OPINION

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 rapid forgetting unless consolidated during offline periods such as sleep to neocortical areas for long-term storage. Here, we propose an alternative to this standard systems consolidation theory (SSCT) — a contextual binding account — in which the hippocampus binds item-related and context-related information. We compare these accounts in light of behavioural, lesion, neuroimaging and sleep studies of episodic memory and contend that forgetting is largely due to contextual interference, 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. More than 100 years ago, memory consolidation was proposed as a way of partially answering this question[1,2]. According to the consolidation account, 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 has been shown to be essential for memory retention and refers to the cascade of molecular processes that occur immediately after learning that stabilize the synaptic and cellular changes produced by learning[3,5]. By contrast, standard systems consolidation theory (SSCT) posits that memories for events or episodes are only temporarily dependent on the hippocampus and will be forgotten unless they go through a consolidation process in which they gradually become fully represented in the neocortex such that they are no longer dependent on the hippocampus[4,6–10]. SSC is assumed to occur during offline periods such as sleep, during which the hippocampus 'replays' previously encoded events to the neocortex; this training of the cortex is posited to lead to the gradual strengthening of cortical associations without strengthening hippocampal associations.

SSCT has been widely accepted in the cognitive neuroscience literature and has garnered support from various areas of research, including behavioural studies of forgetting, lesion and neuroimaging studies and studies of sleep[6–9,11] (but also see REFS[12–14]). Here, we describe an alternative approach that we refer to as 'contextual binding' (CB) theory (BOX 1), which assumes that episodic memory is not consolidated to the cortex and that, instead, gradual changes in context lead to forgetting and temporally extend encoding activity. This account is then assessed in light of the research that has been used as evidence for SSCT. As we describe below, although some findings may be equally well explained by both accounts, a growing body of well-established research findings directly challenge the assumptions of SSCT and provide support for CB (BOX 2). We argue that a CB account of episodic memory and the medial temporal lobe (MTL) provides a more useful way of understanding when forgetting will occur and how memory is gradually altered over time.

The contextual binding model

The assumptions and predictions of the CB model are described in BOX 1. The CB approach assumes that episodic memory is dependent on the hippocampus and reflects the ability to retrieve the context in which items or objects were previously encountered. The term 'context' refers to any aspect of the study episode — including spatial, temporal or other details — that links the test item to the specific study event. For example, participants may encounter several objects in an experimental context and are later required either to retrieve the objects that occurred in that study context (that is, a recall task) or to indicate whether an object was or was not encoded in that context (that is, a recognition memory task). Similarly, to obtain a reward, a rodent might be required to navigate to a previously learned spatial location (for example, as in the Morris water maze task) or to discriminate between objects that were and objects that were not recently studied in a specific environment (termed a delayed non-match-to-sample task).

According to the CB account, the hippocampus binds together item and context information that it receives from other regions, including the neocortex, and therefore is crucial for the recollection of previous episodes. By contrast, the CB account posits that the neocortex is less effective in learning detailed contextual information and instead supports familiarity (that is, discriminating between recently presented and novel items) and semantic memory (the acquisition of knowledge about the world). Evidence that the hippocampus is crucial for recall and recognition and that the cortex supports less-context-associated forms of memory is well documented in humans and rodents[15–19]. Importantly, studies have shown that any given context will gradually change as the physical and mental state of the participant or animal changes[20–23]. Consistent with this, the CB account posits that the episodic memory for an event is not limited to the time period in

which the study item or object is presented but rather extends to include the time before and after the item is presented.

The CB model makes a number of predictions about forgetting and the function of the MTL (BOX 1). For example, it predicts that items that occur immediately before or after the study event will share a similar context and thus can interfere with recollection of the study event. Conversely, conditions such as sleep that reduce the encoding of new (interfering) memories can benefit subsequent recollection of a study item by reducing contextual interference. Moreover, being in a stable context during encoding should enhance the likelihood of remembering temporally contiguous items in an event, and context re-instatement should improve memory retrieval. In addition, because context gradually drifts, encoding-related brain activity should be observed before the study event is initiated and for some time after the nominal encoding event is over.

CB differs from SSC in that CB assumes that the hippocampus has a necessary — and not just temporary — role in episodic memory. Moreover, according to the CB account, the hippocampus and neocortex largely support different types of memory (specifically, recollection and familiarity or semantic memory, respectively) rather than the same types of memory at different times. In addition, the CB account assumes that forgetting reflects interference from events before or after the study event, rather than the failure of systems consolidation after an event is encoded. Finally, according to the CB account, memory-related activity should be observed shortly before and after the study event.

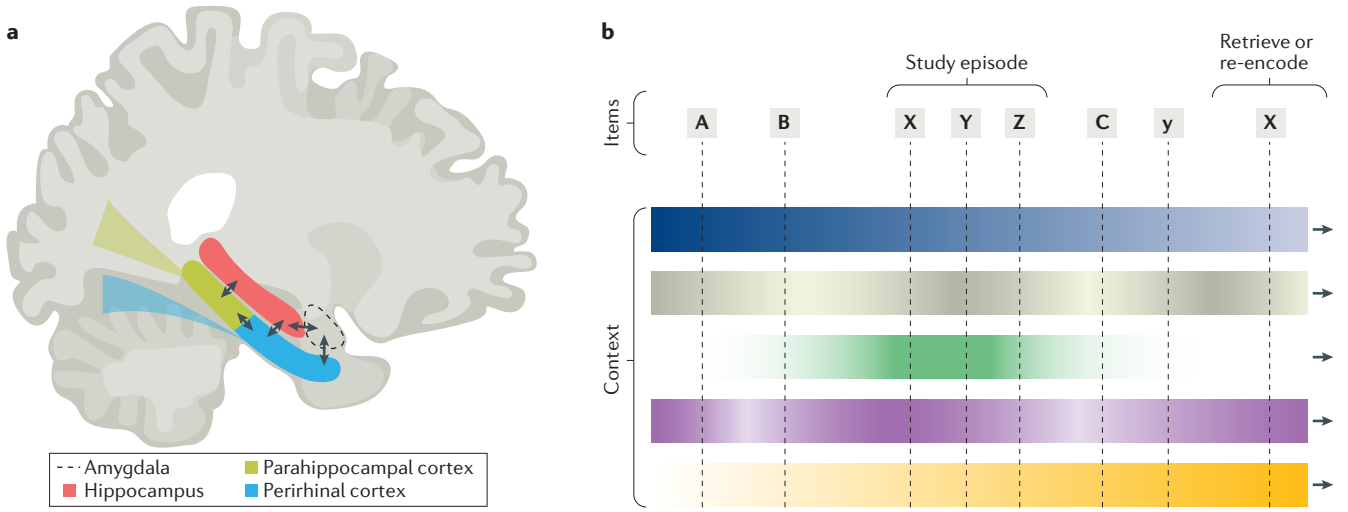
The CB account borrows from several earlier theoretical approaches focused on the role of context in episodic memory[12–15,19,22,24]. For example, it shares several core assumptions with 'multiple-trace/transformation' theory (MTT)[13,17,25], which is a theory of remote memory and amnesia. For example, both MTT and the CB account assume that the hippocampus is 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.

Box 1 | **Contextual binding theory**

Contextual binding theory assumes that the hippocampus (red in part **a** of the figure) is necessary for episodic memory because it binds together the item information and context information that make up the study event. The hippocampus receives information from various regions, including the perirhinal cortex (blue), which receives information about the items in an event from the ventral 'what' stream (faded blue); the amygdala (dashed outline), which provides information about the emotional aspects of the event; and the parahippocampal cortex (green), which receives spatial information from the dorsal 'where' stream (faded green). 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 bindings[175]. This notion is consistent with neurocomputational models that propose that the hippocampus supports memory via a process of pattern separation and completion[8,18,176].

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, environmental or cognitive details of that event (see part **b** of the figure). Some aspects of context can change quickly (for example, the participant may move to a new room or start a new cognitive task), as represented by the green context bar. By contrast, other aspects of context can change gradually — for example, the participant's mood or changes in lighting throughout the day.

Because context gradually changes over time (or 'drifts'), the study event will extend in time beyond the occurrence of the study items themselves. Thus, forgetting can be due to interference from other memories that share similar content or context. In an episodic memory task, participants must remember which items (X, Y and Z) occurred in a specific experimental context (that is, the corresponding portions of the context bars); other episodic memories that share a similar context (B and C) or similar content (y) with the studied items will interfere with memory retrieval because they are confusable and effectively compete with the studied items. Importantly, forgetting will be produced not only by events that occur after the study event but also by events that occur before the study event (for example, A and B). In addition, manipulations that reduce the encoding of interfering materials, such as allowing participants to rest or sleep, would benefit memory by reducing contextual interference. Moreover, if an item is repeated (re-studied or remembered), it will be re-encoded along with new context information. Finally, encoding-related neural activity will be temporally extended because of the gradually changing context, such that it will linger or be potentiated for some period after the nominal study event is over (termed reactivation), and may even be observed before the study event (termed pre-activation). We note that such temporal context effects should be largest in the forward direction, as the context of the post-encoding materials will presumably include information from the prior study event[41]. Part **a** is adapted with permission from REF.[177], Elsevier. Part **b** is adapted with permission from REF.[178], Elsevier.



Box 2 | **Established findings and future directions**

Well-established empirical results relevant in assessing the standard systems consolidation (SSC) and contextual binding (CB) theories are listed in the table. 'Yes' indicates results that are accurately predicted by the theory, whereas 'no' indicates that the results either cannot be explained or require additional post hoc assumptions. Outstanding areas to be addressed by future research are outlined below.

Future directions

The consolidation notion leads one to focus on the period after items have been encoded into memory, whereas the CB approach highlights the importance of the periods before and after encoding and so generates several new predictions. For example, if context is gradually shifting, one should observe encoding-related activity both after the items are encoded, in the form of 'reactivation', as well as before encoding, in the form of 'pre-activation'. In addition to testing this hypothesis, future studies should examine the effects of changing context before and after encoding. For example, if memory reactivation reflects lingering context-related activity, reactivation should be reduced by changes in physical or mental context between encoding and the post-encoding period. In indirect support of this possibility, stressor-induced increases in cortisol immediately after learning can slow forgetting, but only if the stressor occurs in the same spatial context as learning[179] (see also REF.[180]). In addition, more work examining the effects of sleep immediately before encoding will be important. For example, pre-encoding SWS should reduce proactive interference, particularly in episodic memory tasks with a heavy contextual component. The CB account also suggests that the memory-cueing effects observed during sleep should not be limited to sleep; rather, cueing during wake should also benefit memory. Moreover, if post-encoding cueing enhances memory through re-encoding, it should be associated with a relative increase in hippocampal activation during final retrieval. By contrast, an SSC account would presumably not predict an increase in hippocampal activity.

