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A contextual binding theory of episodic memory: Systems consolidation reconsidered

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Abstract

Episodic memory reflects the ability to recollect the temporal and spatial context of past experiences. Episodic memories depend on the hippocampus, but have been proposed to undergo forgetting unless consolidated during off-line periods like sleep to neocortical areas for long-term storage. Here, we propose an alternative to systems consolidation theory — a contextual binding account — in which the hippocampus binds item- and context-related information. We compare this account with behavioral, lesion, neuroimaging and sleep studies of episodic memory, and contend that forgetting is largely due to contextual interference. Accordingly, episodic memory remains dependent on the hippocampus across time, contextual drift produces post-encoding activity, and sleep benefits memory by reducing contextual interference.

One of the central goals of memory research is to understand why we remember some events and forget others. Over 100 years ago, memory consolidation was proposed as a way of partially answering this question^{1,2}. The main idea is that new memories will be rapidly forgotten unless they undergo an active post-encoding consolidation process that fixes those memories into long term storage. Consolidation is thought to occur at both the cellular and the systems levels^{3,4}. Cellular consolidation is essential for memory retention and it refers to the cascade of molecular processes that occur immediately after learning that stabilize the cellular and synaptic changes produced by learning^{3,5}. In contrast, systems consolidation (SC) refers to the idea that memories for events or episodes are only temporarily dependent on the hippocampus and so they will be forgotten unless they go through a consolidation process that effectively transfers the content of those memories to the neocortex such that they are no longer dependent on the hippocampus^{4,6–10}. Systems consolidation is assumed to occur during off-line periods such as sleep, during which the hippocampus replays previously encoded events to the neocortex, leading to the gradual strengthening of cortical associations without strengthening hippocampal associations.

SC theory has been widely accepted in the cognitive neuroscience literature, and it has garnered support from various areas of research, including behavioral studies of forgetting, lesion and neuroimaging studies, and studies of sleep^{6–9,11} (but also see^{12–14}). In the current

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Competing interests

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paper, we describe an alternative approach that we refer to as ‘contextual binding’ (CB) theory which assumes that episodic memory is not consolidated to the cortex and that instead gradually changing context leads to forgetting and temporally extended encoding activity. This approach is then assessed in light of the research that has been used as evidence for SC. Although some findings are found to be equally well explained by both accounts, a growing body of research directly challenges the assumptions of SC and provides support for CB (Box 1). We argue that a CB account of episodic memory and the medial temporal lobe provides a useful way of understanding when forgetting will occur, and how memory is gradually altered over time.

The contextual binding model

The CB approach (see Figure 1) assumes that episodic memory is dependent on the hippocampus and it reflects the ability to retrieve the context in which items or objects were previously encountered. Context refers to any aspect of the study episode that links the test item to the specific study event, such as remembering the spatial, temporal or other details of that event. So, for example, subjects might encounter several objects that are presented in an experimental context, and then at some later time they are either required to retrieve the objects that occurred in that study context (i.e., a recall task), or indicate if an object was or was not encoded in that context (i.e., a recognition task). Similarly, a rodent might be required to navigate to an earlier learned location (i.e., a water maze task) or discriminate between recently studied and relatively novel objects (i.e., object recognition). The hippocampus is assumed to bind together item and context information that it receives from other regions including the neocortex, and so is critical for the recollection of previous episodes. In contrast, the neocortex plays less of a role in learning detailed contextual information, and instead supports familiarity (i.e., discriminating between recently presented and novel items) and semantic memory (i.e., the acquisition of knowledge about the world)^{15–18}. In addition, we assume that context gradually changes as the physical and mental state of the subject changes^{17,23,24,152}, and as such, the episodic memory event that is being remembered cannot be treated as being limited to the time period in which the study item or object is presented, but rather it extends in time to include the time prior to and after the nominal study item is presented.

Because context drifts, this will impact what will be forgotten, and it will produce temporally extended encoding related neural activity. For example, items that occur immediately before or after the study event will share a similar context and thus will interfere with recollection for the study event. Conversely, conditions such as sleep that reduce the encoding of new interfering memories will benefit subsequent recollection, essentially acting like a switch to a non-interfering, novel context. Moreover, context should be beneficial for memory in the sense that it should enhance the likelihood of remembering temporally contiguous items in an event, and should improve memory if it can be reinstated at the time of retrieval. In addition, because context gradually drifts, encoding related brain activity should be observed for some time after the nominal encoding event is over. Moreover, encoding related activity related to the study context, should also be observable even before the study event is initiated. We note that such temporal context effects should be

largest in the forward direction because the context of the post encoding materials will presumably include information from the prior study event¹⁹.

CB differs from SC in that the CB assumes that the hippocampus plays a necessary - and not just temporary - role in episodic memory. Moreover, according to the CB account, the hippocampus and neocortex are assumed to largely support different types of memory (i.e., recollection and familiarity/semantic memory, respectively) rather than the same types of memory at different times. In addition, forgetting is assumed to reflect interference from events that can occur before or after the study event, rather than as reflecting the failure of systems consolidation that occurs after an event is encoded. Finally, context-related activity should be observed shortly before and after the study event.

Forgetting

Both CB and SC theories provide explanations for how memories can be forgotten, but CB provides a more general account of forgetting and it accounts for a number of forgetting effects that SC cannot explain without making additional assumptions.

Graded retroactive interference.

One of the initial motivations for consolidation theory was the finding by Müller and Pilzecker², illustrated in Figure 2A, that forgetting is greatest when interfering information occurs shortly after encoding rather than later in the retention interval^{2,20–22}. This graded retroactive interference was taken as evidence that memories are actively consolidated after encoding, and that this process is disrupted if interfering information is encountered before consolidation is complete. Moreover, it was argued that the results strongly compel a consolidation account because an interference account would predict that interfering materials should have a similar impact on memory whether they occur early or late in the retention interval.

