [126] a possible mechanism of reduced retroactive interference caused by a post-encoding period of SWS, alcohol, or benzodiazepines?

- For the consolidation of declarative memory, is it the stage of sleep (i.e. SWS) that is important or rather the amount of slow wave activity and sleep spindles across all stages that are the critical variables?

- For the consolidation of non-declarative memory, is it the stage of sleep (i.e. REM) that is important or rather the amount of pontogeniculooccipital waves and theta oscillations across all stages that are the critical variables?

- Is the temporal order of the different sleep stages (i.e. SWS always preceding REM sleep) of functional benefit for learning and memory? For example, is it of importance in order to avoid interference-driven amnesia (i.e. catastrophic forgetting)?

Acknowledgments

Glossary

Retrograde facilitation	Enhanced memory performance after an intervention (e.g., drug administration, sleep) following original learning, as compared to a control (e.g., placebo, lack of sleep). The enhanced performance compared with the control usually consists of less forgetting from a prior performance baseline
Retroactive interference	New learning that interferes with previously learned information
Cellular consolidation	Molecular and cellular processes that stabilize information by strengthening synaptic connections. This is achieved by triggering intracellular signaling cascades and activating transcription factors that lead to changes in gene expression. This process is thought to take up to one day, with much emphasis on the first six hours
Systems consolidation	The process that refers to the time-limited role of the hippocampus in declarative memory storage. Information is originally encoded in both hippocampal and cortical regions. Successive reactivation of this hippocampal–cortical network is presumed to allow new memories to be gradually integrated with pre-existing memories and become independent of the hippocampus. Although this form of consolidation is thought to occur over a time-course lasting weeks, months, or even years, systems consolidation is initiated within the first days after memory encoding

Declarative memory (explicit memory)	conscious memory of facts and events. This type of memory is dependent on the hippocampus and other areas of the medial temporal lobe
Non-declarative memory (implicit memory)	unconscious memories such as habits or skills (e.g., learning to ride a bicycle). This type of memory is typically not dependent on the hippocampus, but rather on a variety of other brain regions, including the PFC
Slow Wave Sleep (SWS)	Also referred to as deep sleep, consists of stages three and four of non-rapid eye movement sleep (nREM), ie. electroencephalogram (EEG) waves of duration slower than 4 Hz
Rapid Eye Movement (REM) Sleep	a relatively active sleep characterized by rapid eye movements, low muscle tone and rapid, low-voltage EEG waves
nREM Sleep	Consists of Stages One, Two and SWS. Sleep spindles and slow wave activity within nREM may be better markers for physiological changes associated with consolidation than sleep stages themselves [125]. However, in this Opinion paper, we use the term SWS, as it is commonly used in the animal literature
Slow Wave Activity (SWA)	EEG spectral power in the 1–4.5 Hz band
Spindles	A burst of brain activity visible on an EEG that typically occurs during stage 2 sleep. It consists of 12–14 Hz waves that occur for at least 0.5 seconds
Sharp-waves and Ripples	During sleep or quiet rest, the hippocampal EEG shows a pattern of irregular slow waves, somewhat larger in amplitude than theta waves. This pattern is occasionally interrupted by large surges called *sharp waves*. These events are associated with bursts of spike activity, lasting 50–100 msec, in hippocampal pyramidal cells of the CA1 and CA3 regions. They are also associated with short-lasting high-frequency EEG oscillations called "ripples", with frequencies in the range 150–200 Hz.

