THE ORGANIZATION OF RECENT AND REMOTE MEMORIES

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Abstract | A fundamental question in memory research is how our brains can form enduring memories. In humans, memories of everyday life depend initially on the medial temporal lobe system, including the hippocampus. As these memories mature, they are thought to become increasingly dependent on other brain regions such as the cortex. Little is understood about how new memories in the hippocampus are transformed into remote memories in cortical networks. However, recent studies have begun to shed light on how remote memories are organized in the cortex, and the molecular and cellular events that underlie their consolidation.

Our memories of everyday life — of people, places and events — define who we are[1]. However, these records of life experience are not formed instantaneously. Rather, new memories are gradually transformed from an initially labile state (in which they are vulnerable to disruption) to a more permanent state (in which they are resistant to disruption). Müller and Pilzecker first adopted the term 'consolidation' to describe these post-experience processes of memory stabilization[2,3].

Consolidation involves reorganization at both the synaptic and system levels[4] (BOX 1). Synaptic consolidation is complete within hours of training, and involves the stabilization of changes in synaptic connectivity in localized circuits (for example, the growth of new synaptic connections as well as the restructuring of existing ones)[1,4,5]. By contrast, system consolidation is a more prolonged process and involves gradual reorganization of the brain regions that support memory. For example, this may involve a time-dependent shift in the circuits that support memory recall[1,4].

The French psychologist Ribot was the first to suggest that memories might be gradually reorganized over time[6]. Ribot described how memory loss following brain insult was often related to the age of the memory: the effect on more recent memories was typically greater than that on remotely acquired memories. This dissociation suggested that there is a time-dependent process of memory reorganization, and became known as Ribot's law (or Ribot's gradient). It was only in the mid-twentieth century that a more precise relationship between the locus of brain damage and the gradient was established. In these classic studies[7,8], Penfield, Milner and Scoville characterized memory loss in patients with lesions of the MEDIAL TEMPORAL LOBE (MTL) and provided the first anecdotal evidence that MTL damage preferentially affects recent, but not remote, memories. Later studies that used quantitative methods to characterize memory loss in patients with more circumscribed lesions established that hippocampal damage, in particular, is typically associated with TEMPORALLY-GRADED RETROGRADE AMNESIA[9–12].

Such examples of temporally-graded retrograde amnesia have been taken as evidence that the hippocampus has a time-limited role in the storage and retrieval of some forms of memory. This idea forms the central tenet of most contemporary views of system consolidation: the hippocampus functions as a temporary store for new information, but permanent storage depends on a broadly distributed cortical network[13,14]. Although we have a good understanding of the mechanisms that underlie the formation of new hippocampus-dependent memories, we know much less about how these memories are transformed into lifelong, or remote, memories in cortical networks. In this review, we begin by describing neuropsychological studies that have established a crucial role for the hippocampus in declarative memory. We then shift our focus to how these memories become consolidated in the cortex. Recent studies that use imaging and mouse genetic approaches, alongside traditional pharmacological and

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Box 1 | Synaptic versus system consolidation

Neurobiologists distinguish between two types of memory consolidation — one fast, one slow — and their different kinetic properties reflect qualitatively distinct underlying processes. For example, morphological changes are necessary for the initial stabilization of memories in hippocampal circuits. These changes, which include the growth of new synaptic connections as well as the restructuring of existing synaptic connections, take place in the first few hours that follow learning[1,4,5]. They depend on a cascade that is initiated by synaptic activation, which leads to the recruitment of second messenger systems, activation of transcription factors and, ultimately, synthesis of new proteins required for the structural changes. Any manipulation, whether it be behavioural (for example, retroactive interference), pharmacological (for example, protein synthesis blockers[142]) or genetic (for example, genetic disruption of cAMP responsive element binding protein[143]) that interferes with any part of this cascade will block memory formation. Just as the dictionary definition implies (that is, to consolidate is to strengthen or to secure), similar treatments applied outside the period of consolidation fail to disrupt the memory. The application of molecular biological approaches has been successful in identifying many of the molecular components of this cascade that are necessary for synaptic consolidation. These studies have shown that the molecular building blocks for memory are highly conserved across species (from *Aplysia californica* to *Drosophila melanogaster* to mice) and different memory systems[1].

However, consolidation can also occur at a system level. Consolidation, in this case, refers to a gradual (and usually slower) process of reorganization of the brain regions that support memory. System consolidation seems to be a feature of different types of memory: both declarative[7] and non-declarative[144] memories in humans show time-dependent reorganization at a system level, although their timescales are markedly different. Similar time-dependent reorganization is observed in invertebrates: memories for courtship conditioning in flies[145] and olfactory conditioning in bees[146] are both initially dependent on the antennal lobes, but with time the dependence shifts to the mushroom bodies. These examples indicate that system consolidation might be a general organizing principle across species as well as memory systems. As performance does not necessarily change over time, these changes might serve other purposes (such as memory stabilization).

anatomical lesion approaches, have begun to identify the network of cortical regions that support remote memory and the molecular events that are important for their consolidation. It is becoming clear from these analyses that the prefrontal cortex might have a privileged role in processing remote memory.

The hippocampus and declarative memory

Anterograde amnesia. In humans, MTL damage produces persistent anterograde amnesia — an inability to form new memories. In the most well-known case, patient H.M.[15] had parts of the MTL removed to alleviate a severe form of epilepsy[16]. This surgery successfully reduced the frequency of H.M.'s seizures. However, H.M.'s ablity to form new declarative memories — the type of memories that can be readily brought to conscious recollection — was profoundly impaired[7]. This impairment included an inability to form lasting memories of events (episodic memory) or to acquire new general knowledge or facts normally (semantic memory). In stark contrast, many other forms of mnemonic processing seemed to be largely spared. For example, he could acquire new visuomotor skills, and retain these for up to a year[17]. These, and other examples of spared non-declarative memory (for example, perceptual learning and repetition priming)[15,18] in patients such as H.M., who have damage to the MTL system, have led to the concept that memory is not a unitary phenomenon.

As specific memory deficits are associated with specific patterns of brain damage, these neuropsychological approaches have led to the concept that there are several anatomically distinct memory systems[19–22]. Although there is a consensus that MTL damage profoundly disrupts the formation of new declarative memories, there is considerable debate as to whether all forms of declarative memory are equally affected[23,24]. While some sparing of semantic learning following MTL damage indicates that this form of declarative learning might also depend on brain regions outside the MTL[23], a recent report indicates that patients with almost complete bilateral MTL lesions fail to acquire new semantic knowledge[24].

Retrograde amnesia. H.M.'s surgery also produced retrograde amnesia — a loss of the declarative memories that were acquired during the period that led up to his operation. However, the retrograde amnesia was not complete: although H.M. lost more recent memories, he retained memories from his early childhood[7]. Subsequent analyses revealed that H.M.'s retrograde amnesia extends back approximately 11 years[25]. The discovery that retrograde amnesia following MTL damage was incomplete indicated that the MTL might have a time-limited role in the storage and retrieval of declarative memories, and that, over time, memories might be permanently stored elsewhere.