However, these results are predicted quite naturally by CB without making assumptions about consolidation (also see^{12,23–25}). That is, when interfering items are presented immediately after the initial encoding event, they interfere to a greater extent than items presented later in the retention period because the initial encoded items and the immediately presented interfering items involve greater contextual overlap. Moreover, contextual interference should occur even if the intervening items are not highly similar to the study materials, as was reported by Müller and Pilzecker². We suspect that the reason these graded retroactive interference results are often thought to challenge interference explanations is that earlier theories of interference focused exclusively on interference from similar items, and they attributed little or no role to the importance of context in episodic memory.

Related forgetting effects.

CB, and interference theories in general, also naturally explain a number of other well-established forgetting effects that SC cannot account for without making additional assumptions. For example, forgetting is produced not only when interfering information is presented shortly after the study event, but also when it is presented just before the study event - a well-established experimental phenomenon referred to as proactive

interference^{26,27,28}. CB predicts both retroactive and proactive interference effects, while SC only predicts retroactive effects because consolidation occurs after the study event. Moreover, although Müller and Pilzecker found that the forgetting effects could occur even when the interfering materials were quite dissimilar from the studied materials, forgetting generally increases as the interfering materials become more similar to the study materials^{29,30}. This increased forgetting due to similarity is predicted by interference theories — as forgetting is expected to arise due to interference from similar events — but this is not predicted by consolidation theory.

Context models also provide a way of explaining why context can sometimes have beneficial effects on memory. For example, retroactive interference effects, such as those seen in the study of Müller and Pilzecker², are critically dependent on the context in which the interfering information occurs. Thus, forgetting effects are greatly reduced if the interfering materials are learned in a spatial context than the study materials^{31–33}. In addition, in ‘context reinstatement’ studies, memory performance is generally increased if the test context matches that of the study context^{34,35}, and items that have been forgotten can often be rescued by reinstating the physical or mental context of the original study phase^{36,37}. These types of results are predicted by models that assume that episodic memory involves the binding of item and context information, but are not predicted by SC. In addition, studies of ‘temporal contiguity’ have shown that subjects tend to successively recall and are more likely to recognize items that were presented in nearby positions on a studied list^{19,38}, with such contiguity effects spanning potentially many other intervening memories³⁹. In addition, studies of contiguity effects have indicated that context-related signals in the medial temporal lobe change gradually during the presentation of a study list, and then are reinstated when an item is remembered during test^{40–44}. These results provide direct support for contextual binding models.

One might argue that SC should not be expected to account for these forgetting effects because these studies examine delays of only minutes or days and so may not be relevant if SC takes years or decades to occur, as some have suggested^{8,45,46}. However, others have assumed that SC occurs very rapidly^{7,11,47}, such that even a 60-minute nap immediately after learning can benefit consolidation and, accordingly, neural reactivation immediately after encoding is assumed to reflect SC (see below). Ambiguity about the duration of the proposed consolidation process has led to some degree of theoretical drift and vagueness that has been criticized by some¹³ but because SC theory is used to account for results from studies of both short and long delay periods, all of these results are relevant.

Hippocampal remote memory

If the hippocampus is only temporarily involved in episodic memory then it should be involved in retrieving recently encoded events, but should not be involved in remotely encoded events. However, contrary to the predictions of SC, it is now clear that the hippocampus is critically involved in remote episodic memory.

Graded retrograde amnesia.

Another cornerstone of SC is the observation that patients with hippocampal damage, such as the famous patient HM, exhibit graded retrograde amnesia (Fig2a): they cannot remember events that occurred during the years just before the lesion, but can retrieve memories from more remote time periods, such as childhood^{48–50}. This pattern is consistent with SC, but an examination of the existing literature indicates that graded retrograde amnesia is rare in patients with selective hippocampal lesions, and that, even when it is observed, it is quite variable. For example, more recent work with patient HM revealed that he was severely impaired at retrieving episodic details for both remote and recent time periods (i.e., flat retrograde amnesia), and that he showed relative sparing of semantic memory across those same periods⁵¹ (i.e., absent retrograde amnesia).

In addition, studies examining retrograde amnesia in patients with more selective hippocampal lesions also fail to find compelling evidence for the graded retrograde amnesia predicted by SC. For example, Figure 2c illustrates the published reports of retrograde amnesia as assessed on formal tests in patients with reported selective hippocampal lesions. The results indicate that on tests of semantic memory (i.e., tests for famous faces and public events), in most cases, retrograde memory is unaffected by hippocampal damage. Even in the few patients that appear to exhibit graded retrograde amnesia, the duration over which the gradient is observed is quite variable. For example, some patients exhibit retrograde impairments that extend to periods well over 15 years prior to the lesion⁵², whereas others exhibit deficits extending only 1 to 5 years⁵³. In tests of autobiographical memory, on the other hand, retrograde amnesia is more common, and it tends to lead to similar deficits in both recent and remote time periods, indicating that episodic memory is always dependent on the hippocampus.

Neuroimaging of remote and recent episodic memory.

Several neuroimaging studies have aimed to determine if the hippocampus is more involved in the retrieval of recent than remote memories, as predicted by SC. However, as illustrated in Figure 2d, the hippocampus is most often found to be equally involved in the retrieval of both recent and remote memories. One potential concern is that recent memories may be more vivid or stronger than remote memories and so might lead to greater activation, or conversely, remote memories may be weaker and thus they may lead to additional encoding into memory during the retrieval test, thus leading to greater retrieval-related activation. However, studies controlling for the vividness or strength of memory^{54–57} have reported hippocampal involvement during remote and recent memory retrieval.