The CB approach also raises additional research questions in the study of memory disorders. For example, hippocampal damage has been reported to lead to temporally graded retrograde amnesia in a few cases, such as with salient childhood memories and in some rodent studies of context fear conditioning. If the temporal gradient observed there is due to reminding and re-encoding, as suggested by CB, the temporal gradient should decrease if the memory events are less likely to be re-encoded (for example, if the study items are made less salient or less aversive) and if the context that is experienced during the delay period is made very different from the initial encoding event and thus less likely to promote retrieval of the initial memory. Finally, systems consolidation is sometimes considered necessary because it is thought that the cortex can learn only very slowly and needs the hippocampus to gradually train it[8]. However, amnesic patients can rapidly learn random associations between stimuli when the associations are encoded as single units[181] or using fast-mapping techniques[182,183], and rodents with hippocampal damage can rapidly learn new associations if they are related to well-learned schemas[184]. The occurrence of rapid cortical learning without hippocampal training opens up the exciting possibility that hippocampus-based memory deficits, such as those seen in ageing, might be reduced under appropriate encoding conditions[185].

Findings	Explained or predicted by SSC account?	Explained or predicted by CB account?
Forgetting-related findings		
Retroactive interference	Yes	Yes
Proactive interference	No	Yes
Item similarity	No	Yes
Context re-instatement	No	Yes
Temporal contiguity	No	Yes
Remote memory-related findings		
Flat retrograde amnesia	No	Yes
Graded retrograde amnesia	Yes	Yes
Hippocampal involvement in remote memory	No	Yes
Sleep-related findings		
Post-encoding sleep benefits	Yes	Yes
Pre-encoding sleep benefits	No	Yes
Post-encoding reactivation	Yes	Yes
Memory cueing during sleep	Yes	Yes
Rapid sleep benefits	Possibly	Yes
Normal forgetting rates in amnesia	No	Yes

Moreover, both approaches predict that memory retrieval leads to re-encoding that affects the hippocampus and the neocortex; if this occurs frequently enough, it would lead to the formation of strong neocortical semantic representations that could support decontextualized memory for remote events. The potential role of the hippocampus in supporting semantic memory is considered in more detail in BOX 3. Thus, MTT and the CB account predict that the hippocampus is 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 builds on MTT by specifying the critical role of context in accounting for episodic memory and forgetting, giving rise to additional predictions about manipulations such as interference and sleep — aspects about which MTT does not make any specific predictions. Given that the interference and sleep literatures have been interpreted as providing support for SSC, this is an important shortcoming of the MTT that we believe the CB approach overcomes. By focusing on the crucial role of context in episodic memory, the CB approach builds on other theoretical work, such as the temporal context model[25], that highlights the role of context in facilitating memory and producing forgetting[17,23,24] and therefore, as described in the main text, the CB approach converges with recent empirical work showing how the MTL supports memory for spatiotemporal context.

Forgetting

Both the CB and SSC theories provide explanations for how memories can be forgotten, but CB provides a more general account of forgetting and accounts for several observed forgetting effects that SSCT cannot explain without making additional assumptions.

Graded retroactive interference. One of the initial motivations for consolidation theory was the finding by Müller and Pilzecker[2] that forgetting in tests of human recall is greatest when interfering information occurs shortly after encoding rather than later in the retention interval[2,26–28] (FIG. 1a). This graded retroactive interference was interpreted as evidence that memories are actively consolidated after encoding and that this consolidation is disrupted if interfering information is encountered before consolidation is complete. Moreover, some argued that the results do not support an

Box 3 | **The role of the hippocampus in non-episodic forms of memory**

We contend that episodic memories are not consolidated from the hippocampus to the cortex, as suggested by standard systems consolidation theory (SSCT). However, we believe that future studies will be necessary in order to adequately address the question of whether the hippocampus has a time-dependent role in shaping or training non-episodic forms of memory. For example, as described in the main text, one possibility that is consistent with the CB theory is that recalling or being reminded of an earlier encoded episode could lead to the formation of a new encoding event that would be re-encoded by the hippocampus and the neocortex. In this way, neocortical representations that support semantic memory could be influenced by hippocampal representations over multiple remindings. Such remindings certainly occur and could explain why amnesic patients can sometimes recall salient childhood memories[11,186]. However, as described in the main text, the extent to which such remindings occur is unclear, as many patients show severe deficits for remote memory and many animal studies of contextual fear conditioning do not find preserved remote memory. Thus, the factors that determine when and to what extent semantic memory might benefit from hippocampal training are not yet clear.

Additional studies examining the role of the hippocampus in long-term implicit memory (that is, when repeated materials are identified or processed more effectively) will also be important. The existing literature indicates that implicit memory is well preserved in patients with medial temporal lobe damage[187], and there is little indication that such damage leads to faster forgetting in these tasks, even across delays that include many nights of sleep, indicating that the hippocampus does not play a causal role in gradually training these non-episodic forms of memory. For example, amnesic patients exhibit normal rates of forgetting on perceptual implicit memory tasks, such as picture-naming priming, across 7-day retention intervals[188]; conceptual implicit memory tasks, such as sentence puzzle tasks, across 7 days[189]; rotor pursuit learning, across 2 years[190]; and mirror reading, across 3 months[191]. Thus, these forms of implicit memory do not seem to benefit from a hippocampus-dependent retention or transformation process, at least over the delay periods examined thus far. Nevertheless, there are a number of reports of 'incubation effects' in which performance on non-episodic memory tasks can markedly improve over a delay, such as sleep-related benefits in solving mathematical insight problems[192] and motor learning[110,193]. Although these enhancements are controversial[194], further studies will be needed to determine if the hippocampus has a causal role in producing these memory benefits.

interference account, which would predict that interfering materials should have a similar effect on memory whether they occur early or late in the retention interval.

However, these graded retroactive interference results are predicted quite naturally by CB without making assumptions about consolidation[12,21,23,24]. That is, when items are presented immediately after the initial encoding event, they interfere to a greater extent than do items presented later in the retention period, because the initially encoded items and the immediately presented interfering items have greater contextual overlap. Moreover, contextual interference should occur even if the intervening items are not highly similar to the study materials — an observation reported by Müller and Pilzecker[2]. We speculate that the reason these graded retroactive interference results are often thought to challenge interference explanations of forgetting is that earlier theories of interference focused exclusively on interference from similar items and attributed little or no importance to context in episodic memory.

Related forgetting effects. CB, and interference theories in general, also naturally explain a number of other well-established forgetting effects observed in the human memory literature that SSC cannot account for without making additional assumptions. For example, forgetting is also produced when interfering information is presented just before the study event — a well-established experimental phenomenon referred to as proactive interference[29–31]. CB predicts both retroactive and proactive interference effects, whereas SSC predicts only 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[32,33]. This increased forgetting due to similarity is predicted by interference theories — as forgetting is expected to arise owing to interference from similar events — but this is not predicted by SSCT.

CB theory can also explain why context can sometimes benefit memory. For example, consistent with the observation that retroactive interference effects[2] depend on the context in which the interfering information occurs, forgetting effects are greatly reduced if the interfering and study materials are learned in different spatial contexts[34–36]. In addition, in 'context re-instatement' studies, memory performance is generally increased if the test context matches that of the study context[37,38], and memories for items that have been forgotten can often be rescued by re-instating the physical or mental context of the original study phase[39,40]. These types of result are predicted by models that assume that episodic memory involves the binding of item and context information, but they are not predicted by SSCT. In addition, studies of 'temporal contiguity' have shown that participants tend to successively recall and are more likely to recognize items that were presented in nearby positions in a studied list[41,42], with such contiguity effects spanning many other intervening memories[43]. In addition, other studies of contiguity effects have indicated that context-related neural signals in the MTL change gradually during the presentation of a study list and then are re-instated when an item is remembered during testing[44–48]. These results provide direct support for CB. Context models have also been found to explain various other forgetting effects that are not easily explained as reflecting SSC, such as studies showing that changes in ongoing context that are induced by event boundaries are critical in accounting for forgetting[49], and studies of reconsolidation in which episodic memory for previously studied lists can be updated to include new information, when participants are reminded of the earlier list just before learning new materials[50,51].

One might argue that SSC should not be expected to account for these forgetting effects because these studies examine delays of minutes to days and therefore may not be relevant if SSC takes years or decades to occur, as some have suggested[8,52,53]. However, others have assumed that SSC occurs very rapidly[7,11,54] and can occur during a nap lasting 60 minutes and/or be observed in neural activity signals immediately after encoding (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 some[13], but because SSCT is used to account for results from studies of both short and long delay periods, all of these results should be considered to be relevant.

Remote versus recent memories

If, as SSCT suggests, the hippocampus is only temporarily involved in episodic memory, it should be involved in retrieving recently encoded events but not remotely encoded events (that is, events encoded further back in time). However, contrary to the