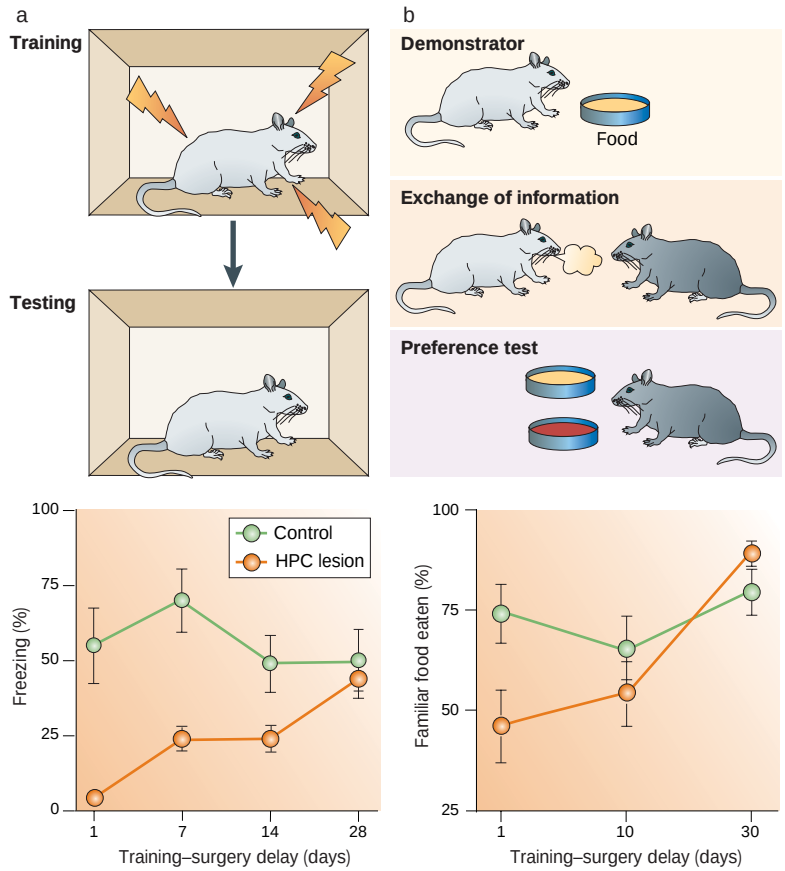
This important finding has subsequently been characterized in detail in many patients with similar brain lesions[13,18,26]. In these case studies, there is considerable variation in the length of the gradient, which ranges from several months to several years (or even decades). At least two factors might account for this variability. First, the length of the gradient seems to be related to the extent of the MTL damage[13]. For example, in two patients where damage was limited to the CA1 region of the hippocampus, retrograde amnesia only extended back 1–2 years[11]. By contrast, in patients with more extensive MTL damage (including the entire hippocampus and parts of the entorhinal cortex) retrograde amnesia covered at least 15 years[11]. In cases where damage extends beyond the MTL, retrograde amnesia can be FLAT, possibly because sites for permanent memory storage are also affected[13]. Second, the length of the gradient might be related to the particular type of declarative memory being tested[26,27–31]. For example, although detailed remote memories might be preserved in patients with MTL damage[27], in some reports they are not always as vivid when compared with healthy individuals[30,32]. To some, this indicates a dissociation between semantic and episodic memories — with an intact hippocampus always necessary for episodic (including contextual or spatial) details[26,33].

Modelling retrograde amnesia in animals. In humans, MTL damage produces temporally-graded retrograde amnesia for at least some forms of declarative memory. However, there are difficulties in studying retrograde amnesia in patients with brain damage. Because these studies rely on retrospective tests, it is difficult to compare performance across time points. In addition,

MEDIAL TEMPORAL LOBE (MTL). A collection of anatomically connected regions that have an essential role in declarative memory (conscious memory for facts and events). The MTL includes the hippocampal region (CA fields, dentate gyrus and subicular complex) and adjacent entorhinal, perirhinal and parahippocampal cortices. The function and organization of the MTL seems to be conserved in humans, non-human primates and rodents.

TEMPORALLY-GRADED RETROGRADE AMNESIA A condition associated with memory loss for past events. Most often associated with damage to the medial temporal lobe, memory loss for more recent events is more pronounced than for the distant past.

Box 2 | Two behavioural models of system consolidation in rodents



Contextual fear conditioning (panel **a**) is a form of Pavlovian conditioning where animals learn an association between a distinctive place (context) and an aversive event (shock)[68]. When placed back into the same context (but not dissimilar contexts), rodents show a range of conditioned fear responses, including freezing. An attractive feature of contextual fear conditioning is that a single training experience is enough to produce a memory that can last for a lifetime[147]. Freezing behaviour is thought to be adaptive because, in the wild, absence of movement would reduce the likelihood of detection by a predator. Electrolytic lesions of the hippocampus (HPC) produce a temporally-graded retrograde amnesia for contextual fear memories in rats[42].

In the socially-acquired food preference task (panel **b**), animals learn about potential food sources by sampling those sources on the breath of littermates. During training rodents interact with a 'demonstrator' rodent that has recently sampled a new, flavoured food. After some delay, when given the choice between two foods, rodents show a preference for the food that they smelled on the breath of the demonstrator rodent. This preference lasts for up to several weeks[38], which makes this task appropriate for studies of system consolidation. This type of learning might be adaptive as it allows rodents to learn about the safety of different food sources[69]. Complete electrolytic lesions of the hippocampus (including the subiculum) produce a temporally-graded retrograde amnesia for socially-acquired food preference in rats[38]. Panel **a** adapted, with permission, from REF. 42 © (1992) American Association for the Advancement of Science. Panel **b** adapted, with permission, from REF. 38 © (2002) Society for Neuroscience.

the extent of the damage varies from one case to another, and lesions are rarely confined to the hippocampus[13]. To address some of these issues, animal models have been developed to enable researchers to study the relationship between hippocampal damage and retrograde amnesia. The main advantage of this approach is that it allows retrograde amnesia to be studied in a prospective manner — the extent of the lesion can be controlled, as can what is learned and when. More than 30 studies[34–67] have directly investigated the impact of disrupting function in the hippocampus and related structures on recent and remote memories (online supplementary information TABLE 1). In these studies, several behavioural models have been used to assess memory, including contextual fear conditioning[68] and socially-acquired food preference (a form of non-spatial learning)[69] (BOX 2). Although there are many differences between these tasks in terms of stimulus properties, motivation and performance demands, they share some unifying features with human declarative memory. All these tasks require animals to represent complex relations among stimuli and/or to form memories that integrate contextual, spatial or temporal information[70].

Typically, these studies show that disrupting hippocampal function preferentially affects recent, rather than remote, memories. Temporally-graded retrograde amnesia has now been shown across a wide range of species, in a broad range of protocols, using a variety of lesion methods (including pharmacological[44,48,59,60] or genetic[49,54] approaches) and following extensive hippocampal lesions (including the subiculum)[34,38], as well as entorhinal[36,37] and perirhinal[41,53] cortex lesions. In these studies, the length of the gradient varies from a few days to several weeks, which is much shorter than that seen in humans. Although systematic studies have not been carried out, the length of the gradient probably depends on factors such as species, complexity of behavioural task, amount of training and the type, extent and location of lesion. It should be noted that, as in humans, temporally-graded retrograde amnesia is not always observed. In some of these cases, failure to observe a gradient is probably confounded by poor performance of control animals in the remote memory test[35,41,67]. In others, extra-hippocampal damage, possibly affecting sites of permanent storage, might account for deficits at remote, as well as recent, time points[71]. Finally, in more demanding spatial memory tests, the hippocampus might always be necessary for topographical details[62,72] or navigational (path integration[61,62,73]) aspects of task performance.

Models of system consolidation

Examples of temporally-graded retrograde amnesia in both humans and animals have led to system-based models of consolidation. Marr[74,75] formulated the first model to account for system consolidation. He proposed that the hippocampus rapidly stores the day's events before the information is transferred to the cortex for subsequent reorganization and reclassification. Marr further proposed that the transfer process depended on REPLAY of waking patterns of neural activity during sleep.