Although there is little support for the assumption that the hippocampus becomes less involved as episodic memories become more remote, do cortical regions such as the medial prefrontal cortex (mPFC) become more involved as memories age? The evidence is mixed. For example, some human neuroimaging studies have shown greater frontal activity for older memories, whereas others have reported less or similar activity for remote memories (for reviews^{58,59}). This is consistent with studies showing that damage to the mPFC does not generally lead to remote memory impairments^{59,60}, but rather is associated with confabulation⁶¹, and decreases in self-related processing⁶². We note however, that rodent

studies have indicated that disruption of mPFC within a 1–2 hour period after learning can lead to memory impairments whereas disruption outside this window does not⁶³. The latter results suggest that the mPFC may play a role in cellular rather than systems consolidation.

Animal studies.

Studies of hippocampal lesions in rodents are consistent with those in the human literature in showing that tasks requiring the retrieval of detailed contextual memories, such as remembering the location of a hidden escape platform in a water maze, or finding a food-well location containing food, hippocampal damage leads to flat retrograde amnesia^{64–73}. Moreover, consistent with the lesion studies, activation studies in rodents that have used the water maze report similar or higher levels of hippocampal activation for remote compared to recent memories^{74–78}.

In contrast, in memory tasks requiring less precise contextual information the results are quite mixed, with some studies showing flat retrograde amnesia and others showing graded effects. For example, several studies of context fear conditioning – in which rodents exhibit freezing behaviors when placed in an enclosure that was previously paired with foot shocks – report that hippocampal lesions equally reduce freezing behavior for remote and for recently learned associations (i.e., flat retrograde amnesia)^{71,79–86}, whereas others report that recent memories are more disrupted than remote memories^{87–96}. Activation studies examining contextual fear conditioning are also quite mixed, with some reporting evidence for hippocampal involvement in remote memory and others failing to^{80,97–99}. However, similar to the effect of lesions, hippocampal activity appears to be correlated with memory precision rather than the age of the memory^{94,100}.

In sum, the results from lesion and activation studies of both humans and rodents indicate that the hippocampus plays a critical role in supporting both remote and recent episodic memory, which is consistent with the CB model and contradicts the predictions of the SC model. There are a few reported cases of graded retrograde impairments in humans rodents that require less contextually rich memory such as fear conditioning. These later results are consistent with SC but they can also be explained by CB. That is, because remote memories will have had more opportunity than recent memories to be remembered and re-encoded before the lesion, they can be supported by the neocortex.

Sleep

In one of the first systematic studies of sleep on memory, Jenkins and Dallenbach¹⁰¹ found that forgetting was slower if subjects were allowed to sleep immediately after learning than if they were required to remain awake (Figure 2e). It is possible that sleep slowed forgetting because memories were consolidated to the cortex during sleep. Another potential explanation, however, is that forgetting was slowed because subjects encoded less interfering information when they were asleep than when they remained awake. As described below, there are other aspects of sleep that are equally well explained by these two different accounts, but there are several findings that appear to preferentially support the CB.

Post-encoding slow wave sleep benefits episodic memory.

After an event has been encoded, it appears to be slow-wave sleep (SWS; i.e., periods of low-frequency oscillations containing brief periods of high-frequency activity that dominates early night sleep), rather than rapid eye movement sleep (REM; i.e., periods of wake-like neural activity that is associated with vivid dreaming that dominates late night sleep), which is the most beneficial for episodic memory¹⁰². Why SWS is more important for episodic memory than REM sleep is currently debated^{102–104}, but this finding is broadly consistent with both the SC and CB accounts. From the perspective of SC, SWS may be particularly important if slow wave activity in the cortex were to drive repeated reactivation of hippocampal representations (via fast-wave ripples) that might then entrain cortical regions^{102,105}. In contrast, from the perspective of CB theory, SWS may be particularly effective at reducing contextual interference because it is deeper than REM sleep in the sense that electrophysiological activity, heart rate and blood pressure observed during SWS are least like that observed during wake. In addition, SWS tends to occur earlier in sleep when interference effects are greatest (i.e., the period shortly after encoding).

The beneficial effects of post-encoding sleep are most pronounced on memory tasks that require subjects to remember associative compared to item information^{106–110} but see^{111,112}, and for recollection-based recognition responses more than familiarity-based responses^{107,108,110,113–116}. These results are consistent with CB in the sense that if sleep reduces contextual interference it should be memory for contextual information that is particularly sensitive to sleep, but how the SC approach would account for these results is not clear.

Reactivation.

There is a growing body of research showing that encoding-related activity can be observed during periods of post-encoding sleep^{102,117–119}, with such reactivation results consistent with both SC and CB. For example, hippocampal activity during SWS is increased after a navigation task, and correlates with subsequent memory¹¹⁹. These results are similar to rodent studies of ‘replay’ that have indicated that during offline states such as sleep, hippocampal place cells fire in a temporal sequence that correlates with the order of place fields recorded during earlier exploration^{120,121}. These reactivation effects were thought to be limited to sleep, thus reflecting off-line hippocampal replay of recent memories. Recent results, however, have indicated that sleep *per se* does not have a privileged role in this process in the sense that replay in rodents also occur in awake animals, reactivation effects in humans are observed during periods of quiet wakefulness, and when subjects are completing demanding math tasks^{102,122–125}. In addition, so far such reactivation effects have only been well established for a short period after learning (e.g., less than an hour after learning in rodents [Kudrimotri et al], and within a hour after learning in humans [refs]). Thus, reactivation is not limited to sleep or rest, but instead seems to occur regardless of sleep status for a short period of time after information has been encoded.