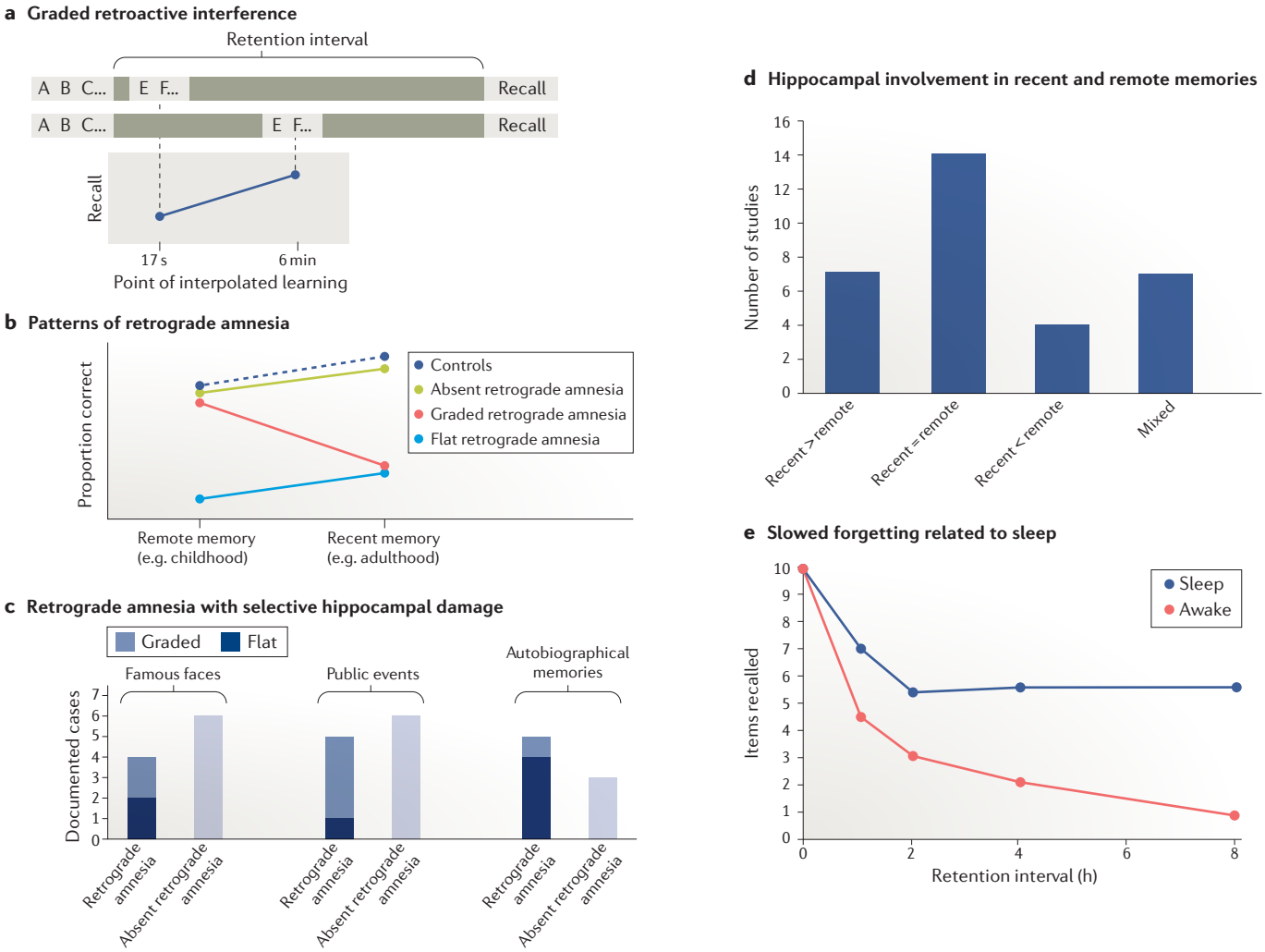


Fig. 1 | **Results that have historically been taken as evidence in support of systems consolidation theory. a** | Graded retroactive interference. Forgetting of an event is greater when subsequent interfering information is encountered shortly after encoding. Müller and Pilzecker[2] presented participants with nonsense syllables (represented here by letters) and tested cued recall after a 1.5-hour retention interval. Importantly, they found that if participants were presented with additional nonsense syllables to learn shortly after the initial encoding phase (top row; left on graph), participants 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 as a disruption of consolidation by the interpolated task, or as an increase in contextual interference. **b** | Retrograde amnesia. Amnesic patients may be impaired at retrieving memory from recent but not remote periods (that is, they may show graded retrograde amnesia) — a pattern consistent with standard systems consolidation (SSC) — but they may also be impaired at retrieving memories of remote and recent events (that is, flat retrograde amnesia) or unimpaired at retrieving memories from either time period (that is, absent retrograde amnesia). **c** | Reports of graded retrograde amnesia in patients with selective hippocampal damage are rare. The graph presents data from patients with selective hippocampal damage who were assessed on standard tests of retrograde amnesia[59,186,197–202]. In the famous faces test, only two patients out of ten (namely, patients L.M. and W.H.[59]) revealed evidence of graded retrograde amnesia. Similarly, in tests of memory for public events, four patients out of eleven (namely, patients G.D., L.M. and W.H.[59] and patient Y.K.[186]) showed evidence of a temporal gradient. On the autobiographical memory interview (AMI), only one patient out of eight (Y.K.[11,186]) exhibited a greater impairment for recent than remote periods. Interestingly, the authors of the lattermost study indicated that Y.K.'s memory reports were entirely lacking in episodic details, suggesting impairments in both remote and recent episodic memory. Four additional patients with selective hippocampal damage were impaired on the AMI[197] compared with controls, but their recall of recent memories was not reported; therefore, they are not included in this figure. Nevertheless, in a subsequent reanalysis, those patients were included with additional patients who 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 AMI[60]. **d** | Retrieval-related hippocampal activity for remote and recent memories. The graph is based on an informal review of publications identified by searching PubMed.gov using the search string "(remote) AND (memory) AND (hippocampus)", and those studies are listed in Supplementary Table 1. Overall, 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[61–64,203–212]. A few studies reported either greater[213–219] or less[213,220–223] hippocampal activation for recent than for remote memories, whereas others reported mixed results[224–230], such as REF.[225], which showed equal involvement of the left hippocampus in remote and recent memories but more activity in the right hippocampus for recent than remote memories. **e** | The effects of sleep on forgetting in episodic memory. Participants learned a sequence of nonsense syllables and, after delays varying from 1 to 8 hours that were filled either with sleep or wake, were tested for recall. Compared with participants who remained awake, participants who slept exhibited markedly slower forgetting rates. This finding can be explained as reflecting a benefit of sleep on consolidation, or reflecting the reduced encoding of interfering information. Data in part **e** are from REF.[109].

predictions of SSCT, evidence suggests that the hippocampus is crucial for the retrieval of recent and remote episodic memory.

Graded retrograde amnesia. Another cornerstone of SSCT is the observation that patients with hippocampal damage, such as the famous patient H.M., exhibit graded retrograde amnesia (FIG. 1a,b); that is, their recall for events during the years just before the lesion is impaired, but they can retrieve memories from more remote time periods, such as childhood[55–57]. Such a pattern would indeed be consistent with SSCT; however, 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 H.M. revealed that he was severely impaired at retrieving details of specific episodes for both remote and recent time periods (that is, he showed 'flat' retrograde amnesia) and that he showed relative sparing of semantic memory compared with episodic memory across those same periods[58] (that is, absent retrograde amnesia).

In addition, studies examining retrograde amnesia in patients with more selective hippocampal lesions also fail to provide compelling evidence for the graded retrograde amnesia predicted by SSC. FIGURE 1c illustrates the published reports of retrograde amnesia as assessed on formal tests in patients with selective hippocampal lesions. The results indicate that on semantic memory tests (for example, tests of memory for famous faces and public events), retrograde memory is in most cases unaffected by hippocampal damage. Even in the few patients who seem 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 more than 15 years before the lesion[59], whereas others exhibit deficits extending only 1–5 years[60]. By contrast, retrograde amnesia of autobiographical memory for personal events, which presumably reflects more episodic information, is more common in patients with hippocampal lesions, but the resulting deficits in recent and remote memory tend to be similar, indicating that episodic memory remains dependent on the hippocampus.

Neuroimaging studies of remote versus recent memories. Several neuroimaging studies have sought to determine if the hippocampus is more active during the retrieval of recent memories than during the retrieval of remote memories, as is predicted by SSCT. However, as illustrated in FIG. 1d, the hippocampus is most often found to be equally involved in the retrieval of both recent and remote memories (see list of included studies in Supplementary Table 1). Potential concerns when interpreting such studies include the possibilities that recent memories may be more vivid or stronger than remote memories and thus might lead to greater activation, or that remote memories may be weaker and thus may lead to additional encoding into memory during the retrieval test, leading to greater retrieval-related activation. However, studies controlling for the vividness or strength of memory[61–64] have reported hippocampal involvement in the retrieval of both remote and recent memories.

Overall, there is little support for the SSC assumption that the hippocampus becomes less involved in retrieval as episodic memories become more remote, but are there any brain regions that become more involved over time? There is some evidence that the medial prefrontal cortex (mPFC) may be involved in remote memory, but the results are quite mixed, and it is not yet clear what role this region plays in episodic memory. For example, some human neuroimaging studies have shown greater frontal activity during retrieval of remote memories, whereas others have reported reduced or similar levels of frontal activity during retrieval of remote memories (reviewed in REFS[65,66]). In addition, mPFC damage does not generally lead to impairments of remote memory[66,67]; rather, it is associated with confabulation[68] and decreases in self-referential processing[69]. Moreover, some evidence suggests that the mPFC may be important for schema learning[70], and other work suggests it may be involved in constructing complex narratives about past and future events[71,72].

Animal studies. Studies of hippocampal lesions in rodents are consistent with those in the human literature in showing that, in tasks that require 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[73–82]. Moreover, consistent with the lesion studies, in the water maze paradigm, rodents exhibit similar or higher levels of hippocampal activation when retrieving remote memories compared with when retrieving recent memories[72,83–86].

By contrast, in memory tasks requiring less precise contextual information, the results are quite mixed. For example, several studies of context fear conditioning — in which rodents exhibit freezing behaviours when placed in an enclosure that was previously paired with foot shocks — report that hippocampal lesions equally reduce freezing behaviour for remote and for recently learned associations (that is, flat retrograde amnesia)[80,87–94]. Other, highly similar studies instead report that hippocampal lesions disrupt recent memories more than remote memories[95–104]. Studies measuring hippocampal activation in contextual fear conditioning are also quite mixed, with some reporting evidence for a role of the hippocampus in remote memory and others failing to do so[88,105–107]. Why the results of these conditioning studies are mixed is not entirely clear, but some evidence suggests that hippocampal activation during testing may depend on the nature of the memory that is retrieved[102,108], such that if animals are required to remember details about a context, then the hippocampus will be engaged and necessary for retrieval[94].

In sum, the results from lesion and activation studies of both humans and rodents indicate that the hippocampus is crucial for the retrieval of both remote and recent episodic memory, consistent with the CB model and in contradiction with the predictions of SSCT. There are a few reported cases of graded retrograde impairments in humans and rodents with hippocampal damage in tasks that require less contextually rich memory, such as in fear conditioning. These latter results are consistent with SSCT but can also be explained by CB in that remote memories will have had more opportunity than recent memories to be remembered and re-encoded before the lesion and thus can be supported by the neocortex.

Sleep

In one of the first systematic studies of sleep on memory, Jenkins and Dallenbach[109] found that forgetting of nonsense syllables was slower if individuals were allowed to sleep immediately after learning than if they were required to remain awake (FIG. 1e). It is possible that sleep slowed forgetting because memories were consolidated to the cortex during sleep. However, another potential explanation is that forgetting was slowed because participants encoded less interfering information if they were asleep than if they remained awake. As described below, there are other effects concerning sleep and memory that are equally well explained by these two different accounts, as well as several findings that seem to preferentially support CB.