The ideas that the hippocampus is a temporary repository, that waking patterns of neural activity are reinstated or replayed during sleep, and that the cortex is important in extracting statistical structure (semantic knowledge) form the bases of contemporary models of

FLAT
A term used to describe retrograde amnesia when both recent and remote memory are similarly impaired.

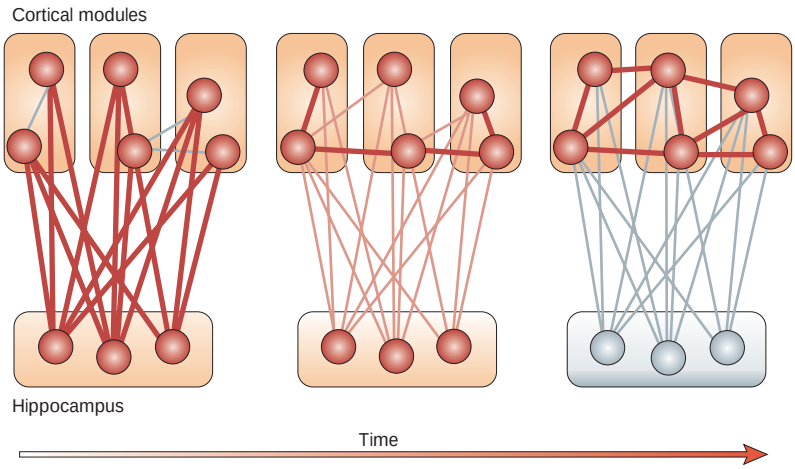


Figure 1 | **Standard consolidation model.** Encoding of perceptual, motor and cognitive information initially occurs in several specialized primary and associative cortical areas. The hippocampus integrates information from these distributed cortical modules that represents the various features of an experience, and rapidly fuses these features into a coherent memory trace[70,127]. Successive reactivation of this hippocampal–cortical network leads to progressive strengthening of cortico-cortical connections (for example, by strengthening existing cortico-cortical connections or establishing new ones). Incremental strengthening of cortico-cortical connections eventually allows new memories to become independent of the hippocampus and to be gradually integrated with pre-existing cortical memories[13,14]. A key feature of this model is that changes in the strength of the connections between the hippocampal system and the different cortical areas are rapid and transient, whereas changes in the connections between the cortical areas are slow and long-lasting[13,14].

memory formation[13,14] (FIG. 1). According to these models, experience is initially encoded in parallel in hippocampal and cortical networks. Subsequent reactivation of the hippocampal network reinstates activity in different cortical networks. This coordinated replay across hippocampal–cortical networks leads to gradual strengthening of cortico-cortical connections, which eventually allows new memories to become independent of the hippocampus and to be gradually integrated with pre-existing cortical memories. In these models, memories are assumed to decay more rapidly in the hippocampus than in the cortex.

An alternative view is based on two observations. First, MTL damage can produce ungraded retrograde amnesia for some types of declarative memory, such as autobiographical/episodic[30,76] and detailed spatial memories[32,62]. Second, the recall of detailed, remote autobiographical/episodic memories engages the hippocampus[77–80]. To account for these observations, the multiple trace theory (BOX 3) proposes that, although experience is initially encoded in distributed hippocampal–cortical networks, the hippocampus is always required for rich contextual or spatial detail[26]. This theory predicts that complete hippocampal lesions should produce temporally-graded retrograde amnesia for only semantic (and not episodic) memories[33]. However, the finding that patient E.P., who has extensive bilateral MTL lesions, has excellent autobiographical and spatial memories from his youth[31] is inconsistent with this prediction. At present, there is some debate about whether spared remote memories in patients like E.P. are as vivid and detailed as in healthy subjects[32].

REPLAY
Recapitulation of experience-dependent patterns of neural activity previously observed during awake periods.

SLOW-WAVE SLEEP
(SWS). Stage of non-REM deep sleep that is characterized by the presence of high-amplitude, slow delta waves of brain activity.

RAPID EYE MOVEMENT
(REM). A period of sleep, during which dreaming is thought to occur. REM sleep is characterized by increased brain-wave activity, bursts of rapid eye movement, accelerated respiration and heart rate and muscle relaxation.

HIPPOCAMPAL PLACE CELLS
Cells in the hippocampus that fire in a location-specific manner. These cells are thought to form the basis of cognitive maps, which allow animals to navigate through their environment.

RIPPLES
High frequency (~200 Hz) oscillations of neuronal activity which last 30–200 ms and occur in cells of the CA1 region of the hippocampus during periods of slow-wave sleep and behavioural immobility.

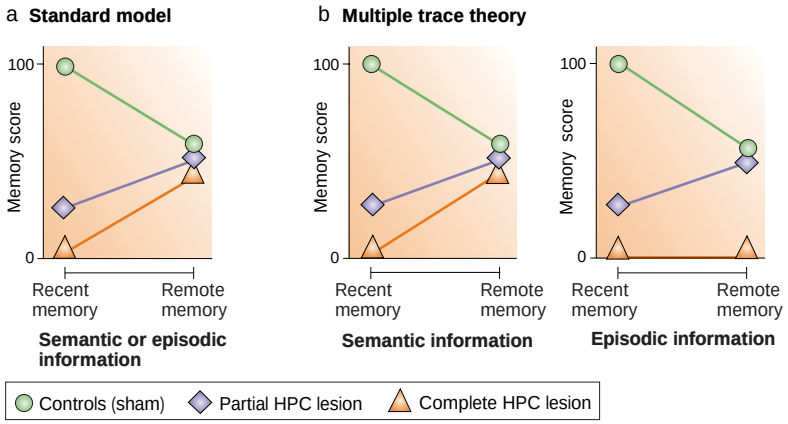
Memory reactivation

Cellular correlates of memory reactivation. Memory reactivation is the core mechanism in consolidation models. Reactivation of the hippocampal memory trace is thought to lead to the reinstatement of experience-dependent patterns of neural activity in the cortex, and subsequent stabilization and refinement of cortical traces. This iterative process is proposed to lead, eventually, to storage and recall becoming completely dependent on the cortex, and independent of the hippocampus. Memories can be reactivated during either 'online' states (such as task-relevant situations) or 'offline' states (such as during sleep or quiet wakefulness/day dreaming).

Indirect evidence for the idea that memory replay during sleep contributes to consolidation comes from human studies documenting the beneficial effects of sleep on memory. For example, brief naps or overnight sleep improve various forms of non-declarative memory including motor skills, visual and texture discrimination learning[81–83], and some forms of declarative memory[84]. Furthermore, overnight sleep can restore 'lost' memories[85] and even enhance 'insight'[86]. However, the relative contributions of different sleep phases (for example, SLOW-WAVE SLEEP (SWS) and RAPID EYE MOVEMENT (REM) sleep) to the consolidation of declarative and non-declarative memory remain uncertain[87,88].