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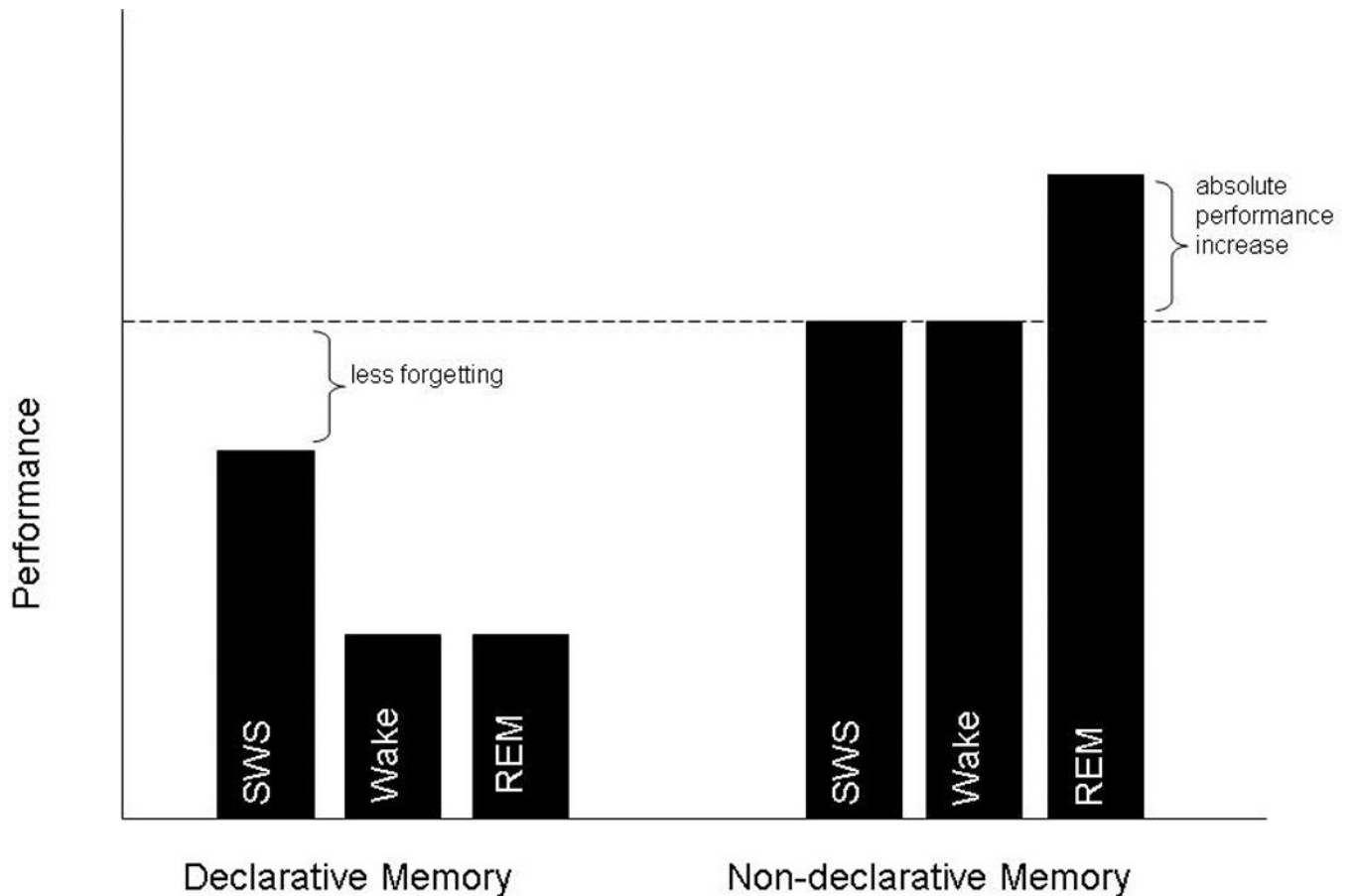
Figure 1.
A qualitative model graph that schematically depicts performance changes typically observed in declarative (e.g. verbal memory) and non-declarative (e.g. perceptual learning) memory tasks in human subjects. Changes in memory performance from initial encoding (dotted line) to after a period of SWS, wake, or REM for both declarative memory and non-declarative memory tasks. On declarative memory tasks, performance is always best at initial encoding. Memories show less forgetting after a period of SWS, compared with an equal period of REM or waking (e.g. [10, 67, 121]). For non-declarative memory, performance shows an absolute improvement in performance compared to encoding, but only after a period of REM sleep, and not after an equal period of SWS or wake (e.g. [6, 8, 17]).
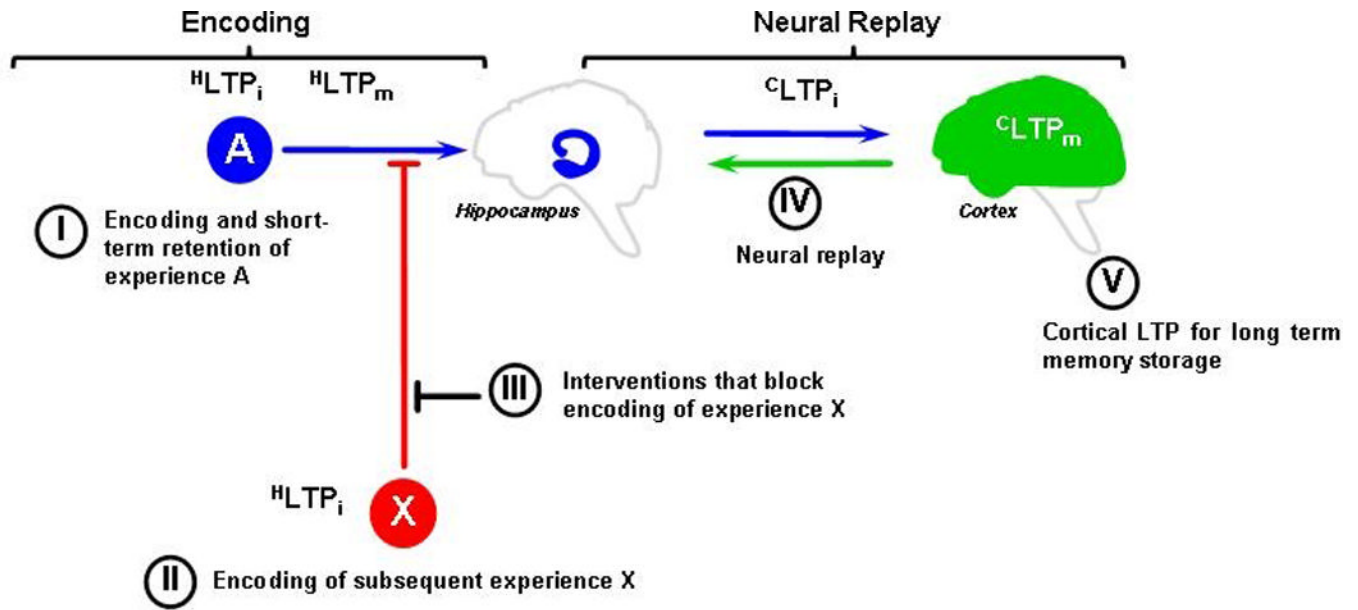
Figure 2.
Timeline of cellular and systems consolidation. The hippocampus integrates information about new experience (A) from primary and associative cortical areas and rapidly fuses the features into a coherent memory trace by LTP induction (^{h}LTP$_i$) and maintenance (^{h}LTP$_m$) (I). Subsequent new experience (X) will be encoded by distributed cortical areas, and induce hippocampal LTP. New ^{h}LTP$_m$ of X will interfere