Post-encoding slow-wave sleep benefits episodic memory. After an event has been encoded, slow-wave sleep (SWS; that is, periods of low-frequency oscillations containing brief periods of high-frequency activity that dominate early-night sleep), rather than rapid eye movement (REM) sleep (that is, periods of wake-like neural activity that are associated with vivid dreaming and that dominate late-night sleep), seems to be the most beneficial for episodic memory[110]. Why SWS is more important for episodic memory than REM sleep is currently debated[110–112], but this finding is broadly consistent with both the SSC and CB accounts. From the perspective of SSCT, SWS may be particularly important if slow-wave activity in the cortex were to drive repeated reactivation of hippocampal representations (via sharp wave–ripples) that might entrain cortical regions[110,113]. 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 the 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 (that is, the period shortly after encoding), when interference from additional items is posited to be the greatest.

The beneficial effects of post-encoding sleep on memory are more pronounced for tests of associative information than item information[114–118] (but see REFS[119–121]) and are greater for recollection-based recognition responses than for familiarity-based responses[115,116,118,122–125]. These results are consistent with CB theory in the sense that if sleep reduces contextual interference, memory for contextual information should be particularly sensitive to sleep. How the SSC approach would account for these results is not clear.

Reactivation. A growing body of research shows that encoding-related activity in the hippocampus and neocortex can be observed during periods of post-encoding sleep[110,126–128], and such reactivation results are consistent with both SSC and CB. For example, in humans, hippocampal activity during SWS is increased after a navigation task and correlates with subsequent memory[128]. Similarly, during offline states such as sleep, rodents exhibit 'replay': firing of hippocampal place cells in a temporal sequence consistent with the order of place fields recorded during earlier exploration trajectories[129,130]. These reactivation effects were thought to be limited to sleep; however, replay in rodents also occurs in awake animals, and reactivation effects in humans are observed during periods of quiet wakefulness and even during completion of cognitively demanding tasks[110,131–134]. In addition, such reactivation effects have thus far only been well established during a short period after learning[135,136]. Thus, reactivation is not limited to sleep or rest but instead seems to occur regardless of sleep–wake status for a short period of time after information has been encoded.

Such reactivation results could reflect the hippocampus replaying memories to consolidate them to the cortex or neural activity arising from CB. According to the CB model, during encoding, one would expect to see the activity of the hippocampus and cortical regions that support the information being bound to the study context. Importantly, however, to the extent that learning increases the excitability of activated neurons[137,138], encoding-related regions would be expected to show enhanced levels of spontaneous activity and co-activity for a short period after learning. Thus, according to the CB account, encoding-related activity (that is, reactivation) after the study event is expected and should be particularly evident if the context remains unchanged. Moreover, effective encoding should lead to greater encoding-related activity in the post-encoding period and better subsequent retrieval, which is consistent with reports that post-encoding activation correlates with memory performance. Notably, given that context drifts, encoding-related activity during the study event and the post-encoding period would not be expected to be identical, so each would provide some unique encoding-related signal. This idea is consistent with work indicating that learning temporarily increases the excitability of neurons, causing them to be reactivated during the formation of memories for other events that occur close together in time, resulting in these events becoming linked by a shared network of neurons[139–141]. These results are also consistent with the finding that neural activity related to a specific encoding context can persist even when the initial encoding context is no longer presented[142].

The effects of sleep on memory-related activity are still poorly understood. Interestingly, some studies have suggested that reactivation is stronger for weakly encoded materials[143], a finding that is not predicted by the CB account. However, other studies have shown that reactivation effects are stronger for well-encoded materials[144,145], so further empirical work is warranted. Moreover, given that the reactivation results observed thus far have been limited to a short post-encoding period, another interpretation of these results is that they reflect cellular consolidation rather than SSC (BOX 4). In addition, disrupting sharp wave–ripples in rodents impairs subsequent memory[146], indicating that ripples may have an important role in post-encoding sleep; however, whether this finding reflects a disruption of systems consolidation, of context-related residual activity or of cellular consolidation is currently unknown.

Box 4 | **Relating contextual binding 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 contextual interference relates to other post-encoding processes that affect memory, such as cellular consolidation and synaptic downregulation, remains to be explored. Cellular consolidation involves a cascade of molecular processes that occur in the hours shortly after learning[3], but how cellular consolidation is related to the processes underlying contextual binding is largely unknown, and there are several new questions that will need to be empirically addressed. For example, how do cellular consolidation processes in the hippocampus and in the neocortex relate to changes observed in episodic and semantic memory? Does cellular consolidation affect forms of hippocampus-based contextual memory, such as recollection, in ways are that different from how it affects other forms of memory, such as familiarity and semantic memory[195]? Conversely, to what extent does contextual interference affect cellular consolidation? Given the importance of context in episodic memory, what are the cellular processes that are influenced by changes in spatial and mental context[196]? In addition, synaptic strength is known to be downregulated during periods of rest and sleep, to counteract the net increase in synaptic potentiation that is induced by prolonged periods of active wake[112]. How CB is related to synaptic downregulation is not yet known. Although the processes underlying synaptic downregulation are thought to be observed across the cortex, do the regions that support episodic memory have a special role in governing which synapses — and thus, which memories — are downregulated? Downregulation is thought to suppress weakly represented information while preferentially preserving information that is strongly represented in memory either because it is consistent with pre-existing representations or strongly encoded. One possibility that has yet to be explored is whether memory items that are well bound to the ongoing experimental context may be preferentially protected from the effects of downregulation.

Memory cueing during sleep. Another finding that can be explained by both SSC and CB is that cueing recently encoded memories during SWS enhances subsequent episodic memory[147,148]. For example, if participants learn location–object associations in the presence of an odour, and then are allowed to sleep, subsequent memory is improved if the odour is re-presented during SWS[149–152]. 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 seem to be reduced if the cue is presented later in the night, such as during REM sleep, or if presented to awake participants engaged in a demanding primary task[153–155]. Whether cueing facilitates consolidation of episodic information to the cortex or simply enhances the retrieval and re-encoding of the initial study episode is not yet known. Further work will be needed to further assess these two accounts (BOX 2).

Beneficial effects of sleep on memory are rapid. Although much of the sleep–memory literature seems equally consistent with both the SSC and CB approaches, some findings seem to favour the CB account. FIGURE 1e indicates that the beneficial effects of sleep are evident remarkably quickly after encoding[109]. That is, whereas only 46% of items could be remembered after 1 hour of wake, 71% of the items could still be remembered after 1 hour of sleep. Indeed, even 60-minute naps produce sizeable sleep benefits in episodic memory, often similar to those observed after an entire night of sleep[156,157]. Moreover, sleep slows forgetting of items learned just before sleep, with reduced or no effect on the memory of items learned earlier in the day[117,158,159].

The increased benefit of sleep immediately after learning is explained by CB theory, which predicts that interference effects are largest when study materials and interfering materials occur close in time. Although the results are often interpreted as being consistent with SSC, they do present some puzzles for the approach. If the observed sleep benefits reflect consolidation, a large proportion of memories that would otherwise have been forgotten would need to be rapidly (within an hour) consolidated to the cortex, a notion that is difficult to reconcile with results and theoretical proposals suggesting that SSC is a slow process that takes years or decades[8,9]. In addition, according to the data, SSC would 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 in the literature reflect something other than SSC, such as CB or cellular consolidation[160], both of which would be expected to occur at this very short timescale.

Proactive effects of sleep. If, as proposed in the CB model, sleep benefits memory by reducing contextual interference, sleep just before learning should also benefit memory by reducing proactive interference. Indeed, memory for pictures is improved if participants nap immediately before or after learning[161]. In addition, sleep-deprived individuals are less able to encode new episodic memories[162,163]; even mild sleep disruption, which decreases SWS without reducing total sleep time, can reduce subsequent episodic encoding[164]. Moreover, the ability to encode new episodic memories decreases gradually throughout the day, yet can be restored by a brief nap[165]. Although these proactive effects of sleep on memory are consistent with the CB model, they are not predicted by SSCT, which instead proposes that consolidation facilitates the encoding of only recent events and not future events.

Normal forgetting rates in amnesia. If, as held by SSCT, the hippocampus is crucial for consolidating memories to the cortex during sleep, it would follows that compared with control individuals, individuals with hippocampal damage should show accelerated forgetting across delays that include sleep[166–168]. However, the empirical literature generally contradicts this prediction. One study compared H.M.'s picture recognition memory at 10-minute, 1-day and 7-day retention intervals with that of healthy controls; the initial performances (at the 10-minute delay) of H.M. and the controls were matched by manipulating the duration of stimulus presentation[169]. Despite the control-matched performance of H.M. at the 10-minute delay, H.M. seemed to perform worse than the controls at the later intervals, suggesting that he exhibited accelerated forgetting. However, subsequent studies failed to replicate this effect, indicating that his forgetting rate was normal across a 7-day retention interval[170] and a 6-month interval[171]. Thus, even extensive MTL damage, as seen in H.M., does not seem 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 N.A., who suffered a diencephalic lesion, exhibited normal forgetting across a 32-hour retention interval[172], similar to amnesic individuals with the amnestic disorder Korsakoff syndrome[169,172,173]. In addition, normal forgetting rates were reported in a group of patients with extensive MTL lesions as well as in patients with diencephalic lesions[174]. Thus, lesion results indicate that the hippocampus does not have a causal role in slowing episodic forgetting, at least across retention intervals lasting between days and months. Therefore, the pronounced benefit of sleep on memory in healthy individuals must instead be explained in some other way, such as by producing a reduction in contextual interference.

Conclusions

SSC has been a useful scientific construct in accounting for results from across various different research domains. As we show above, however, SSCT fails to account for a growing body of findings from the same research paradigms that motivated its original development, including studies of forgetting, lesion and activation studies and studies of sleep. Although results from any one research area may be questioned, the fact that the challenges to SSCT come from across all these different areas is particularly troubling for this approach. In addition, a growing body of results from across these areas provide strong support for a CB account of episodic memory that does not depend on systems consolidation.

Moving forward, one important aspect of episodic memory that the work discussed above highlights is that an episodic memory should not be treated as being limited to the period in which the study item or object is presented but rather should be treated as extending in time before and after the nominal study event. Thus, memory manipulations during the retention period need not affect a hypothetical consolidation process but rather they can influence the temporally extended encoding of the study event itself. The CB approach provides an account of the existing literature that is consistent with a long history of context models of episodic memory, and it generates several novel predictions that we hope will be useful in guiding future studies (BOX 2).

Overall, 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 this approach 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 for time-dependent changes in memory performance and for brain activity observed both before and after encoding.