More direct evidence comes from demonstrations that patterns of brain activity that are associated with earlier learning are selectively replayed during subsequent sleep in humans[89–91] and other species such as non-human primates[92], rodents[93–99] and songbirds[100]. In a series of important experiments, McNaughton, Wilson and colleagues showed that coordinated replay occurs in the hippocampus and in both hippocampal–cortical and cortico-cortical networks[101,102]. When the activity of HIPPOCAMPAL PLACE CELLS was recorded during spatial exploration in rats, cells that were co-active during exploration showed correlated firing patterns during SWS[97]. Along with other examples, this study shows that replay of hippocampal CA1 firing patterns can occur in subsequent rest or sleep states. Furthermore, hippocampal replay retains the original temporal order, and occurs preferentially during high frequency bursts of activity known as sharp-wave RIPPLES[93–99]. Although this high frequency oscillatory activity might promote strengthening of synaptic connections in the hippocampus, it is also thought to coordinate memory consolidation in target cortical regions. Consistent with this, hippocampal ripple activity occurs in temporal correlation with cortical slow-wave SPINDLES recorded in the medial prefrontal cortex[94]. Such coordinated replay of experience-dependent activity during SWS in hippocampal–cortical[94,103] and cortico-cortical[92] networks could promote the gradual stabilization of memory in the cortex. Future studies might further strengthen the link between experience-dependent replay in sleep and memory consolidation by showing that blocking this activity impairs memory.

Box 3 | Multiple trace theory



Multiple trace theory (MTT)[26] was proposed in 1997 as an alternative to standard consolidation models. At the heart of the debate is how to account for instances where MTL damage produces extensive retrograde amnesia. Although one argument is that flat gradients are associated with extensive damage to extra-hippocampal regions, which affect possible sites of permanent storage[13,18], Nadel and Moscovitch argued that the length of the gradient depended on the extent of hippocampal damage as well as the type of memory being probed. In particular, they noted that when damage included the whole hippocampal formation, retrograde amnesia for autobiographical (episodic) information was extensive, spanning much of a subject's lifetime. These observations led to the formulation of MTT. HPC, hippocampus.

The main features of the multiple trace theory

- Memories are encoded in hippocampal–cortical networks
- Memory reactivation leads to the generation of multiple traces in the hippocampus, which are linked to cortical networks
- Traces in the hippocampus provide spatial and temporal context
- Traces in the cortex are context-free (or semantic) in nature
- Retrieval of contextually rich episodic memories always depends on hippocampal–cortical networks
- Retrieval of remote semantic memories is possible in the absence of a functional hippocampus

According to this model, there are two conditions in which hippocampal damage might be associated with temporally-graded retrograde amnesia. Incomplete hippocampal lesions should preferentially affect recent rather than remote episodic or semantic memories, as trace proliferation should render older memories more resistant to hippocampal damage. Complete hippocampal lesions should abolish all episodic memories, regardless of their age. Furthermore, semantic components of remote memories might be spared even after complete hippocampal lesions. Predictions of standard models (**a**) and MTT (**b**) are contrasted above.

This theory shares one important assumption with standard consolidation models — that is, reactivation of memories initiates a process of reorganization. Where it differs is in terms of the locus of this reorganization. Although standard models predict that reorganization occurs in cortical networks, MTT predicts that reactivation should also lead to the generation of new traces within the hippocampus.

SPINDLES
Low frequency oscillations (7–14 Hz) of neuronal activity which last 1–4 s and occur in thalamic and neocortical networks during slow-wave sleep.

Molecular correlates of memory reactivation. Successive reactivations are thought to promote gradual remodelling of the hippocampal–cortical circuits that support memory. Around 100 known genes (and ~400 unidentified genes) have been shown to be upregulated during sleep, independent of circadian time[104]. It is likely that at least some of these genes are involved in stabilizing changes in synaptic strength and structure in reactivated memory circuits. One gene that is regulated in an experience-dependent manner during sleep is ZIF268. ZIF268 is a transcription factor that regulates long-term plasticity and stabilization of retrieved memories[105,106]. For example, after rats had explored a novel environment, upregulation of ZIF268 was observed, during subsequent sleep, in the hippocampus as well as in various cortical regions such as the piriform and frontal cortices[107]. Similarly, the induction of long-term potentiation (LTP) in the dentate gyrus in awake, behaving rats led, during subsequent sleep, to upregulation of ZIF268 in various cortical regions, including the entorhinal, auditory, somatosensory and frontal cortices[108]. Importantly, tetracaine-induced inactivation of the hippocampus prior to the onset of REM sleep blocks the upregulation of ZIF268 in these cortical regions. This indicates that gene expression in the cortex might be under the control of the hippocampus and, therefore, that cortical remodelling might depend on hippocampal activity — at least in the first few hours after training[108]. In these studies, upregulation of ZIF268 expression occurred during REM sleep. As replay predominantly occurs during SWS, this supports a two-stage model in which sustained high frequency activity during SWS leads to structural changes in cortical networks that are stabilized during subsequent REM sleep[93].

Mouse genetic studies. Data from these studies indicate that the gradual remodelling of hippocampal–cortical circuits depends on many rounds of synaptic modification. These changes are initiated in a reactivation-dependent manner (either during online or offline situations) and require expression of new genes. The idea that recurrent reactivation-dependent synaptic modifications in hippocampal and cortical networks are essential for the consolidation of memory[109,110] has been tested using genetic approaches in mice. To address the importance of maintaining the integrity of the hippocampal trace in the days after training, mice were generated in which the NR1 subunit of the NMDA (*N*-methyl-D-aspartate) receptor (NMDAR) in CA1 can be deleted in an inducible manner[49]. Mice with normal NMDAR function were trained in two hippocampus-dependent learning tasks: the MORRIS WATER MAZE and contextual fear conditioning. Suppressing NMDAR function in the week immediately after training blocked the formation of remote memories, although suppressing NMDAR function at later time points did not. Similarly, overexpression of a dominant-negative form of α-calcium/calmodulin kinase II (α-CaMKII)[111] in the forebrain in the week immediately after training, but not thereafter, blocks the formation of remote contextual fear memories[54]. These results are consistent with the idea that hippocampal replay is vital for memory consolidation in cortical networks. They identify a crucial week-long window during which normal hippocampal activity is important for memory consolidation. This time window is consistent with the observation that hippocampal lesions in the first week after training, but not