Such reactivation results could reflect the hippocampus replaying memories in order to transfer those memories to the cortex, or they could reflect neural activity arising from contextual binding. According to the CB model, during encoding, one would expect to see

the activity of the hippocampus and cortical regions supporting the information being bound to the study context. Importantly however, to the extent that learning increases the activation sensitivity of related synapses, encoding-related regions will show enhanced levels of spontaneous activity and co-activity for a short period after learning. Thus, one would expect to see a reflection of this “reverberative” activity (i.e., reactivation) after the study event. This should be particularly evident if the context remains unchanged. Moreover, because effective encoding should lead to greater residual activity and better subsequent retrieval, the residual post-encoding activation would be correlated with memory performance, as has been reported. Given that context is drifting, the variance captured by activity during the study event and the post-encoding event would not be expected to be identical. This idea is consistent with work indicating that learning temporarily increases the excitability of neurons and causes them to be activated during the formation of memories for other events that occur close in time, resulting in these events becoming linked because they involve some of the same neurons^{126–128}. These results are also consistent with the finding that neural activity related to a specific encoding context (i.e., words presented in the context of complex visual scenes) can linger for several minutes during the encoding of subsequent words, even when the context (i.e., visual scenes) is no longer present¹²⁹.

Interestingly, there have been studies that have suggested that reactivation is stronger for weakly encoded materials¹³⁰, a finding that is not predicted by the CB account. However, other studies have shown that reactivation effects are stronger for well encoded materials^{131,132}, so further empirical work in this area is warranted. Moreover, given the reactivation results observed so far have been limited to a short period after encoding, another interpretation of these results is that they reflect cellular consolidation rather than SC (see Box 2). Other studies have indicated that disrupting sharp-wave ripples in rodents impairs subsequent memory¹³³, indicating that ripples may play a critical role in post-encoding sleep; however, whether these results reflect a disruption of systems consolidation, a disruption of context-related residual activity, or a disruption of cellular consolidation is unknown. As far as we are aware, there are no studies indicating that naturally occurring post-encoding reactivation causes hippocampal episodic memories to be forgotten while simultaneously strengthening cortical traces.

Memory-cueing during sleep.

Another finding that can be explained by both SC and CB is the observation that cueing recently encoded memories during SWS enhances subsequent episodic memory^{134,135}. For example, if subjects learn a set of location-object associations in the presence of an odor, and then are allowed to sleep, subsequent memory is improved if the odor cue is re-presented during SWS^{136–139}. Although the conditions under which these cueing effects are observed are not yet well understood, they have been observed using olfactory and auditory retrieval cues, and they appear to be reduced if the cue is presented later in the night such as during REM sleep or if presented to awake subjects who are engaged in a demanding primary task^{140–142}. Whether retrieval cueing results in consolidation of episodic information from the hippocampus to the cortex, or whether it simply reflects the retrieval and re-encoding of the initial study episode is not yet known, and further work will be needed to further assess these two accounts (Box 1).

Beneficial effects of sleep on memory are rapid.

Although much of the sleep literature seems equally consistent with both the SC and CB approaches, other findings seem to favor the CB account. For example, an examination of Figure 2e indicates that the beneficial effects of sleep occur remarkably quickly. That is, even after only one hour, sleep effectively increased recall from 46% to 71%. If this sleep benefit reflects SC, this means that the hippocampus transferred a large proportion of memories from the hippocampus to the cortex that normally would have been forgotten during this time. This rapid induction of sleep benefits in episodic memory has now been well documented. For example, even 60 minute naps are found to produce sizable sleep benefits in episodic memory that are often similar to those observed after an entire night of sleep^{143,144}. Moreover, sleep has been found to slow forgetting if sleep occurs immediately after learning and has reduced or no impact on materials learned earlier in the day^{109,145,146}.

The fact that sleep benefits memory primarily when it occurs immediately after learning is explained by CB theory, which predicts that interference effects will be largest when the study materials and the interfering materials occur close in time. Although the results are often interpreted as being consistent with SC, they do present some puzzles for the approach. If the observed sleep benefits reflect consolidation it means that a large proportion of memories that would have been forgotten are transferred to the cortex within an hour, which is difficult to reconcile with results and theoretical proposals suggesting that SC is a slow process that takes years or decades^{8,9}. In addition, the results suggest that SC does not preserve memory for the events from across the day, but rather is limited primarily to storing events that happen immediately before falling asleep. Another possibility is that the sleep effects that have been reported in the literature reflect something other than SC, such as cellular consolidation, which would be expected to occur at this very short time scale.

Proactive effects of sleep.

If the beneficial effects of sleep are due to a reduction of contextual interference, then in the same way that interfering materials encoded before learning can interfere with memory (i.e., proactive interference), sleep should also benefit memory if it is inserted just prior to learning. Consistent with these expectations, memory for pictures is improved if subjects nap immediately before or after learning¹⁴⁷. In addition, the capacity to encode new episodic memories is reduced after sleep deprivation^{148,149}, and even mild sleep disruption, which decreases slow wave activity without reducing total sleep time, can reduce subsequent episodic encoding¹⁵⁰. Moreover, the ability to encode new episodic memories decreases gradually across the day, yet can be restored by a brief nap¹⁵¹. Although these proactive effects of sleep on memory are consistent with the CB model, they are not predicted by SC theory, which instead proposes that consolidation facilitates recently encoded events, rather than augmenting the encoding of future events.

Normal forgetting rates in amnesia.

If the hippocampus is critical for consolidating memories to the cortex during sleep, then patients with hippocampal damage should show accelerated forgetting across delays that include sleep^{152–154}. There is little evidence to support this prediction, however. For example, an early study in patient H.M. examined recognition memory at 10 minute, 1 day,

and 7 day retention intervals under conditions in which healthy controls were matched by increasing study duration at the 10 minute delay¹⁵⁵. Although the patient performed normally at the 10 minute delay, he seemed to perform worse than the controls at the later intervals, suggesting that he might exhibit accelerated forgetting. However, subsequent studies failed to replicate this effect, and instead showed that his forgetting rate was normal across a retention interval of 7 days in one study¹⁵⁶, and 6 months in another¹⁵⁷. Thus, even extensive MTL damage, as seen in HM, does not appear to lead to accelerated forgetting across delays that include periods of sleep.