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https://doi.org/10.1038/s41583-019-0150-4

Published online: 12 March 2019

1. Ribot, T. *Diseases of Memory: an Essay in the Positive Psychology* Vol. 43 (D. Appleton & Company, NY,1882).
2. Müller, G. E. & Pilzecker, A. *Experimentelle Beiträge zur Lehre vom Gedächtniss [German]* Vol. 1 (J. A. Barth, Leipzig, 1900).
3. Kandel, E. R., Dudai, Y. & Mayford, M. R. The molecular and systems biology of memory. *Cell* **157**, 163–186 (2014).
4. Dudai, Y. The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* **55**, 51–86 (2004).
5. Bekinschtein, P. et al. Persistence of long-term memory storage: new insights into its molecular signatures in the hippocampus and related structures. *Neurotox. Res.* **18**, 377–385 (2010).
6. Frankland, P. W. & Bontempi, B. The organization of recent and remote memories. *Nat. Rev. Neurosci.* **6**, 119–130 (2005).
7. Marr, D. Simple memory: a theory for archicortex. *Phil. Trans. R. Soc. Lond. B* **262**, 23–81 (1971).
8. McClelland, J. L., McNaughton, B. L. & O'Reilly, R. C. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* **102**, 419–457 (1995).
9. Squire, L. R. & Alvarez, P. Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* **5**, 169–177 (1995).
10. Squire, L. R., Genzel, L., Wixted, J. T. & Morris, R. G. Memory consolidation. *Cold Spring Harb. Perspect. Biol.* **7**, a021766 (2015).
11. Diekelmann, S. & Born, J. The memory function of sleep. *Nat. Rev. Neurosci.* **11**, 114–126 (2010).
12. Lewandowsky, S., Ecker, U. K. H., Farrell, S. & Brown, G. D. A. Models of cognition and constraints from neuroscience: a case study involving consolidation. *Aust. J. Psychol.* **64**, 37–45 (2012).
13. Nadel, L. & Moscovitch, M. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* **7**, 217–227 (1997).
14. Sutherland, R. J. & Lehmann, H. Alternative conceptions of memory consolidation and the role of the hippocampus at the systems level in rodents. *Curr. Opin. Neurobiol.* **21**, 446–451 (2011).
15. Eichenbaum, H., Yonelinas, A. P. & Ranganath, C. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* **30**, 123–152 (2007).
16. Fortin, N. J., Wright, S. P. & Eichenbaum, H. Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature* **431**, 188 (2004).
17. Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A. & Rosenbaum, R. S. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr. Opin. Neurobiol.* **16**, 179–190 (2006).
18. Norman, K. A. & O'Reilly, R. C. Modeling hippocampal and neocortical contributions to recognition memory: a complementary-learning-systems approach. *Psychol. Rev.* **110**, 611–646 (2003).
19. Yonelinas, A. P. Components of episodic memory: the contribution of recollection and familiarity. *Phil. Trans. R. Soc. Lond. B* **356**, 1363–1374 (2001).
20. Bower, G. H. in *Coding* Processes in *Human Memory* (eds. Merton, A. W. & Martin, E.) 85–123 (V. H. Winston & Sons, 1972).
21. Estes, W. K. Statistical theory of spontaneous recovery and regression. *Psychol. Rev.* **62**, 145–154 (1955).
22. Kahana, M. J., Howard, M. W., Zaromb, F. & Wingfield, A. Age dissociates recency and lag recency effects in free recall. *J. Exp. Psychol. Learn. Mem. Cogn.* **28**, 530–540 (2002).
23. Mensink, G. M. & Raaijmakers, J. G. W. A model for contextual fluctuation. *J. Math. Psychol.* **33**, 172–186 (1989).
24. Polyn, S. M., Norman, K. A. & Kahana, M. J. A context maintenance and retrieval model of organizational processes in free recall. *Psychol. Rev.* **116**, 129–156 (2009).
25. Sekeres, M. J., Winocur, G. & Moscovitch, M. The hippocampus and related neocortical structures in memory transformation. *Neurosci. Lett.* **680**, 39–53 (2018).
26. Dewar, M., Alber, J., Cowan, N. & Della Sala, S. Boosting long-term memory via wakeful rest: intentional rehearsal is not necessary, consolidation is sufficient. *PLOS ONE* **9**, e109542 (2014).
27. Dewar, M. T., Cowan, N. & Sala, S. D. Forgetting due to retroactive interference: a fusion of Muller and Pilzecker's (1900) early insights into everyday forgetting and recent research on anterograde amnesia. *Cortex* **43**, 616–634 (2007).
28. Lechner, H. A., Squire, L. R. & Byrne, J. H. 100 years of consolidation — remembering Müller and Pilzecker. *Learn. Mem.* **6**, 77–87 (1999).
29. Postman, L. & Keppel, G. Conditions of cumulative proactive-inhibition. *J. Exp. Psychol. Gen.* **106**, 376–403 (1977).
30. Watkins, O. C. & Watkins, M. J. Buildup of proactive inhibition as a cue-overload effect. *J. Exp. Psychol. Hum. Learn.* **1**, 442–452 (1975).
31. Dallett, K. & Wilcox, G. S. Contextuall stimui and proactive inhibition. *J. Exp. Psychol.* **78**, 475–480 (1968).
32. McGeoch, J. A. & McDonald, W. T. Meaningful relation and retroactive inhibition. *Am. J. Psychol.* **43**, 579–588 (1931).
33. Melton, A. W. & von Lackum, W. J. Retroactive and proactive inhibition in retention: Evidence for a two-factor theory of retroactive inhibition. *Am. J. Psychol.* **54**, 157–173 (1941).
34. Bilodeau, I. M. & Schlosberg, H. Similarity in stimulating conditions as a variable in retroactive inhibition. *J. Exp. Psychol.* **41**, 199–204 (1951).
35. Greenspoon, J. & Ranyard, R. Stimulus conditions and retroactive inhibition. *J. Exp. Psychol.* **53**, 55–59 (1957).
36. Strand, B. Z. Change of context and retroactive inhibition. *J. Verbal Learning Verbal Behav.* **9**, 202–206 (1970).
37. Godden, D. R. & Baddeley, A. D. Context-dependent memory in two natural environments — on land and underwater. *Br. J. Psychol.* **66**, 325–331 (1975).
38. Tulving, E. & Thomson, D. M. Word-blindness in episodic memory. *Psychon. Sci.* **29**, 262 (1972).
39. Gardiner, J. M., Craik, F. I. & Birtwistle, J. Retrieval cues and release from proactive inhibition. *J. Verbal Learning Verbal Behav.* **11**, 778–783 (1972).
40. Kroll, N. E. A., Ogawa, K. H. & Nieters, J. E. Eyewitness memory and the importance of sequential information. *Bull. Psychon. Soc.* **26**, 395–398 (1988).
41. Kahana, M. J. Associative retrieval processes in free recall. *Mem. Cognit.* **24**, 103–109 (1996).
42. Schwartz, G., Howard, M. W., Jing, B. & Kahana, M. J. Shadows of the past: temporal retrieval effects in recognition memory. *Psychol. Sci.* **16**, 898–904 (2005).
43. Howard, M. W., Youker, T. E. & Venkatadass, V. S. The persistence of memory: contiguity effects across hundreds of seconds. *Psychon. Bull. Rev.* **15**, 58–63 (2008).
44. Folkerts, S., Rutishauser, U. & Howard, M. W. Human episodic memory retrieval is accompanied by a neural contiguity effect. *J. Neurosci.* **3**, 2312–2317 (2018).
45. Howard, M. W., Viskontas, I. V., Shankar, K. H. & Fried, I. Ensembles of human MTL neurons "jump back in time" in response to a repeated stimulus. *Hippocampus* **22**, 1833–1847 (2012).
46. Manning, J. R., Polyn, S. M., Baltuch, G. H., Litt, B. & Kahana, M. J. Oscillatory patterns in temporal lobe reveal context reinstatement during memory search. *Proc. Natl Acad. Sci. USA* **108**, 12893–12897 (2011).
47. Palombo, D. J., Di Lascio, J. M., Howard, M. W. & Verfaellie, M. Medial temporal lobe amnesia is associated with a deficit in recoveing temporal context. *J. Cogn. Neurosci.* **31**, 236–248 (2019).
48. Yaffe, R. B. et al. Reinstatement of distributed cortical oscillations occurs with precise spatiotemporal dynamics during successful memory retrieval. *Proc. Natl Acad. Sci. USA* **111**, 18727–18732 (2014).
49. Radvansky, G. A. & Zacks, J. M. Event boundaries in memory and cognition. *Curr. Opin. Behav. Sci.* **17**, 133–140 (2017).
50. Sederberg, P. B., Gershman, S. J., Polyn, S. M. & Norman, K. A. Human memory reconsolidation can be explained using the temporal context model. *Psychon. Bull. Rev.* **18**, 455–468 (2011).
51. Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J. & Madsen, J. R. Theta and gamma oscillations during encoding predict subsequent recall. *J. Neurosci.* **23**, 10809–10814 (2003).
52. Squire, L. R. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99**, 195–231 (1992).
53. Squire, L. R., Slater, P. C. & Chace, P. M. Retrograde amnesia: temporal gradient in very long term memory following electroconvulsive therapy. *Science* **187**, 77–79 (1975).
54. Tse, D. et al. Schemas and memory consolidation. *Science* **316**, 76–82 (2007).
55. Corkin, S. Lasting consequences of bilateral medial temporal lobectomy — clinical course and experimental findings in H.M. *Semin. Neurol.* **4**, 249–259 (1984).
56. Penfield, W. & Milner, B. Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch. Neurol. Psychiatry* **79**, 475–497 (1958).
57. Scoville, W. B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* **20**, 11–21 (1957).
58. Steinvorth, S., Levine, B. & Corkin, S. Medial temporal lobe structures are needed to re-experience remote autobiographical memories: evidence from H.M. and W.R. *Neuropsychologia* **43**, 479–496 (2005).
59. Rempel-Clower, N. L., Zola, S. M., Squire, L. R. & Amaral, D. G. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J. Neurosci.* **16**, 5233–5255 (1996).
60. Bayley, P. J., Hopkins, R. O. & Squire, L. R. The fate of old memories after medial temporal lobe damage. *J. Neurosci.* **26**, 13311–13317 (2006).
61. Addis, D. R., Moscovitch, M., Crawley, A. P. & McAndrews, M. P. Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. *Hippocampus* **14**, 752–762 (2004).
62. Gilboa, A., Winocur, G., Grady, C. L., Hevenor, S. J. & Moscovitch, M. Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. *Cereb. Cortex* **14**, 1214–1225 (2004).
63. Sheldon, S. & Levine, B. Same as it ever was: vividness modulates the similarities and differences between the neural networks that support retrieving remote and recent autobiographical memories. *Neuroimage* **83**, 880–891 (2013).
64. Viard, A. et al. Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: an fMRI study. *Cereb. Cortex* **17**, 2453–2467 (2007).
65. Cabeza, R. & St Jacques, P. Functional neuroimaging of autobiographical memory. *Trends Cogn. Sci.* **11**, 219–227 (2007).
66. Dede, A. J. & Smith, C. N. The functional and structural neuroanatomy of systems consolidation for autobiographical and semantic memory. *Curr. Top. Behav. Neurosci.* **37**, 119–150 (2016).
67. Nieuwenhuis, I. L. & Takashima, A. The role of the ventromedial prefrontal cortex in memory consolidation. *Behav. Brain Res.* **218**, 325–334 (2011).
68. Schnider, A. *The Confabulating Mind: How the Brain Creates Reality* (Oxford Univ. Press, 2008).
69. Philippi, C. L., Duff, M. C., Denburg, N. L., Tranel, D. & Rudrauf, D. Medial PFC damage abolishes the self-reference effect. *J. Cogn. Neurosci.* **24**, 475–481 (2012).
70. Gilboa, A. & Marlatte, H. Neurobiology of schemas and schema-mediated memory. *Trends Cogn. Sci.* **21**, 618–631 (2017).
71. Bertossi, E., Tesini, C., Cappelli, A. & Ciaramelli, E. Ventromedial prefrontal damage causes a pervasive impairment of episodic memory and future thinking. *Neuropsychologia* **90**, 12–24 (2016).
72. Barry, D. N., Coogan, A. N. & Commins, S. The time course of systems consolidation of spatial memory from recent to remote retention: a comparison of the immediate early genes Zif268, c-Fos and Arc. *Neurobiol. Learn. Mem.* **128**, 46–55 (2016).