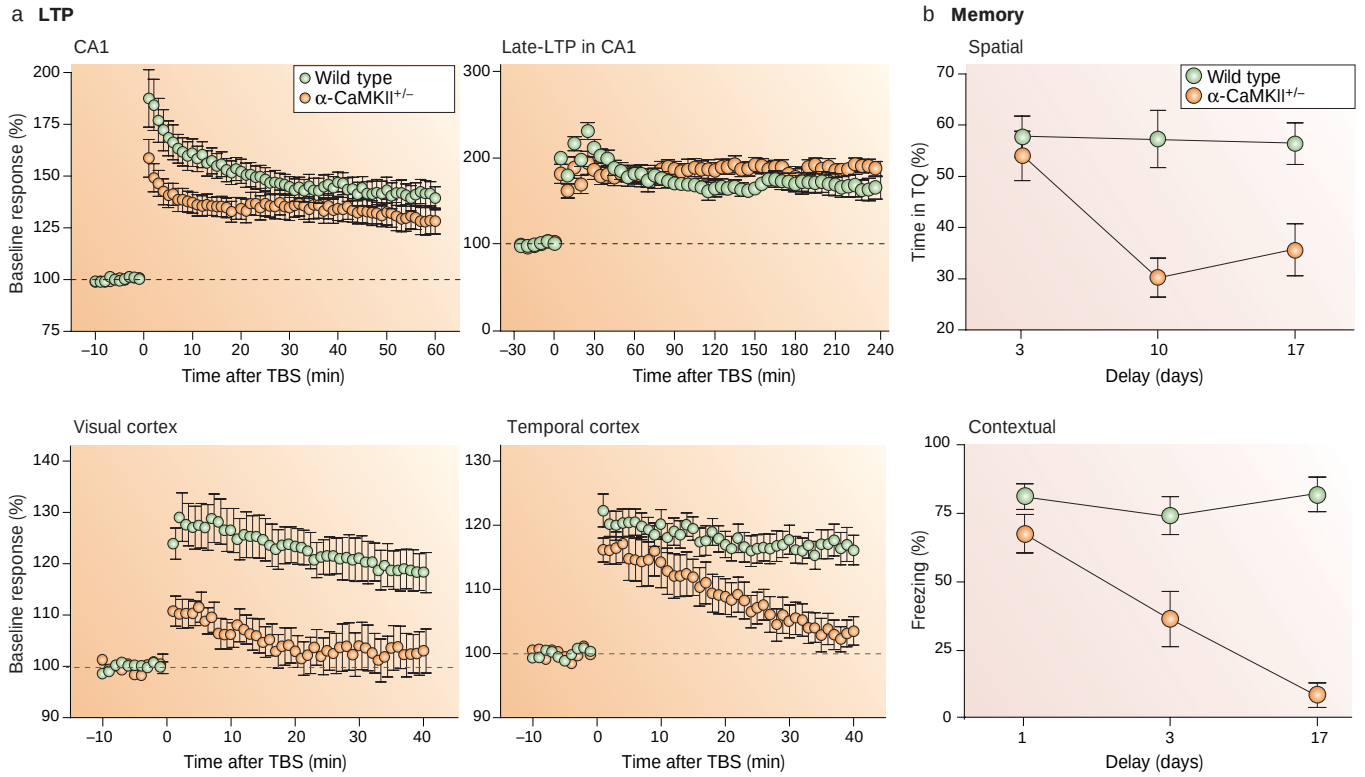


Figure 2 | **Deficient cortical plasticity and memory consolidation in α-CaMKII$^{+/-}$ mice. a** | Physiology experiments indicate that a heterozygous null mutation for α-CaMKII has dissociable effects on hippocampal and cortical plasticity. Both early and late long-term potentiation (LTP) is normal in the CA1 region of the hippocampus in brain slices from wild-type and α-CaMKII$^{+/-}$ mice. By contrast, LTP is impaired in the visual and temporal cortices in slices from α-CaMKII$^{+/-}$ mice. In these experiments, LTP was induced using theta-burst stimulation (TBS) protocols[113]. **b** | When trained in two forms of hippocampal-dependent learning (spatial learning in the water maze and contextual fear conditioning), α-CaMKII$^{+/-}$ mice show premature memory loss. At longer delays, α-CaMKII$^{+/-}$ mice spend less time searching the training quadrant (TQ) during the spatial probe test, and show decreased freezing in the training context, respectively. This indicates that normal α-CaMKII-dependent plasticity in the cortex might be crucial for the development of remote memories[113].

ZIF268
ZIF268 is a transcription factor that regulates the expression of many genes that have diverse cellular functions. Expression of ZIF268 correlates with neuronal firing and is, therefore, commonly used as a marker of neuronal activity.

MORRIS WATER MAZE
A task used to assess spatial memory, most commonly in rodents. Animals use an array of extra-maze cues to locate a hidden escape platform that is submerged below the water surface. Learning in this task is hippocampus-dependent.

α-CaMKII
α-calcium/calmodulin-dependent protein kinase II (α-CaMKII) is a signalling enzyme activated by Ca^{2+} influx through the NMDA (*N*-methyl-D-aspartate) receptor. It is expressed in excitatory forebrain neurons and has a crucial role in neuronal plasticity.

thereafter, abolish contextual fear memories in rats[42], and indicates that proper maintenance of the hippocampal trace is essential for establishing remote memories in the cortex. The results also indicate that reactivation might initiate several rounds of NMDAR/α-CaMKII-dependent synaptic modification. This might re-stabilize reactivated traces in the hippocampus and remodel reactivated traces in the cortex[109,110].

Alternative approaches have focused on the role of cortical plasticity. During consolidation, the strengthening of cortico-cortical connections is thought to be crucial in allowing cortical memories to gain independence from the hippocampus. Therefore, disrupting cortical plasticity should hinder the formation of remote hippocampus-independent memories, and result in premature memory loss at extended retention delays. This prediction is supported by studies of two strains of mice with abnormal cortical function. Mice that are heterozygous for a null mutation of α-CaMKII (α-CaMKII$^{+/-}$ mice) have global deficits in cortical plasticity, but normal hippocampal plasticity[112] (FIG. 2). Accordingly, they show normal learning and memory at short retention delays (1–3 days) — time points at which memory would normally depend on the hippocampus. However, their memory is impaired at longer delays (10–50 days) when it would normally have become dependent on the cortex[113,114]. These data indicate that deficits in cortical plasticity might prevent the formation of hippocampus-independent memories in α-CaMKII$^{+/-}$ mice.

A similar pattern of memory loss was observed in mice that overexpress a dominant-negative mutant form of p21-activated kinase (PAK). PAK regulates spinogenesis in neuronal cultures[115], and altered spine structure and synaptic function are observed in mice that overexpress dominant-negative PAK[116]. These abnormalities were shown to be limited to the cortex, where neurons had fewer dendritic spines and an increased proportion of larger synapses. These alterations in synaptic architecture were associated with abnormal bidirectional plasticity (enhanced LTP and decreased long-term depression). When tested in the water maze, dominant-negative *Pak*-transgenic mice learned normally and had normal memory when tested 1 day later. However, their memory was impaired 21 days after training, which is consistent with abnormal cortical function. More rapid memory loss was observed when these mice were tested using contextual fear conditioning[116].