Several subsequent studies with various groups of individuals with memory disorders have verified this pattern. For example, the amnesic patient NA, who suffered a diencephalic lesion, exhibited normal forgetting across a retention interval of 32 hours¹⁵⁸, similar to amnestics with Korsakoff syndrome^{155,158,159}. In addition, normal forgetting rates have been reported in a group of patients with extensive MTL lesions, as well as a group with diencephalic lesions¹⁶⁰. Thus, lesion results indicate that the hippocampus does not play a causal role in slowing episodic forgetting, at least across retention intervals varying from days to months. Thus, the pronounced beneficial effects of sleep that have been observed in healthy subjects after brief periods of sleep must then be explained in some other way, such as arising because of a reduction in contextual interference.

Conclusions

SC has been a useful scientific construct in accounting for results from across various different research domains. As we show above, however, SC fails to account for a growing body of findings from the same research paradigms that motivated its original development; that is, from studies of forgetting, lesion, and activation studies of remote memory, as well as studies of the effects of sleep on memory. Overall, such results provide support for a CB account of episodic memory consistent with memory theories that do not depend on systems consolidation.

Moving forward, one important aspect of episodic memory that current work discussed above highlights is that an episodic memory should not be treated limited to the period in which the study item or object is presented, but rather extending in time before and after the nominal study event (for additional predictions of the CB theory see box 1). Thus, manipulations that occur during the retention period need not impact a hypothetical consolidation process, but rather may affect the temporally extended encoding of the study event itself. Such considerations provide an account of the existing literature once thought to support the notion of consolidation, leading to a number of novel predictions that we hope will be useful in guiding future studies.

In sum, we propose that the construct of systems consolidation may have outlived its usefulness and should be replaced by theories that acknowledge the critical role of context in episodic memory and forgetting such as CB theory. Even if CB is found to be wanting, and alternative accounts are proposed, we hope that the ideas discussed here will lead researchers to consider a wider variety of theoretical explanations when they find that memory performance or brain activity changes during a retention interval.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1 |**Current results and future studies.**

<u>Forgetting</u>	<u>Systems Consolidation</u>	<u>Contextual Binding</u>
Retroactive interference	✓	✓
Proactive interference	✗	✓
Item similarity	✗	✓
Context reinstatement	✗	✓
Temporal contiguity	✗	✓
<u>Hippocampal remote memory</u>		
Flat retrograde amnesia	✗	✓
Graded retrograde amnesia	✓	✓
Hippo. involvement in remote memory	✗	✓
<u>Sleep</u>		
Post-encoding sleep benefits	✓	✓
Pre-encoding sleep benefits	✗	✓
Post-encoding reactivation	✓	✓
Memory cuing during sleep	✓	✓
Rapid sleep benefits	✓/?	✓
Normal forgetting rates in amnesia	✗	✓

a | Well established empirical results relevant in assessing the systems consolidation and contextual binding theories. A check mark indicates results that are accurately predicted by the theory, whereas an x indicates that the results either cannot be explained or they require additional post hoc assumptions.

b | Further tests of contextual binding theory:

What is the relationship between memory encoding activity and pre-encoding activity?

Whereas the consolidation construct leads one to examine brain activity that occurs after the study event has been encoded, CB suggests that neural activity that occurs prior to encoding will also play a critical role. To the extent that pre-encoding activity reflects processing of ongoing context that is shared with the subsequent encoding event, one should observe ‘memory pre-activation’ that is predictive of subsequent memory. Because time moves in a forward direction, post-encoding activity should be more similar to the encoding activity than pre-encoding activity, but it should be possible to observe pre-activation effects that parallel the reactivation effects.

What is the effect of changing context on pre- and post-encoding activity?

The CB approach suggests that studies examining the effects of changing context prior to and after encoding will be useful in understanding phenomenon once thought to involve consolidation. For example, to the extent that memory reactivation results reflect lingering context-related activity, those effects should be reduced under conditions in which the physical or mental context changes between the encoding and the post-encoding period. Evidence in support of this possibility comes from studies of post-encoding stress, which have indicated that stress-related increases in cortisol immediately after learning can slow forgetting, presumably by facilitating consolidation. Importantly,

recent work has indicated that these consolidation effects only occur when the stressor occurs in the same spatial context as the initial learning¹⁶¹. See also:

How does pre-encoding sleep impact encoding?

Although most prior memory studies of sleep have focused on post-encoding sleep, more work examining the effects of sleep immediately prior to encoding will be important. For example, given the importance of SWS in reducing retroactive interference, one would predict that pre-encoding SWS should also reduce proactive interference. Moreover, CB predicts that sleep effects should have larger effects on episodic tasks that have a heavy contextual component, as is seen in studies of post-encoding sleep, but whether this holds for pre-encoding sleep is not yet known.

Under what conditions does post-encoding memory-cuing improve memory?

CB suggest these effects should be most pronounced for contextual driven episodic memory tests. Moreover, these effects should not be limited to sleep, as some studies have suggested, rather cueing an earlier memory while the subject is awake should also lead to benefits in memory. Moreover, if post-encoding cueing enhances memory by leading subjects to re-encode the item, one would expect it to lead to an increase in hippocampal activation during the time of final retrieval, whereas a consolidation account presumably would not predict an increase in hippocampal involvement.

Are there conditions that consistently lead to graded retrograde amnesia?