73. Bolhuis, J. J., Stewart, C. A. & Forrest, E. M. Retrograde amnesia and memory reactivation in rats with ibotenate lesions to the hippocampus or subiculum. *Q. J. Exp. Psychol. B* **47**, 129–150 (1994).
74. Clark, R. E., Broadbent, N. J. & Squire, L. R. Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life. *Hippocampus* **15**, 340–346 (2005).
75. Clark, R. E., Broadbent, N. J. & Squire, L. R. Hippocampus and remote spatial memory in rats. *Hippocampus* **15**, 260–272 (2005).
76. Clark, R. E., Broadbent, N. J. & Squire, L. R. The hippocampus and spatial memory: findings with a novel modification of the water maze. *J. Neurosci.* **27**, 6647–6654 (2007).
77. Hollup, S. A., Kjelstrup, K. G., Hoff, J., Moser, M. B. & Moser, E. I. Impaired recognition of the goal location during spatial navigation in rats with hippocampal lesions. *J. Neurosci.* **21**, 4505–4513 (2001).
78. Martin, S. J., de Hoz, L. & Morris, R. G. Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. *Neuropsychologia* **43**, 609–624 (2005).
79. Mumby, D. G., Astur, R. S., Weisend, M. P. & Sutherland, R. J. Retrograde amnesia and selective damage to the hippocampal formation: memory for places and object discriminations. *Behav. Brain Res.* **106**, 97–107 (1999).
80. Ocampo, A. C., Squire, L. R. & Clark, R. E. Hippocampal area CA1 and remote memory in rats. *Learn. Mem.* **24**, 563–568 (2017).
81. Sutherland, R. J. et al. Retrograde amnesia after hippocampal damage: recent versus remote memories in two tasks. *Hippocampus* **11**, 27–42 (2001).
82. Winocur, G., Moscovitch, M., Caruana, D. A. & Binns, M. A. Retrograde amnesia in rats with lesions to the hippocampus on a test of spatial memory. *Neuropsychologia* **43**, 1580–1590 (2005).
83. Bonaccorsi, J. et al. System consolidation of spatial memories in mice: effects of enriched environment. *Neural Plast.* **2013**, 956312 (2013).
84. Kee, N., Teixeira, C. M., Wang, A. H. & Frankland, P. W. Imaging activation of adult-generated granule cells in spatial memory. *Nat. Protoc.* **2**, 3033–3044 (2007).
85. Lopez, J. et al. Context-dependent modulation of hippocampal and cortical recruitment during remote spatial memory retrieval. *Hippocampus* **22**, 827–841 (2012).
86. Teixeira, C. M., Pomedli, S. R., Maei, H. R., Kee, N. & Frankland, P. W. Involvement of the anterior cingulate cortex in the expression of remote spatial memory. *J. Neurosci.* **26**, 7555–7564 (2006).
87. Broadbent, N. J. & Clark, R. E. Remote context fear conditioning remains hippocampus-dependent irrespective of training protocol, training-surgery interval, lesion size, and lesion method. *Neurobiol. Learn. Mem.* **106**, 300–308 (2013).
88. Goshen, I. et al. Dynamics of retrieval strategies for remote memories. *Cell* **147**, 678–689 (2011).
89. Lehmann, H., Lacanilao, S. & Sutherland, R. J. Complete or partial hippocampal damage produces equivalent retrograde amnesia for remote contextual fear memories. *Eur. J. Neurosci.* **25**, 1278–1286 (2007).
90. Lehmann, H., Rourke, B. K., Booker, A. & Glenn, M. J. Single session contextual fear conditioning remains dependent on the hippocampus despite an increase in the number of context–shock pairings during learning. *Neurobiol. Learn. Mem.* **106**, 294–299 (2013).
91. Quinn, J. J., Ma, Q. D., Tinsley, M. R., Koch, C. & Fanselow, M. S. Inverse temporal contributions of the dorsal hippocampus and medial prefrontal cortex to the expression of long-term fear memories. *Learn. Mem.* **15**, 368–372 (2008).
92. Sparks, F. T., Spanswick, S. C., Lehmann, H. & Sutherland, R. J. Neither time nor number of context-shock pairings affect long-term dependence of memory on hippocampus. *Neurobiol. Learn. Mem.* **106**, 309–315 (2013).
93. Sutherland, R. J., O'Brien, J. & Lehmann, H. Absence of systems consolidation of fear memories after dorsal, ventral, or complete hippocampal damage. *Hippocampus* **18**, 710–718 (2008).
94. Lehmann, H. et al. Making context memories independent of the hippocampus. *Learn. Mem.* **16**, 417–420 (2009).
95. Anagnostaras, S. G., Maren, S. & Fanselow, M. S. Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *J. Neurosci.* **19**, 1106–1114 (1999).
96. Corcoran, K. A. et al. NMDA receptors in retrosplenial cortex are necessary for retrieval of recent and remote context fear memory. *J. Neurosci.* **31**, 11655–11659 (2011).
97. Frankland, P. W. et al. Stability of recent and remote contextual fear memory. *Learn. Mem.* **13**, 451–457 (2006).
98. Kim, J. J. & Fanselow, M. S. Modality-specific retrograde amnesia of fear. *Science* **256**, 675–677 (1992).
99. Kitamura, T. et al. Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. *Cell* **139**, 814–827 (2009).
100. Maren, S., Aharonov, G. & Fanselow, M. S. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav. Brain Res.* **88**, 261–274 (1997).
101. Wang, S. H., Teixeira, C. M., Wheeler, A. L. & Frankland, P. W. The precision of remote context memories does not require the hippocampus. *Nat. Neurosci.* **12**, 253–255 (2009).
102. Wiltgen, B. J. et al. The hippocampus plays a selective role in the retrieval of detailed contextual memories. *Curr. Biol.* **20**, 1336–1344 (2010).
103. Winocur, G., Frankland, P. W., Sekeres, M., Fogel, S. & Moscovitch, M. Changes in context-specificity during memory reconsolidation: selective effects of hippocampal lesions. *Learn. Mem.* **16**, 722–729 (2009).
104. Winocur, G., Sekeres, M. J., Binns, M. A. & Moscovitch, M. Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat. *Hippocampus* **23**, 330–341 (2013).
105. Frankland, P. W., Bontempi, B., Talton, L. E., Kaczmarek, L. & Silva, A. J. The involvement of the anterior cingulate cortex in remote contextual fear memory. *Science* **304**, 881–883 (2004).
106. Lux, V., Atucha, E., Kitsukawa, T. & Sauvage, M. M. Imaging a memory trace over half a life-time in the medial temporal lobe reveals a time-limited role of CA3 neurons in retrieval. *eLife* **5**, e11862 (2016).
107. Tayler, K. K., Tanaka, K. Z., Reijmers, L. G. & Wiltgen, B. J. Reactivation of neural ensembles during the retrieval of recent and remote memory. *Curr. Biol.* **23**, 99–106 (2013).
108. Guo, N. et al. Dentate granule cell recruitment of feedforward inhibition governs engram maintenance and remote memory generalization. *Nat. Med.* **24**, 438–449 (2018).
109. Jenkins, J. G. & Dallenbach, K. M. Oblivescence during sleep and waking. *Am. J. Psychol.* **35**, 605–612 (1924).
110. Rasch, B. & Born, J. About sleep's role in memory. *Physiol. Rev.* **93**, 681–766 (2013).
111. Luthi, A. Sleep spindles: where they come from, what they do. *Neuroscientist* **20**, 243–256 (2014).
112. Tononi, G. & Cirelli, C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* **81**, 12–34 (2014).
113. Buzsaki, G. Two-stage model of memory trace formation: a role for "noisy" brain states. *Neuroscience* **31**, 551–570 (1989).
114. Lewis, P. A., Cairney, S., Manning, L. & Critchley, H. D. The impact of overnight consolidation upon memory for emotional and neutral encoding contexts. *Neuropsychologia* **49**, 2619–2629 (2011).
115. Plihal, W. & Born, J. Effects of early and late nocturnal sleep on declarative and procedural memory. *J. Cogn. Neurosci.* **9**, 534–547 (1997).
116. Studte, S., Bridger, E. & Mecklinger, A. Nap sleep preserves associative but not item memory performance. *Neurobiol. Learn. Mem.* **120**, 84–93 (2015).
117. Talamini, L. M., Nieuwenhuis, I. L., Takashima, A. & Jensen, O. Sleep directly following learning benefits consolidation of spatial associative memory. *Learn. Mem.* **15**, 233–237 (2008).
118. van der Helm, E., Gujar, N., Nishida, M. & Walker, M. P. Sleep-dependent facilitation of episodic memory details. *PLOS ONE* **6**, e27421 (2011).
119. Mawdsley, M., Grasby, K. & Talk, A. The effect of sleep on item recognition and source memory recollection among shift-workers and permanent day-workers. *J. Sleep Res.* **23**, 538–544 (2014).
120. Schonauer, M., Pawlizki, A., Kock, C. & Gais, S. Exploring the effect of sleep and reduced interference on different forms of declarative memory. *Sleep* **37**, 1995–2007 (2014).
121. Sawangjit, A. et al. The hippocampus is crucial for forming non-hippocampal long-term memory during sleep. *Nature* **564**, 109–113 (2018).
122. Atienza, M. & Cantero, J. L. Modulatory effects of emotion and sleep on recollection and familiarity. *J. Sleep Res.* **17**, 285–294 (2008).
123. Daurat, A., Terrier, P., Foret, J. & Tiberge, M. Slow wave sleep and recollection in recognition memory. *Conscious Cogn.* **16**, 445–455 (2007).
124. Drosopoulos, S., Wagner, U. & Born, J. Sleep enhances explicit recollection in recognition memory. *Learn. Mem.* **12**, 44–51 (2005).
125. Sterpenich, V. et al. Sleep-related hippocampo-cortical interplay during emotional memory recollection. *PLOS Biol.* **5**, e282 (2007).
126. Bergmann, T. O., Molle, M., Diedrichs, J., Born, J. & Siebner, H. R. Sleep spindle-related reactivation of category-specific cortical regions after learning face-scene associations. *Neuroimage* **59**, 2733–2742 (2012).
127. Deuker, L. et al. Memory consolidation by replay of stimulus-specific neural activity. *J. Neurosci.* **33**, 19373–19383 (2013).
128. Peigneux, P. et al. Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* **44**, 535–545 (2004).
129. Foster, D. J. & Wilson, M. A. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* **440**, 680–683 (2006).
130. Lee, A. K. & Wilson, M. A. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* **36**, 1183–1194 (2002).
131. Staresina, B. P., Alink, A., Kriegeskorte, N. & Henson, R. N. Awake reactivation predicts memory in humans. *Proc. Natl Acad. Sci. USA* **110**, 21159–21164 (2013).
132. Tambini, A. & Davachi, L. Persistence of hippocampal multivoxel patterns into postencoding rest is related to memory. *Proc. Natl Acad. Sci. USA* **110**, 19591–19596 (2013).
133. Tambini, A., Ketz, N. & Davachi, L. Enhanced brain correlations during rest are related to memory for recent experiences. *Neuron* **65**, 280–290 (2010).
134. Tompary, A., Duncan, K. & Davachi, L. Consolidation of associative and item memory is related to post-encoding functional connectivity between the ventral tegmental area and different medial temporal lobe subregions during an unrelated task. *J. Neurosci.* **35**, 7326–7331 (2015).
135. Kudrimoti, H. S., Barnes, C. A. & McNaughton, B. L. Reactivation of hippocampal cell assemblies: effects of behavioral state, experience, and EEG dynamics. *J. Neurosci.* **19**, 4090–4101 (1999).
136. Giri, B., Miyawaki, H., Mizuseki, K., Cheng, S. & Diba, K. Hippocampal reactivation extends for several hours following novel experience. *J. Neurosci.* **39**, 866–875 (2019).
137. Crestani, A. P. et al. Metaplasticity contributes to memory formation in the hippocampus. *Neuropsychopharmacology* **44**, 408–414 (2019).
138. Moyer, J. R. Jr., Power, J. M., Thompson, L. T. & Disterhoft, J. F. Increased excitability of aged rabbit CA1 neurons after trace eyeblink conditioning. *J. Neurosci.* **20**, 5476–5482 (2000).
139. Cai, D. J. et al. A shared neural ensemble links distinct contextual memories encoded close in time. *Nature* **534**, 115–118 (2016).
140. Dragoi, G. & Tonegawa, S. Preplay of future place cell sequences by hippocampal cellular assemblies. *Nature* **469**, 397–401 (2011).
141. Rogerson, T. et al. Synaptic tagging during memory allocation. *Nat. Rev. Neurosci.* **15**, 157–169 (2014).
142. Manning, J. R. et al. A neural signature of contextually mediated intentional forgetting. *Psychon. Bull. Rev.* **23**, 1534–1542 (2016).
143. Schapiro, A. C., McDevitt, E. A., Rogers, T. T., Mednick, S. C. & Norman, K. A. Human hippocampal replay during rest prioritizes weakly learned information and predicts memory performance. *Nat. Commun.* **9**, 3920–3931 (2018).
144. Gruber, M. J., Ritchey, M., Wang, S. F., Doss, M. K. & Ranganath, C. Post-learning hippocampal dynamics promote preferential retention of rewarding events. *Neuron* **89**, 1110–1120 (2016).
145. Murty, V. P., Tompary, A., Adcock, R. A. & Davachi, L. Selectivity in postencoding connectivity with high-level visual cortex is associated with reward-motivated memory. *J. Neurosci.* **37**, 537–545 (2017).