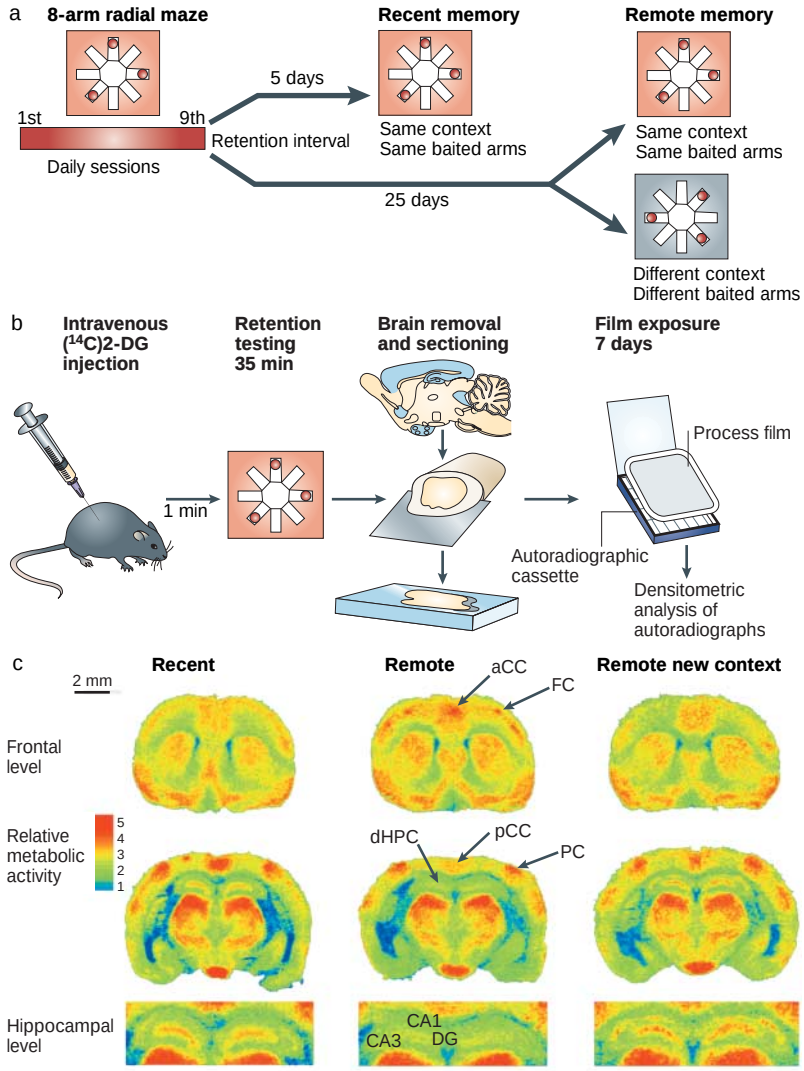


Figure 3 | **Time-dependent reorganisation of brain circuitry that underlies spatial discrimination memories. a** | Behavioural protocol. Mice were first trained to forage for food in an 8-arm radial maze. Training took place over 9 consecutive days, and the same 3 arms were baited on each day. Retention of this spatial discrimination memory was then tested either 5 days (recent memory) or 25 days (remote memory) later. An additional group of mice was tested at the remote time-point with the maze located in a different context. **b** | (^{14}C)2-DEOXYGLUCOSE ((^{14}C)2-DG) procedure. Testing-induced changes in neuronal activity were visualized using the (^{14}C)2-deoxyglucose autoradiographic method[148], a technique that is similar to position emission tomography (PET) scan imaging in humans. **c** | Colour-coded autoradiographs of coronal sections following recent memory test (left), remote memory test (centre) or remote memory test in the alternate context (right). The lower section of each panel shows a magnified view of the dorsal hippocampus (CA1, CA3 and dentate gyrus, DG). Increasing the retention interval resulted in decreased metabolic activity in the dorsal hippocampus (dHPC) and increased activity in several cortical areas including the frontal (FC) and anterior cingulate (aCC) cortices. These data indicate that the hippocampus has a transient role in memory storage, and that, over time, distributed cortical areas become capable of mediating recall of remote memories independently. By contrast, testing mice in the different context at the remote time-point re-engages the hippocampus, indicating that this brain region is required to encode new information. PC, parietal cortex; pCC, posterior cingulate cortex. Adapted, with permission, from REF. 118 © (1999) Macmillan Magazines Ltd.

Memory reorganization

Reactivation is thought to result in gradual remodelling of hippocampal–cortical memory networks and, consequently, changes in memory organization. Recent studies have used imaging approaches to track changes in networks over periods of weeks in healthy animals[44,114,117,118]. By testing memory at recent and remote time points, researchers have been able to characterize how the circuits that support memories are gradually reorganized over time, to identify sites of permanent storage in the cortex, and to provide evidence for reorganization at both regional and sub-regional levels.

Reorganization at the regional level. In the replay studies described above, there was typically only a 1-hour delay between neural activity recordings during behavioural tests and subsequent reactivation in either sleep or rest states. The longest delay used was 96 hours[93]. As system consolidation in animals takes place over weeks, it would be useful to track reactivation over a much longer time period. However, the probability that a specific trace is reactivated is thought to decline exponentially with time[14], which makes signal detection of offline reactivation a problem at longer delays. An alternative approach is to investigate memory reactivation during online states, such as after memory retrieval. This approach offers experimental control over the timing of the reactivation. Using this strategy, Bontempi and colleagues tracked changes in the organization of spatial discrimination memory in mice (FIG. 3). This group used either (^{14}C)2-deoxyglucose uptake to map changes in brain metabolic activity at the regional level[118], or expression of activity-regulated genes such as *c-fos* and *Zif268* to visualize changes in neuronal activity at the cellular level[44]. The recall of recent spatial memories was associated with activation of the hippocampus and entorhinal cortex. By contrast, the recall of remote spatial memories was predominantly associated with activation of cortical regions such as the prefrontal, frontal, anterior cingulate, retrosplenial and temporal cortices.

This same dissociation was observed in studies of contextual fear conditioning in mice. The expression of activity-dependent genes (*Zif268* and *c-fos*) was elevated in the hippocampus after the recall of recent contextual fear memories, whereas these genes were upregulated in multiple cortical regions, such as the anterior cingulate, prefrontal and temporal cortices, following recall of remote memories[114]. These imaging studies indicate that spatial and contextual memories are represented in distributed cortical networks. Activation of some cortical regions was observed following recall of recent memories[114], indicating that these cortical regions are important in the initial stages of consolidation. However, within cortical regions, recall of remote spatial and contextual memories was associated with activation of more expansive neuronal networks[44,114]. These expanded networks could reflect the integration of the current memory with pre-existing memories in the cortex — a process that might underlie the generation of semantic knowledge[14]. Finally, the hippocampus was not activated after recall of spatial or contextual remote memories, which indicates that cortical memories are independent of the hippocampus at these extended delays[13]. In fact, there is evidence that the hippocampus is inhibited (relative to controls) in these studies, which indicates that hippocampal activity might be actively suppressed during the recall of remote memories.