with consolidation of A by blocking LTP maintenance (causing A to be forgotten) (II). A period of reduced hippocampal plasticity (III) (i.e. inhibition of LTP induction and no new memory encoding) by SWS, NMDAR antagonists, amnesia-inducing drugs or quiet rest result in (1) retrograde facilitation (i.e. less forgetting) of A; and 2) sets the stage for the onset of cortical neural replay (^{c}LTP$_i$) of events associated with the encoding of experience A. Neural replay (IV) is the reactivation of memory traces [54] by means of hippocampal sharp wave/ ripple complexes [53] that occur during periods of reduced hippocampal plasticity. Final stage of consolidation is the maintenance of LTP in the cortex (^{c}LTP$_m$), which is essential for long-term memory storage [124] (V).
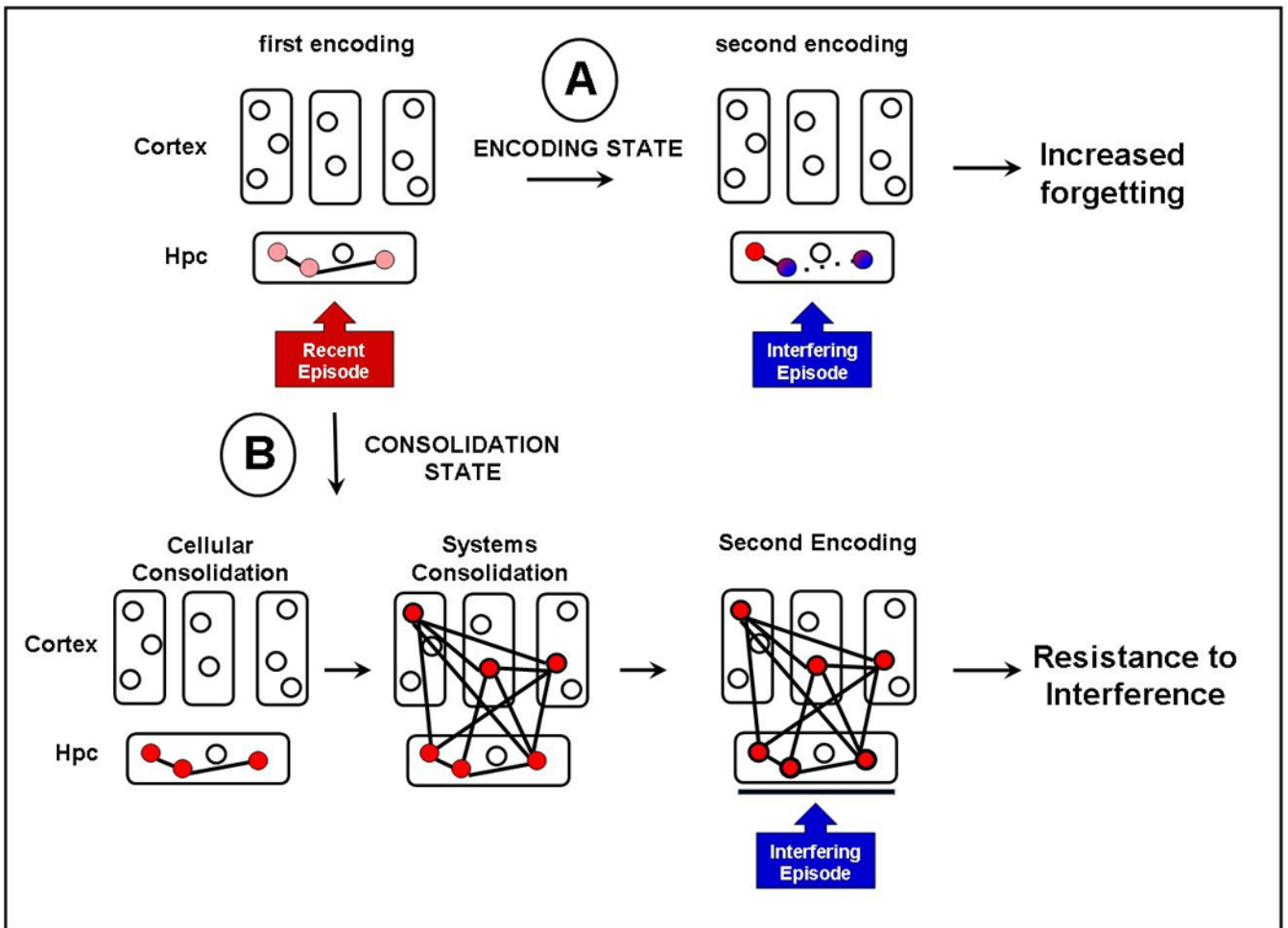
Figure 3.
Working model to illustrate encoding and consolidation states during memory formation.
These states are not assumed to operate in parallel at full efficiency. Instead, A shows how
the encoding of new memories (ie. second encoding, light red circles indicate newly
encoded information still vulnerable to interference, whereas circles filled with red and blue
indicate memories that have already been degraded by new encoding) during the active
wake state takes priority and inhibits cellular and systems consolidation of recently formed
memories (ie. first encoding), which leads to increased forgetting. During the consolidating
state (B), the hippocampus (Hpc) has low input from the cortex and low synaptic plasticity
(ie. the interfering episode encoding is blocked) allowing for recent memories to undergo
cellular and systems consolidation. These conditions are present during SWS, NMDAR
antagonists and some amnesia-inducing drugs. Hence, we propose, that such conditions
allow the processes of consolidation to opportunistically unfold, resulting in resistance to
interference (indicated by the bold connection lines), as compared with equivalent periods of
awake or REM sleep Adapted from [31].

Table 1

Points of emphasis for three competing views of how SWS facilitates declarative memory.

Points of Emphasis	Competing Hypotheses		
	Unique-to-Sleep Consolidation	Opportunistic Consolidation	Passive Interference Reduction
Less Forgetting Occurs During Periods of Reduced Encoding (including SWS)		*	*
Consolidation Yields Better Performance Than Achieved During Training	*		
Cellular & Systems Consolidation Occur Preferentially During Periods of Reduced Encoding		*	
Systems Consolidation Occurs Specifically During SWS	*		
Consolidation Yields Increased Resistance to Interference		*	

The asterisks represent common points of emphasis associated with the different hypotheses.