146. Girardeau, G., Benchenane, K., Wiener, S. I., Buzsaki, G. & Zugaro, M. B. Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.* **12**, 1222–1223 (2009).
147. Paller, K. A. Sleeping in a brave new world: opportunities for improving learning and clinical outcomes through targeted memory reactivation. *Curr. Dir. Psychol. Sci.* **26**, 532–537 (2017).
148. Schouten, D. I., Pereira, S. I., Tops, M. & Louzada, F. M. State of the art on targeted memory reactivation: sleep your way to enhanced cognition. *Sleep Med. Rev.* **32**, 123–131 (2017).
149. Diekelmann, S., Buchel, C., Born, J. & Rasch, B. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nat. Neurosci.* **14**, 381–386 (2011).
150. Rasch, B., Buchel, C., Gais, S. & Born, J. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* **315**, 1426–1429 (2007).
151. Rihm, J. S., Diekelmann, S., Born, J. & Rasch, B. Reactivating memories during sleep by odors: odor specificity and associated changes in sleep oscillations. *J. Cogn. Neurosci.* **26**, 1806–1818 (2014).
152. Schreiner, T. & Rasch, B. Boosting vocabulary learning by verbal cueing during sleep. *Cereb. Cortex* **25**, 4169–4179 (2015).
153. Cairney, S. A., Lindsay, S., Sobczak, J. M., Paller, K. A. & Gaskell, M. G. The benefits of targeted memory reactivation for consolidation in sleep are contingent on memory accuracy and direct cue–memory associations. *Sleep* **39**, 1139–1150 (2016).
154. Donohue, K. C. & Spencer, R. M. Continuous re-exposure to environmental sound cues during sleep does not improve memory for semantically unrelated word pairs. *J. Cogn. Educ. Psychol.* **10**, 167–177 (2011).
155. Rudoy, J. D., Voss, J. L., Westerberg, C. E. & Paller, K. A. Strengthening individual memories by reactivating them during sleep. *Science* **326**, 1079 (2009).
156. Tucker, M. A. & Fishbein, W. Enhancement of declarative memory performance following a daytime nap is contingent on strength of initial task acquisition. *Sleep* **31**, 197–203 (2008).
157. Tucker, M. A. et al. A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiol. Learn. Mem.* **86**, 241–247 (2006).
158. Gais, S., Lucas, B. & Born, J. Sleep after learning aids memory recall. *Learn. Mem.* **13**, 259–262 (2006).
159. Payne, J. D., Chambers, A. M. & Kensinger, E. A. Sleep promotes lasting changes in selective memory for emotional scenes. *Front. Integr. Neurosci.* **6**, 108 (2012).
160. Pennartz, C. M. A., Uylings, H. B. M., Barnes, C. A. & McNaughton, B. L. Memory reactivation and consolidation during sleep: from cellular mechanisms to human performance. *Prog. Brain Res.* **138**, 143–166 (2002).
161. Cellini, N., Torre, J., Stegagno, L. & Sarlo, M. Sleep before and after learning promotes the consolidation of both neutral and emotional information regardless of REM presence. *Neurobiol. Learn. Mem.* **133**, 136–144 (2016).
162. Drummond, S. P. & Brown, G. G. The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacology* **25**, S68–73 (2001).
163. Drummond, S. P., Gillin, J. C. & Brown, G. G. Increased cerebral response during a divided attention task following sleep deprivation. *J. Sleep Res.* **10**, 85–92 (2001).
164. Van Der Werf, Y. D. et al. Sleep benefits subsequent hippocampal functioning. *Nat. Neurosci.* **12**, 122–123 (2009).
165. Mander, B. A., Santhanam, S., Saletin, J. M. & Walker, M. P. Wake deterioration and sleep restoration of human learning. *Curr. Biol.* **21**, R183–184 (2011).
166. Elliott, G., Isaac, C. L. & Muhlert, N. Measuring forgetting: a critical review of accelerated long-term forgetting studies. *Cortex* **54**, 16–32 (2014).
167. Isaac, C. L. & Mayes, A. R. Rate of forgetting in amnesia: I. Recall and recognition of prose. *J. Exp. Psychol. Learn. Mem. Cogn.* **25**, 942–962 (1999).
168. Kopelman, M. D. Organic retrograde amnesia. *Cortex* **38**, 655–659 (2002).
169. Huppert, F. A. & Piercy, M. Normal and abnormal forgetting in organic amnesia: effect of locus of lesion. *Cortex* **15**, 385–390 (1979).
170. Freed, D. M., Corkin, S. & Cohen, N. J. Forgetting in H. M.: a second look. *Neuropsychologia* **25**, 461–471 (1987).
171. Freed, D. M. & Corkin, S. Rate of forgetting in H. M.: 6-month recognition. *Behav. Neurosci.* **102**, 823–827 (1988).
172. Squire, L. R. Two forms of human amnesia: an analysis of forgetting. *J. Neurosci.* **1**, 635–640 (1981).
173. Huppert, F. A. & Piercy, M. Recognition memory in amnesic patients: effect of temporal context and familiarity of material. *Cortex* **12**, 3–20 (1976).
174. McKee, R. D. & Squire, L. R. Equivalent forgetting rates in long-term memory for diencephalic and medial temporal lobe amnesia. *J. Neurosci.* **12**, 3765–3772 (1992).
175. Yonelinas, A. P. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. *Behav. Brain Res.* **254**, 34–44 (2013).
176. Rolls, E. T. A theory of hippocampal function in memory. *Hippocampus* **6**, 601–620 (1996).
177. Yonelinas, A. P. & Ritchey, M. The slow forgetting of emotional episodic memories: an emotional binding account. *Trends Cogn. Sci.* **19**, 259–267 (2015).
178. DuBrow, S., Rouhani, N., Niv, Y. & Norman, K. A. Does mental context drift or shift? *Curr. Opin. Behav. Sci.* **17**, 141–146 (2017).
179. Shields, G. S., Sazma, M. A., McCullough, A. M. & Yonelinas, A. P. The effects of acute stress on episodic memory: a meta-analysis and integrative review. *Psychol. Bull.* **143**, 636–675 (2017).
180. Gisquet-Verrier, P. et al. Integration of new information with active memory accounts for retrograde amnesia: a challenge to the consolidation/reconsolidation hypothesis? *J. Neurosci.* **35**, 11623–11633 (2015).
181. Quamme, J. R., Yonelinas, A. P. & Norman, K. A. Effect of unitization on associative recognition in amnesia. *Hippocampus* **17**, 192–200 (2007).
182. Sharon, T., Moscovitch, M. & Gilboa, A. Rapid neocortical acquisition of long-term arbitrary associations independent of the hippocampus. *Proc. Natl Acad. Sci. USA* **108**, 1146–1151 (2011).
183. Coutanche, M. N. & Thompson-Schill, S. L. Rapid consolidation of new knowledge in adulthood via fast mapping. *Trends Cogn. Sci.* **19**, 486–488 (2015).
184. Tse, D. et al. Schema-dependent gene activation and memory encoding in neocortex. *Science* **333**, 891–895 (2011).
185. Bastin, C. et al. Associative memory in aging: the effect of unitization on source memory. *Psychol. Aging* **28**, 275–283 (2013).
186. Hirano, M. & Noguchi, K. Dissociation between specific personal episodes and other aspects of remote memory in a patient with hippocampal amnesia. *Percept. Mot. Skills* **87**, 99–107 (1998).
187. Schacter, D. L., Chiu, C. Y. & Ochsner, K. N. Implicit memory: a selective review. *Annu. Rev. Neurosci.* **16**, 159–182 (1993).
188. Cave, C. B. & Squire, L. R. Intact and long-lasting repetition priming in amnesia. *J. Exp. Psychol. Learn. Mem. Cogn.* **18**, 509–520 (1992).
189. McAndrews, M. P., Glisky, E. L. & Schacter, D. L. When priming persists: long-lasting implicit memory for a single episode in amnesic patients. *Neuropsychologia* **25**, 497–506 (1987).
190. Tranel, D., Damasio, A. R., Damasio, H. & Brandt, J. P. Sensorimotor skill learning in amnesia: additional evidence for the neural basis of nondeclarative memory. *Learn. Mem.* **1**, 165–179 (1994).
191. Cohen, N. J. & Squire, L. R. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science* **210**, 207–210 (1980).
192. Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. Sleep inspires insight. *Nature* **427**, 352–355 (2004).
193. Laureys, S., Peigneux, P., Perrin, F. & Maquet, P. Sleep and motor skill learning. *Neuron* **35**, 5–7 (2002).
194. Pan, S. C. & Rickard, T. C. Sleep and motor learning: Is there room for consolidation? *Psychol. Bull.* **141**, 812–834 (2015).
195. Miranda, M. & Bekinschtein, P. Plasticity mechanisms of memory consolidation and reconsolidation in the perirhinal cortex. *Neuroscience* **370**, 46–61 (2018).
196. Mather, M., Clewett, D., Sakaki, M. & Harley, C. W. Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory. *Behav. Brain Sci.* **39**, e200 (2016).
197. Bayley, P. J., Hopkins, R. O. & Squire, L. R. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron* **38**, 135–144 (2003).
198. Bright, P. et al. Retrograde amnesia in patients with hippocampal, medial temporal, temporal lobe, or frontal pathology. *Learn. Mem.* **13**, 545–557 (2006).
199. Cipolotti, L. et al. Long-term retrograde amnesia…the crucial role of the hippocampus. *Neuropsychologia* **39**, 151–172 (2001).
200. Kapur, N. & Brooks, D. J. Temporally-specific retrograde amnesia in two cases of discrete bilateral hippocampal pathology. *Hippocampus* **9**, 247–254 (1999).
201. Reed, J. M. & Squire, L. R. Retrograde amnesia for facts and events: findings from four new cases. *J. Neurosci.* **18**, 3943–3954 (1998).
202. Zola-Morgan, S., Squire, L. R. & Amaral, D. G. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J. Neurosci.* **6**, 2950–2967 (1986).
203. Bernard, F. A. et al. The hippocampal region is involved in successful recognition of both remote and recent famous faces. *Neuroimage* **22**, 1704–1714 (2004).
204. Bonnici, H. M., Chadwick, M. J. & Maguire, E. A. Representations of recent and remote autobiographical memories in hippocampal subfields. *Hippocampus* **23**, 849–854 (2013).
205. Haist, F., Bowden Gore, J. & Mao, H. Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nat. Neurosci.* **4**, 1139–1145 (2001).
206. Maguire, E. A., Henson, R. N., Mummery, C. J. & Frith, C. D. Activity in prefrontal cortex, not hippocampus, varies parametrically with the increasing remoteness of memories. *Neuroreport* **12**, 441–444 (2001).
207. Rissman, J., Chow, T. E., Reggente, N. & Wagner, A. D. Decoding fMRI signatures of real-world autobiographical memory retrieval. *J. Cogn. Neurosci.* **28**, 604–620 (2016).
208. Ryan, L. et al. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus* **11**, 707–714 (2001).
209. Soderlund, H., Moscovitch, M., Kumar, N., Mandic, M. & Levine, B. As time goes by: hippocampal connectivity changes with remoteness of autobiographical memory retrieval. *Hippocampus* **22**, 670–679 (2012).
210. Stark, C. E. & Squire, L. R. fMRI activity in the medial temporal lobe during recognition memory as a function of study-test interval. *Hippocampus* **10**, 329–337 (2000).
211. Steinvorth, S., Corkin, S. & Halgren, E. Ecphory of autobiographical memories: an fMRI study of recent and remote memory retrieval. *Neuroimage* **30**, 285–298 (2006).
212. Tsukiura, T. et al. Time-dependent contribution of the hippocampal complex when remembering the past: a PET study. *Neuroreport* **13**, 2319–2323 (2002).
213. Gais, S. et al. Sleep transforms the cerebral trace of declarative memories. *Proc. Natl Acad. Sci. USA* **104**, 18778–18783 (2007).
214. Milton, F. et al. An fMRI study of long-term everyday memory using SenseCam. *Memory* **19**, 733–744 (2011).
215. Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J. & Fink, G. R. Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain* **126**, 650–668 (2003).
216. Smith, C. N. & Squire, L. R. Medial temporal lobe activity during retrieval of semantic memory is related to the age of the memory. *J. Neurosci.* **29**, 930–938 (2009).
217. Takashima, A. et al. Shift from hippocampal to neocortical centered retrieval network with consolidation. *J. Neurosci.* **29**, 10087–10093 (2009).
218. Takashima, A. et al. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. *Proc. Natl Acad. Sci. USA* **103**, 756–761 (2006).
219. Yamashita, K. et al. Formation of long-term memory representation in human temporal cortex related to pictorial paired associates. *J. Neurosci.* **29**, 10335–10340 (2009).