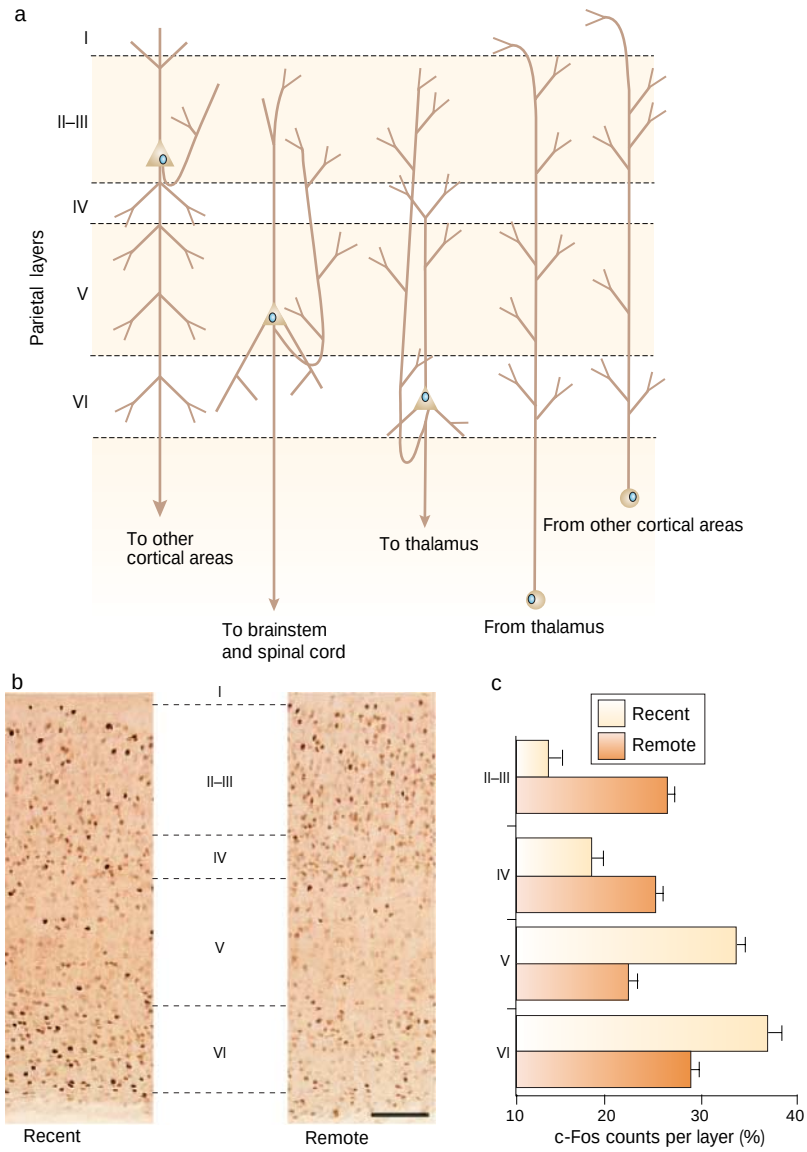


Figure 4 | **Laminar reorganization in the parietal cortex. a** | Schematic diagram of the parietal cortex showing local arborisation of dendrites and axons within layers, as well as more distant projections to and from the thalamus and other cortical areas. **b** | Mice were trained in a spatial discrimination procedure[44], and their memory tested either 1 day (recent memory) or 30 days (remote memory) later. Expression of the activity-dependent gene, *c-fos*, was used as a marker of neuronal activation. Immunoreactivity of c-Fos was pronounced in deep cortical layers (V–VI) following the recent memory test, and in more superficial layers (II–III and IV) following the remote memory test. **c** | Quantitative levels of c-Fos protein in the different cortical layers. Note the shift in activation from deep cortical layers V–VI to superficial layers II–III and IV as memories progressively mature. Remote memory storage in layers II–III is likely to involve slow changes in the strengthening of cortico-cortical connections by Hebbian mechanisms (coincident activation from cortico-cortical and thalamo-cortical inputs). Panel **a** adapted, with permission, from REF. 121 © Springer-Verlag, Heidelberg. Panels **b** and **c** adapted, with permission, from REF. 44 © American Association for the Advancement of Science.

The imaging studies provide evidence for time-dependent reorganization of the cortical circuits that support spatial and contextual memories. Such remodelling might be mediated by either weight plasticity (that is, rapid modification of existing connections between neurons) or wiring plasticity (that is, slower structural changes leading to the addition/elimination of synapses and modulation of axonal and dendritic growth)[119]. Growth-associated protein 43 (GAP43), a marker of synaptogenesis[120], is induced in the cortex following recall of both spatial and contextual fear memories[44,114], which is consistent with the idea that cortical consolidation involves rewiring. Furthermore, in α-CaMKII$^{+/-}$ mice, which have deficient cortical plasticity and deficits in remote contextual fear memory, time-dependent changes in cortical organization are not observed[114]. This indicates that normal cortical levels of α-CaMKII might be necessary for establishing hippocampus-independent contextual memories in the cortex.

Reorganization at the sub-regional level. Reorganization might also occur at the sub-regional level across different cortical layers. In this case, only cellular imaging approaches would be sufficiently sensitive to detect shifting patterns of activation within regions. Some cortical regions showed similar levels of activation after recall of recent or remote spatial discrimination memories[44]. However, in the parietal cortex, the pattern of neuronal activation shifted from the deep cortical layers V–VI to more superficial layers (II–III and IV) over time (FIG. 4). This is important from a functional point of view, because layers II and III are the origin and termination of most cortico-cortical connections[121]. Therefore, this laminar reorganization is consistent with the idea that new cortico-cortical connections are established over time. Such connections might support the coordinated activation of several cortical networks organized in 'CELL ASSEMBLIES'. This concept was originally proposed by Hebb[122] and has recently been supported in a study that showed coordinated replay of waking patterns of neural activity in three cortical regions (motor, somatosensory and parietal cortices)[92].

Reorganization at the sub-regional level could also explain why it has been difficult to find evidence for increased cortical activation in studies of human remote memory. Sub-regional changes in organization might not result in greater levels of activation at the regional level. Therefore, the lack of sub-regional spatial resolution of functional imaging techniques might make these techniques insensitive to more localized changes in organization[123].

Targeted disruption of system consolidation. Post-training, hippocampal lesions preferentially disrupt recent, but not remote, memories. Is it possible to affect system consolidation by targeting extra-hippocampal regions? For example, this might be achieved by creating a lesion that blocks dialogue between the hippocampus and cortex shortly after training. A lesion of this type would allow hippocampal memories to form normally, but prevent their subsequent consolidation in cortical networks. This prediction is supported by a recent study[65], in which it was shown that a lesion of the temporoammonic (TA) projection from layer III of the entorhinal cortex to the hippocampal CA1 region allows the hippocampus to function normally but disrupts cortical–hippocampal interactions. Rats with TA lesions showed normal spatial learning in the Morris water maze, and normal memory

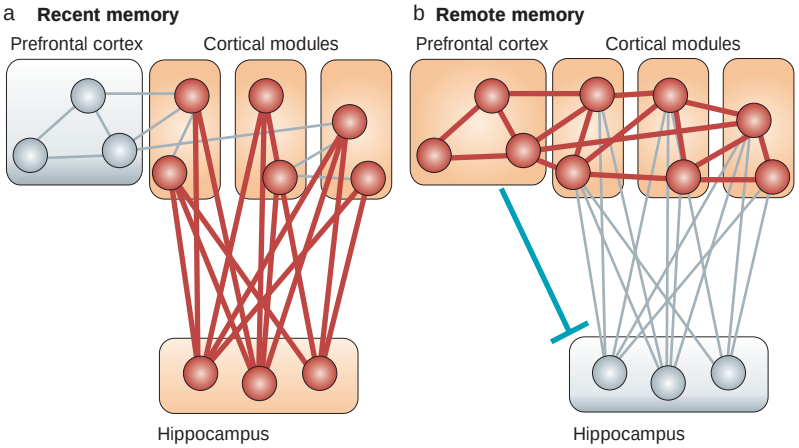


Figure 5 | **Prefrontal cortex and remote memory.** Results from imaging and inactivation studies using animal models indicate that the prefrontal cortex might have dual roles during remote memory recall. Initially, memories are encoded in hippocampal–cortical networks, as previously proposed[13,14,26]. At this early time point, the hippocampus is crucial in integrating information from distributed cortical modules, each representing individual components of a memory (**a**). However, as the memory matures connections between the different cortical modules are strengthened, allowing the memory to function independently of the hippocampus. At this later time point, the integrative role is assumed by the prefrontal cortex (**b**), via reciprocal connections with the sensory, motor and limbic cortices. Consistent with this model, lesions or pharmacological inactivation of the prefrontal cortex disrupt recall of remote, but not recent, memories. Conversely, lesions or pharmacological inactivation of the hippocampus produces the opposite pattern of results, that is, they impair recent, but not remote, memory. This model also proposes that the prefrontal cortex regulates hippocampal activity during memory recall. The hippocampus is normally active when processing the external environment. However, when incoming information matches a previously stored remote, cortical memory, the prefrontal cortex activity inhibits hippocampal activity by either direct[149] or indirect[22,150] connections to prevent encoding of redundant information. In the absence of a match condition, there is no inhibition and the hippocampus will be engaged as usual.

when tested one day later, which is consistent with spared hippocampal function. However, when the animals were tested after a 28 day delay, spatial memory was impaired. This indicates that cortical–hippocampal interactions are required for the formation of remote spatial memory. This requirement for ongoing cortical input through the TA pathway was time-limited since similar lesions 1 day (but not 21 days) after the completion of training blocked the formation of remote spatial memories.

