

THE ORGANIZATION OF RECENT AND REMOTE MEMORIES

Paul W. Frankland[‡] and Bruno Bontempi[§]*

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 are¹. 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 levels⁴ (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 time⁶. 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

**Programs in Integrative Biology and Brain & Behaviour, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.*

[‡]Department of Physiology and Institute of Medical Science, University of Toronto, Toronto, Canada.

[§]Laboratoire de Neurosciences Cognitives, CNRS UMR 5106,

Université de Bordeaux 1, Avenue des Facultés,

33405 Talence, France.

Correspondence to P.W.F. e-mail: paul.frankland@sickkids.ca

doi:10.1038/nrn1607

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 blockers¹⁴²) or genetic (for example, genetic disruption of cAMP responsive element binding protein¹⁴³) 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 systems¹.

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 declarative⁷ and non-declarative¹⁴⁴ 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 flies¹⁴⁵ and olfactory conditioning in bees¹⁴⁶ 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 epilepsy¹⁶. This surgery successfully reduced the frequency of H.M.'s seizures. However, H.M.'s ability to form new declarative memories — the type of memories that can be readily brought to conscious recollection — was profoundly impaired⁷. 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 visuospatial skills, and retain these for up to a year¹⁷. 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 MTL²³, a recent report indicates that patients with almost complete bilateral MTL lesions fail to acquire new semantic knowledge²⁴.

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 childhood⁷. Subsequent analyses revealed that H.M.'s retrograde amnesia extends back approximately 11 years²⁵. 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.

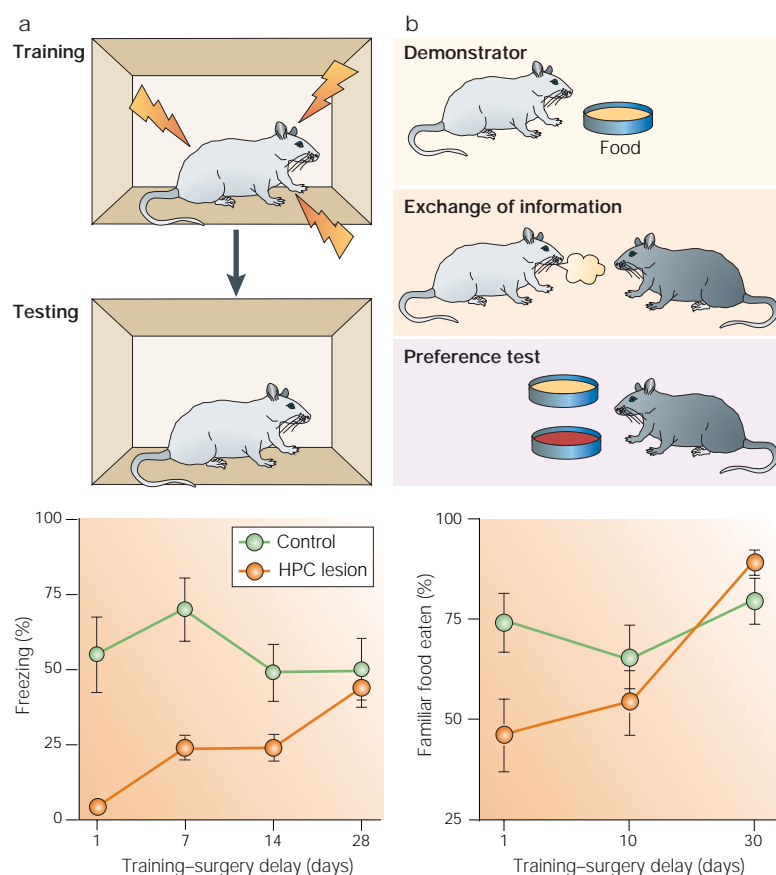
This important finding has subsequently been characterized in detail in many patients with similar brain lesions^{13,18,26}. In these case studies, there is considerable variation in the length of the gradient, which ranges from several months to several years (or even decades). At least two factors might account for this variability. First, the length of the gradient seems to be related to the extent of the MTL damage¹³. For example, in two patients where damage was limited to the CA1 region of the hippocampus, retrograde amnesia only extended back 1–2 years¹¹. 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 years¹¹. In cases where damage extends beyond the MTL, retrograde amnesia can be FLAT, possibly because sites for permanent memory storage are also affected¹³. 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 damage²⁷, 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 lifetime¹⁴⁷. 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 rats⁴².