220. Bosshardt, S. et al. One month of human memory consolidation enhances retrieval-related hippocampal activity. *Hippocampus* **15**, 1026–1040 (2005).
221. Bosshardt, S. et al. Effects of memory consolidation on human hippocampal activity during retrieval. *Cortex* **41**, 486–498 (2005).
222. Piolino, P. et al. Re-experiencing old memories via hippocampus: a PET study of autobiographical memory. *Neuroimage* **22**, 1371–1383 (2004).
223. Rekkas, P. V. & Constable, R. T. Evidence that autobiographic memory retrieval does not become independent of the hippocampus: an fMRI study contrasting very recent with remote events. *J. Cogn. Neurosci.* **17**, 1950–1961 (2005).
224. Donix, M. et al. Age-dependent differences in the neural mechanisms supporting long-term declarative memories. *Arch. Clin. Neuropsychol.* **25**, 383–395 (2010).
225. Douville, K. et al. Medial temporal lobe activity for recognition of recent and remote famous names: an event-related fMRI study. *Neuropsychologia* **43**, 693–703 (2005).
226. Furman, O., Mendelsohn, A. & Dudai, Y. The episodic engram transformed: time reduces retrieval-related brain activity but correlates it with memory accuracy. *Learn. Mem.* **19**, 575–587 (2012).
227. Harand, C. et al. The hippocampus remains activated over the long term for the retrieval of truly episodic memories. *PLOS ONE* **7**, e43495 (2012).
228. Janzen, G., Jansen, C. & van Turennout, M. Memory consolidation of landmarks in good navigators. *Hippocampus* **18**, 40–47 (2008).
229. Maguire, E. A. & Frith, C. D. Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. *J. Neurosci.* **23**, 5302–5307 (2003).
230. Ritchey, M., Montchal, M. E., Yonelinas, A. P. & Ranganath, C. Delay-dependent contributions of medial temporal lobe regions to episodic memory retrieval. *eLife* **4**, e05025 (2015).

Acknowledgements
This paper is based on discussions with students and faculty participating in a graduate seminar at the University of California–Davis, including A. Borders, G. Shields, R. Goodrich, M. Ramey, T. Baer, I. Pastor, C. Riddell, M. Sazma, A. McCullough, C. Carrasco, M. Ritchey, D. Ragland, M. Starrett, M. Liang, A. Barnett, Z. Reagh, B. Cohn-Sheehy, J. Crivelli-Decker, W. Reilly, M. Gruber, N. Bouffard, H. Dimsdale-Zucker, J. Wilmot, Y. Ota, K. Puhger and J. Krueger. This work was supported by the US National Eye Institute of the US National Institutes of Health (NIH) under Award Number R01EY025999 (A.P.Y.); NIH/National Institute of Neurological Disorders and Stroke (NINDS) grants NS076856 (A.D.E.) and NS093052 (A.D.E. and A.P.Y.); and NINDS grants R01NS088053 and R21NS101694 (B.J.W.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Author contributions
All authors contributed to the research of data for the article, the discussion of content and the writing, reviewing and editing of this manuscript before submission.

Competing interests
The authors declare no competing interests.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Reviewer information
Nature Reviews Neuroscience thanks P. Frankland, M. Moscovitch, R. J. Sutherland and the other, anonymous reviewer for their contribution to the peer review of this work.

Supplementary information
Supplementary information is available for this paper at https://doi.org/10.1038/s41583-019-0150-4.