An alternative strategy to disrupt remote, but not recent, memories is to target the cortical regions that are supposed to store remote memories. Several experiments have provided evidence that manipulations of the cortex preferentially affect remote, but not recent, memories[44,52,59,60,114]. In these studies, the prefrontal cortex (including the prelimbic and anterior cingulate cortices) has emerged as a particular hotspot for these effects[44,52,114]. In humans, the prefrontal cortex is thought to be important in strategic retrieval of stored information[124]. In animals, anatomical lesions and pharmacological inactivation of the prelimbic cortex and anterior cingulate cortex preferentially disrupt remote trace eye-blink conditioning and spatial discrimination memories, respectively[44,52]. Similarly, pharmacological inactivation of the anterior cingulate cortex preferentially blocks recall of remote contextual fear memories[114]. Brain imaging approaches indicate that remote contextual and spatial memories are encoded in a broad network of cortical regions in mice[44,114,118]. In principle, the distributed nature of remote memories should make them resistant to disruption by focal cortical lesions[125], as a sufficient portion of the network survives and can support the memory[14,122]. However, pharmacological and anatomical lesion studies indicate that the prefrontal cortex might be an essential node in this network[44,52,114].

The prefrontal cortex and remote memory

These imaging and inactivation studies have provided a more detailed picture of how memories are organized at different points in their life. Although the imaging data show that remote spatial and contextual memories might be supported by a broad cortical network, the inactivation experiments indicate that some parts of this network might be more important than others[44,52,114,118]. These studies have identified different regions of the prefrontal cortex as playing a crucial role during remote memory recall. The prefrontal cortex consists of several highly interconnected regions, including the anterior cingulate, prelimbic and infralimbic cortices. These regions are reciprocally connected to sensory, motor and limbic cortices[126], and are therefore ideally situated to integrate and synthesize information from a large number of different sources[121]. This potential for integration indicates that the ability of the prefrontal cortex to process remote memories might mirror that of the hippocampus to process recent memories (FIG. 5). Initially, the hippocampus is thought to integrate information from distributed, but relatively independent, cortical modules that represent the various features of an experience, and then to rapidly fuse these various features into a coherent memory trace[70,127]. Consistent with this, recall of recent memories is associated with activation of the hippocampus, and lesioning or inactivating the hippocampus preferentially disrupts the recall of recent memories. As memories mature, this integrative function might be transferred to the prefrontal cortex (and possibly other association cortices) through the strengthening of cortico-cortical connections. This process would allow cortical networks to function independently of the hippocampus, because the prefrontal cortex could integrate information from multiple cortical regions[128]. Consistent with this, inactivation or lesions of the prelimbic or anterior cingulate cortices block recall of remote memory[44,52,114], even in the presence of an intact hippocampus. Whether or not the prefrontal cortex is involved in storage or retrieval (for example, effortful recall[129]) of remote memories remains to be determined.

The prefrontal cortex might have another important function during memory recall (FIG. 5). Imaging studies in animals show that hippocampal activity is actively inhibited when remote spatial and contextual memories are successfully recalled[44,114,118]. From a functional point of view, this makes sense as it prevents the hippocampus from re-encoding existing memories, and it also indicates that the cortex might be more than just a passive, permanent repository for memory. Although the source of this inhibition is not known, the prefrontal cortex exerts top-down inhibitory control over posterior cortical

(^{14}C)2-DEOXYGLUCOSE
A functional brain imaging technique that is commonly used in rodents to estimate the level of neuronal activity in specific brain regions. The glucose analogue, (^{14}C)2-deoxyglucose, is administered to the animals and is subsequently taken up and trapped by active neurons.

CELL ASSEMBLIES
Large collections of neurons that show coordinated firing activity. Activation of any part of this network can reconstitute activity in the entire cell assembly. These cell assemblies are thought to form the basic neuronal code of representation.

regions during sensory processing[130] and voluntary recall[131] and might, therefore, exert similar influences over hippocampal function during the recall of remote memories. Whether inhibition occurs might depend on whether incoming information corresponds to a previously stored cortical memory. If retrieval is successful, hippocampal function will be rapidly inhibited. If there is a mismatch (for example, if the information has been forgotten), then there will be no inhibition and the hippocampus will be re-engaged. This idea is consistent with the existence of match and mismatch comparator neurons in the cortex, especially in the prefrontal cortex[132]. These predictions are partially supported in α-CaMKII$^{+/-}$ mice, which forget at extended retention delays. In remote memory tests, the hippocampus is re-engaged, which indicates that, in the absence of a 'match' condition in the cortex, the hippocampus comes back online in these mutant mice[114].

Future directions

In the past, neuropsychological studies of both humans and animals have established that damage to the MTL (including the hippocampus) produces temporally-graded retrograde amnesia for at least some forms of memory. These gradients imply that memories are gradually reorganized as they mature, and recent studies are starting to shed new light on how this reorganization progresses. These studies have used imaging and genetic techniques, as well as pharmacological and anatomical lesion approaches, to identify the network of cortical regions that supports remote memory, and the molecular events that are important for their consolidation. In the future, studies will focus on aspects of consolidation models that have been neglected and those that are controversial. We will briefly highlight three such areas.

First, although memories are rapidly encoded in hippocampal networks[70,127], it takes rather more time for them to be embedded in cortical networks and become independent of the hippocampus. This has led to the idea that the hippocampus is a fast learner and the cortex is a slow one[14,133]. Connectionist models propose that this helps to avoid catastrophic interference and protects existing cortical memories from being erased by newly formed ones. However, it is not clear which neurobiological differences between the cortex and hippocampus would account for this apparent division of labour. It is possible that different forms of plasticity predominate in the hippocampus and cortex, which could account for the differential learning rates[119,134]. In the hippocampus, rapid encoding might involve changing the weighting between already connected neurons (for example, by an LTP-like mechanism). In contrast, there are vast numbers of neurons in the cortex, yet only a small fraction of all possible connections among these neurons exist. The dominant form of cortical plasticity might involve the formation of new connections between previously unconnected neurons[119]. This form of wiring plasticity is important in experience-dependent remodelling in primary sensory cortices[135]. An intriguing possibility is that similar mechanisms might underlie the gradual consolidation of memories in associative cortical networks.

Second, Marr proposed that the hippocampus rapidly stores the day's events before this information is transferred to the neocortex. This hypothesis was motivated, in part, by consideration of the finite storage capability of the hippocampus[136]. Although the involvement of the hippocampus almost definitely exceeds 24 hours (and is permanent in some models[26,62]), a necessary component of most contemporary consolidation models is that redundant memories must be routinely cleared from the hippocampus. In connectionist models, the rate of clearance regulates how rapidly memories are consolidated in the cortex (with high decay rates being associated with shorter gradients[14]). However, little is known about how memories are erased. At the molecular and cellular levels, several candidate mechanisms have been identified. For example, in the absence of any behavioural manipulation, inhibiting protein phosphatase 1 (PP1)[137] or NMDARs[138] after learning reduces memory loss, which might indicate that basal PP1 and/or NMDAR-dependent processes gradually expunge memories. Another interesting possibility is that adult neurogenesis contributes to the clearance of hippocampal traces[139]. Newly formed neurons in the dentate gyrus rapidly make synaptic connections with neurons in CA3. The incremental addition of new neurons to this memory network might lead to trace instability and, eventually, erasure. In support of this model, retention of fear memories is facilitated in mice with reduced levels of adult neurogenesis[139]. Interestingly, adult neurogenesis occurs at a much slower rate in the cortex, consistent with proposed slower rates of decay[14].

As in humans studies, a central issue in animal experiments of system consolidation is whether the recalled memory is qualitatively the same or different at recent and remote time points. It is possible that performance in recent and remote memory tests might be based on different types of knowledge, with remote memories becoming more semantic in nature[32]. Using tests that effectively tax episodic components of memory at remote time points may or may not reveal a role for the hippocampus. Resolution of this debate depends on finding ways to distinguish episodic versus semantic components of memories in animal models[140,141].

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The authors declare no competing financial interests.

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