In the limited number of cases in which hippocampal damage does lead to temporally graded retrograde amnesia, if those results are due to CB rather than SC, then context manipulations should be found to modulate those effects. For example, evidence for temporal gradients should be decreased if the stimuli are less likely to lead to re-encoding (e.g., less aversive or less appetitive learning in rodent studies) or under conditions in which the delay context is less likely to cue the initial encoding event and thus reduce the likelihood that the initial memory is incidentally retrieved.

Under what conditions does the neocortex exhibit rapid learning without the hippocampus?

Systems consolidation is sometimes thought to be necessary because the cortex can only learn very slowly, and it needs the hippocampus to gradually train it⁸. However, there are cases in which the cortex learns very quickly, such as in amnesic patients when random associations are treated as single units¹⁶², or in rodents when learning is related to well learned schemas¹⁶³. Now that we know that the cortex can support instantaneous learning, this opens up opportunities to try to reduce hippocampal based memory deficits, such as those seen in aging ().

Box 2 |**The role of the hippocampus in non-episodic forms of memory**

As presented in the main text, we contend that episodic memories are not consolidated from the hippocampus to the cortex, as is suggested by systems consolidation theory. However, does the hippocampus play a time-dependent role in shaping non-episodic memory forms of memory, such as semantic memory, implicit memory and skill learning? We believe that future studies will be necessary in order to adequately answer this question.

One possibility that is consistent with the CB theory is that subjects might remember, or be reminded of, an earlier event, and this could lead to a new encoding event that would be expected to impact both the hippocampus and the neocortex. In this way, neocortical representations that support semantic memory could be influenced by hippocampal representations over multiple reminders. Such reminders certainly occur and can explain why amnesic patients are sometimes able to recall salient childhood memories^{11,164}, and why rodents sometimes show preserved context fear conditioning for remote learning^{87–96}. However, the extent to which this occurs is unclear, as many patients show severe deficits for remote memory and many studies of animal context fear conditioning do not show preserved remote memory. Thus, the factors that determine when semantic memory might benefit from hippocampal training is not yet clear.

Additional studies examining the role of the hippocampus in implicit memory and skill learning will also be important. For example, implicit memory and skill learning are well preserved in patients with medial temporal lobe damage¹⁶⁵, and there little indication that this damage leads to faster forgetting in these tasks, even across delays that include many nights of sleep, as one would expect if the hippocampus gradually trained these non-episodic forms of memory. For example, amnesic patients exhibit normal rates of forgetting on perceptual implicit memory tasks including picture naming priming, across 7 day retention intervals¹⁶⁶; conceptual implicit memory, such as sentence puzzle tasks, across 7 days¹⁶⁷; rotor pursuit learning, across 2 years¹⁶⁸; and mirror reading, across 3 months¹⁶⁹. Thus, these forms of memory do not seem to benefit from a hippocampally dependent retention or transformation process, at least over the delay periods examined so far. Nevertheless, there are a number of reports of ‘incubation effects’ where performance on non-episodic memory tasks can significantly improve over time, such as sleep-related benefits in transitive inference^{170,171}, probabilistic learning^{172,173}, remote associates^{174,175}, and mathematical insight problems¹⁷¹. In addition, there is evidence that sleep can lead to enhancements in motor learning^{102,176}, although whether these enhancements reflect some form of consolidation is controversial¹⁷⁷. In either case, studies designed to determine if the hippocampus plays a causal role in producing these memory benefits will be important.

Box 3 |**How is contextual binding related to cellular consolidation and synaptic downregulation?**

According to the CB account of episodic memory, contextual interference continues to act on memory after the nominal learning event is over. How does contextual interference relate to other post-encoding processes that affect memory? For example, cellular consolidation, which involves a cascade of molecular processes that occur in the hours shortly after learning³ could be involved in transforming memory during retention. How these processes are related to contextual binding is not yet known, and so the current proposal gives rise to new questions that will need to be empirically addressed. For example, does cellular consolidation differentially impact forms of hippocampally based contextual memory such as recollection, compared to other forms of memory such as familiarity and semantic memory¹⁷⁸? Conversely, to what extent does contextual binding impact cellular consolidation? Given the importance of context in producing interference effects in episodic memory, cellular consolidation process might be disrupted by changes in spatial and mental context.

In addition, synaptic activity is known to be downregulated during periods of rest and sleep, to counteract the increased levels of activity induced by prolonged periods of active wake¹⁰⁴. How CB might be related to synaptic downregulation not yet known. Although the processes underlying synaptic downregulation are thought to be observed across the cortex, do the regions that support episodic memory play any special role in governing which synapses — and thus, which memories — benefit from downregulation? For example, downregulation is thought to suppress weakly represented information while preferentially preserving information that is strongly represented in memory either because it is consistent with preexisting representations or is strongly encoded. One possibility that has yet to be explored is whether items that are well integrated with the ongoing experimental context may be preferentially protected from the effects of downregulation.

CB borrows from several earlier theoretical approaches^{12–15,18,25,181}, but shares a number of core assumptions with ‘multiple-trace/transformation’ theory^{13,16} in the sense that the hippocampus is assumed to be necessary for the storage and retrieval of detail-rich episodic memories, whereas the neocortex supports the acquisition of less contextually-detailed information such as semantic knowledge. Moreover, according to both of these approaches, the retrieval of a memory is expected to lead to the re-encoding that would impact both the hippocampus and the neocortex. If this occurs frequently enough, it would lead to a strong neocortical semantic representations that could support decontextualized memory for remote events. Thus, the two approaches predict that the hippocampus will be necessary for retrieving recent and remote contextually rich memories, whereas the neocortex can support decontextualized memories, and may be particularly effective for repeatedly remembered remote memories. However, CB goes further by specifying the critical role of context in accounting for episodic memory and forgetting, and so it gives rise to additional predictions about manipulations such as interference and sleep, areas that multiple-trace/transformation theory does not make any

specific predictions about. Given that the interference and sleep literatures have been interpreted as providing support for SC, this is a significant shortcoming of the multiple trace approach that we believe the CB approach overcomes. By focusing on the critical role of context in episodic memory, the CB approach builds on other theoretical work that highlight the role that context plays in both facilitating memory and producing forgetting^{17,23,24,152}, and as described in the main text, it converges with recent empirical work showing how the medial temporal lobe supports memory for spatiotemporal context.

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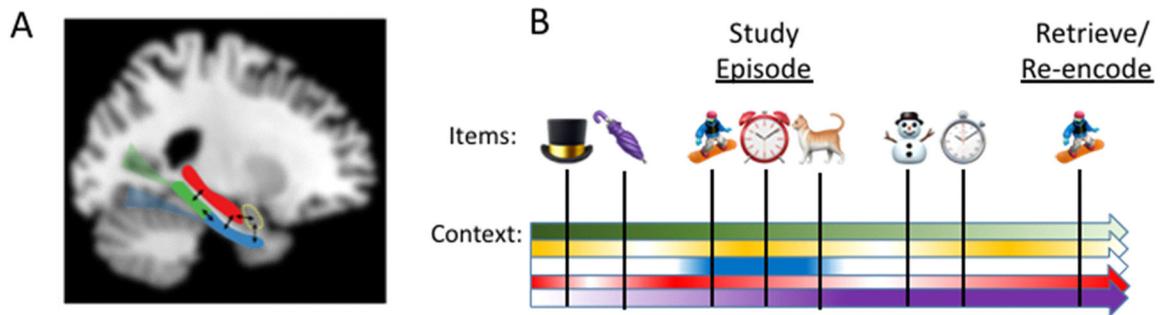


Fig. 1 | Contextual binding theory.

a | Contextual binding theory assumes that the hippocampus (red) is necessary for episodic memory because it binds together the item and context information that makes up the study event. The hippocampus receives information from various regions including the perirhinal cortex and the ventral ‘what’ stream, and is thought to provide information about the items in an event (e.g., objects and people), the amygdala (dotted yellow) which provides information about the emotional aspects of the event, and the parahippocampal cortex (green) which receives spatial information from the dorsal ‘where’ stream. The regions outside the hippocampus are assumed to support the learning of simple associations, and so can learn about regularities and occurrences in the environment, whereas the hippocampus is unique in supporting memory for individual episodes, and so is said to support complex or high-resolution bindings¹⁷⁹, in the sense that it links together the multiple objects and detailed contextual information that makes up an event. This approach is consistent with neurocomputational models that propose that the hippocampus supports memory via a process of pattern separation and completion^{8,17,180}. **b |** According to the CB model, context can reflect any aspect of the study episode that links the test item to the specific study event, such as the spatial, temporal or cognitive details of that event. Some aspects of context can change quickly like moving to a new room or initiating a new cognitive task (e.g., the blue arrow), whereas other aspects of context can change gradually like changes in the subject’s mood or changes in lighting throughout the day. Because context gradually drifts, the study event will extend in time beyond the occurrence of the study items themselves. In this way, forgetting is assumed to be due to interference from other memories that share similar content or context. That is, because episodic memory requires subjects to recollect which items (i.e., snowboarder, clock, cat) occurred in a specific experimental context (i.e., the related portion of the context arrows), other episodic memories that share a similar context to the studied items (i.e., umbrella and snowman) or that have similar content (i.e., stopwatch) will interfere with memory retrieval because they are confusable and effectively compete with each other. Importantly, because forgetting is the result of contextual interference, forgetting will be produced not only by events that occur after the study event, but also by events that occur prior to the study event (i.e., top-hat and umbrella). In addition, manipulations that reduce the encoding of interfering materials, such as allowing subjects to rest or sleep, are expected to benefit memory by reducing contextual interference. Moreover, if an item is repeated (e.g., the item may be re-studied or the initial event may be remembered) it will be re-encoded along with new context information. Finally, neural activity that is related to the encoding of the study event will be temporally extended because of the gradually changing context, such that encoding related activity will linger

after the nominal study event is over (i.e., re-activation), and in fact, may even be observed prior to the onset of the study event (i.e., pre-activation).

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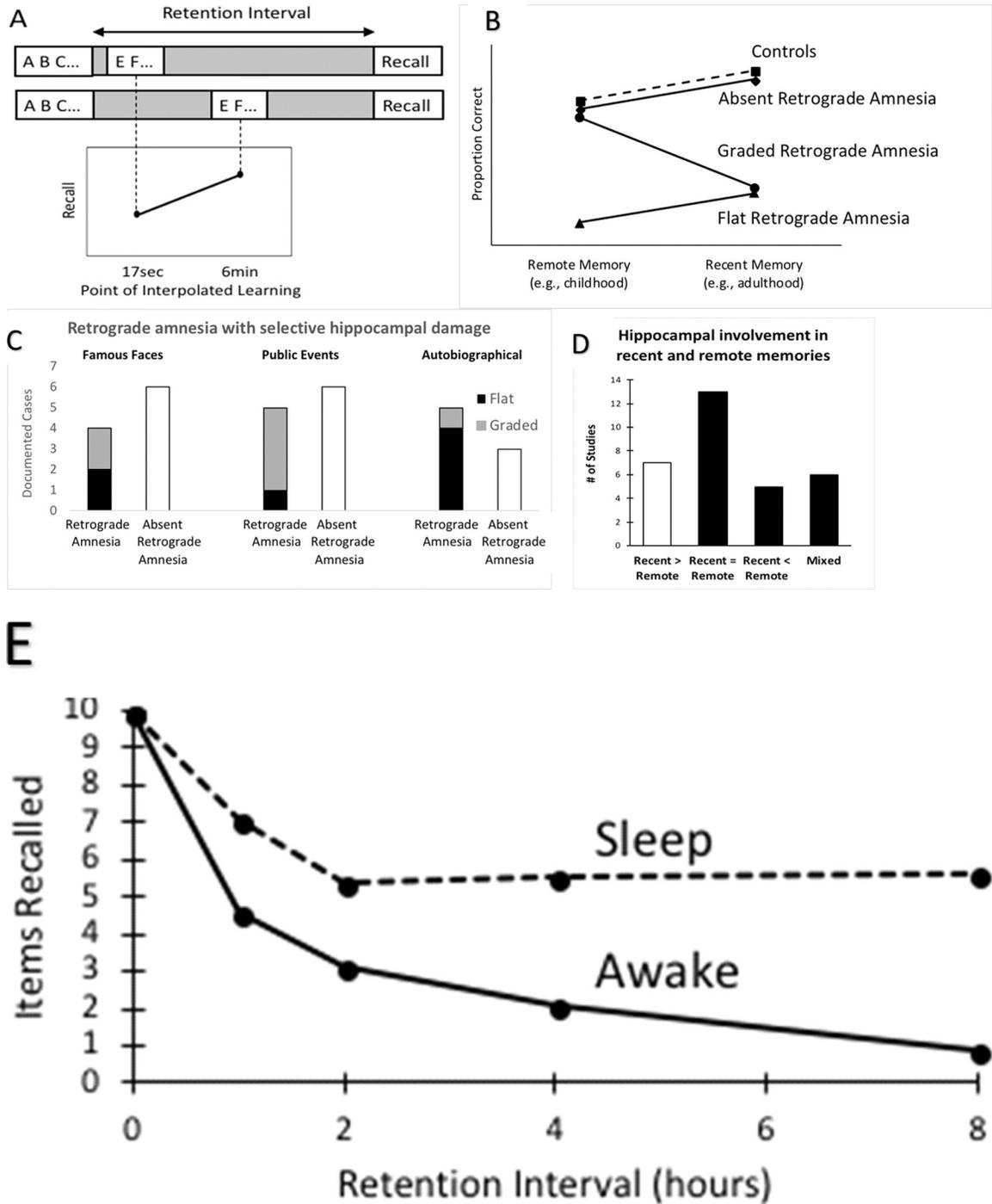


Fig. 2 | Results that have historically been taken as evidence in support of systems consolidation theory.

a | Graded retroactive interference. Forgetting of an event is greater when subsequent interfering information is encountered shortly after encoding. Müller and Pilzecker² presented subjects with nonsense syllables (represented here by letters) and tested cued recall after a 1.5 hour retention interval. Importantly, they found that if subjects were presented with additional nonsense syllables to learn shortly after the initial encoding phase

(top row; left on graph), subjects recalled fewer of the initial items than if the additional nonsense syllables were presented later in the retention interval (bottom row; right on graph). The finding can be explained if the interpolated task disrupts consolidation, or if it produces more contextual interference. **b** | Retrograde amnesia. Amnesic patients may be, impaired at retrieving memory from recent but not remote periods (i.e., graded retrograde amnesia) - a pattern consistent with SC - but they may also be impaired at retrieving memories for both remote and recent events (i.e., flat retrograde amnesia) or they may be unimpaired for both time periods (i.e., absent retrograde amnesia). **c** | Reports of graded retrograde amnesia in patients with selective hippocampal damage are rare. A number of patients with selective hippocampal damage have been assessed on standard tests of retrograde amnesia^{52,164,182–187}. In the famous faces test, only 2 patients (i.e., patients LM and WH⁵²) out of 10 revealed evidence of graded retrograde amnesia. Similarly, in tests of memory for public events, only 4 patients (i.e. GD, LM & WH⁵², and patient YK¹⁶⁴) out of 11 showed evidence of a temporal gradient. On the autobiographical memory interview (AMI), only one patient out of 8 (i.e., YK^{11,164}) exhibited a greater impairment for recent than remote periods. Interestingly, the authors of the lattermost study indicated that YK's memory reports were entirely lacking in episodic details, suggesting impairments in both remote and recent autobiographical memory. Four additional patients with selective hippocampal damage were assessed on the AMI¹⁸², and were unimpaired at the remote period, but the recent period results were not reported, so they are not included in this figure. Nevertheless, in a subsequent reanalysis, those patients were included with additional patients that could not be scanned and as a group they exhibited only a mild memory impairment for recent items that was limited to autobiographical memory questions and not the personal semantic memory items of the AMI⁵³. **d** | Retrieval related hippocampal activity for remote and recent memories. Human neuroimaging studies suggest that the hippocampus is involved in retrieving both recent and remote memories. That is, the most common finding is that the hippocampus is similarly involved during the retrieval of both remote and recent memories^{54–57,188–196}. A few studies reported either greater^{197–203} or less^{204–208} hippocampal activity for recent than for remote memories, whereas others reported mixed results^{209–215} such as²¹⁴ the left hippocampus being equally involved in remote and recent memories whereas the right hippocampus was more active for recent than remote memory (the figure was based on an informal review by searching Pubmed using the search string “(remote) AND (memory) AND (hippocampus)”, as well as well as examining citations and references. These studies are characterized in more detail in supplementary Table 1). **e** | The effects of sleep on forgetting in episodic memory (based on Table 3 from Jenkins and Dallenbach, 1924¹⁰¹). Subjects learned a sequence of nonsense syllables and were then tested for recall after delays varying in length from 1 to 8 hours that were filled either with sleep or wake. Compared to the awake condition, subjects who slept exhibited significantly slower forgetting rates. The finding can be explained if sleep facilitates consolidation or if it reduces the encoding of interfering information.