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 weeks³⁸, 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 sources⁶⁹. Complete electrolytic lesions of the hippocampus (including the subiculum) produce a temporally-graded retrograde amnesia for socially-acquired food preference in rats³⁸. 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 hippocampus¹³. 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 conditioning⁶⁸ 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 information⁷⁰.

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^{144,48,59,60} 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 points⁷¹. 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.

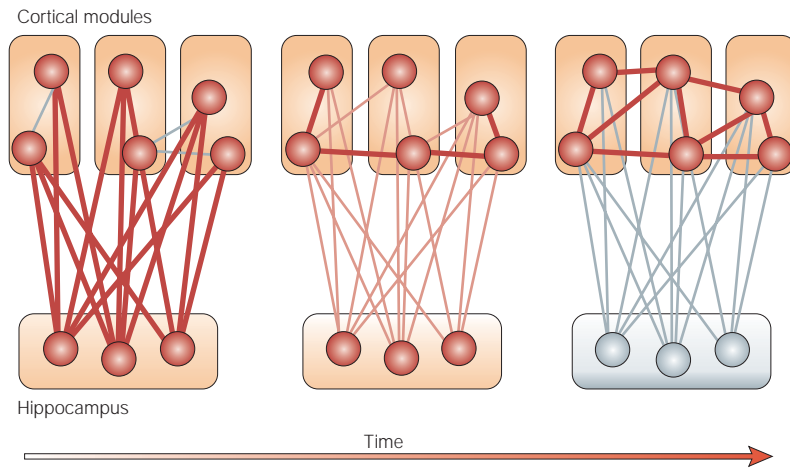


Figure 1 | Standard consolidation model. Encoding of perceptual, motor and cognitive information initially occurs in several specialized primary and associative cortical areas. The hippocampus integrates information from these distributed cortical modules that represents the various features of an experience, 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}.

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 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 detail²⁶. This theory predicts that complete hippocampal lesions should produce temporally-graded retrograde amnesia for only semantic (and not episodic) memories³³. However, the finding that patient E.P., who has extensive bilateral MTL lesions, has excellent autobiographical and spatial memories from his youth³¹ 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 subjects³².

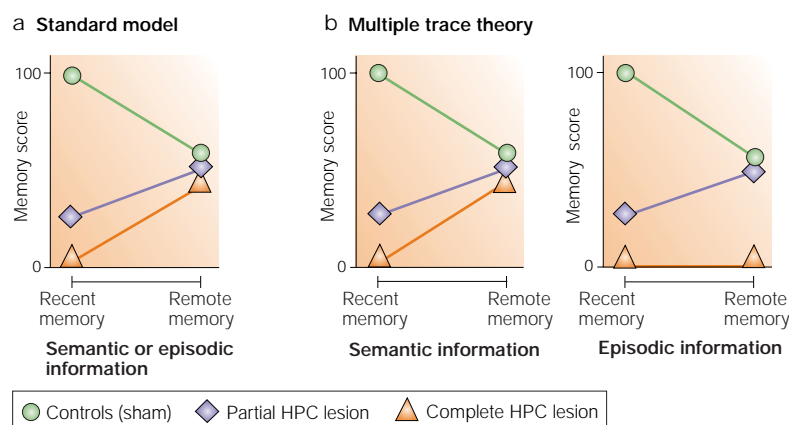
Memory reactivation

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 memory⁸⁴. Furthermore, overnight sleep can restore ‘lost’ memories⁸⁵ 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 primates⁹², rodents^{93–99} and songbirds¹⁰⁰. 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 SWS⁹⁷. 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 cortex⁹⁴. Such coordinated replay of experience-dependent activity during SWS in hippocampal–cortical^{94,103} and cortico-cortical⁹² 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.

Molecular correlates of memory reactivation. Successive reactivations are thought to promote gradual remodeling 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 time¹⁰⁴. 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 cortices¹⁰⁷. 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 cortices¹⁰⁸. 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 training¹⁰⁸. 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 sleep⁹³.

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 manner⁴⁹. 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 memories⁵⁴. 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

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.

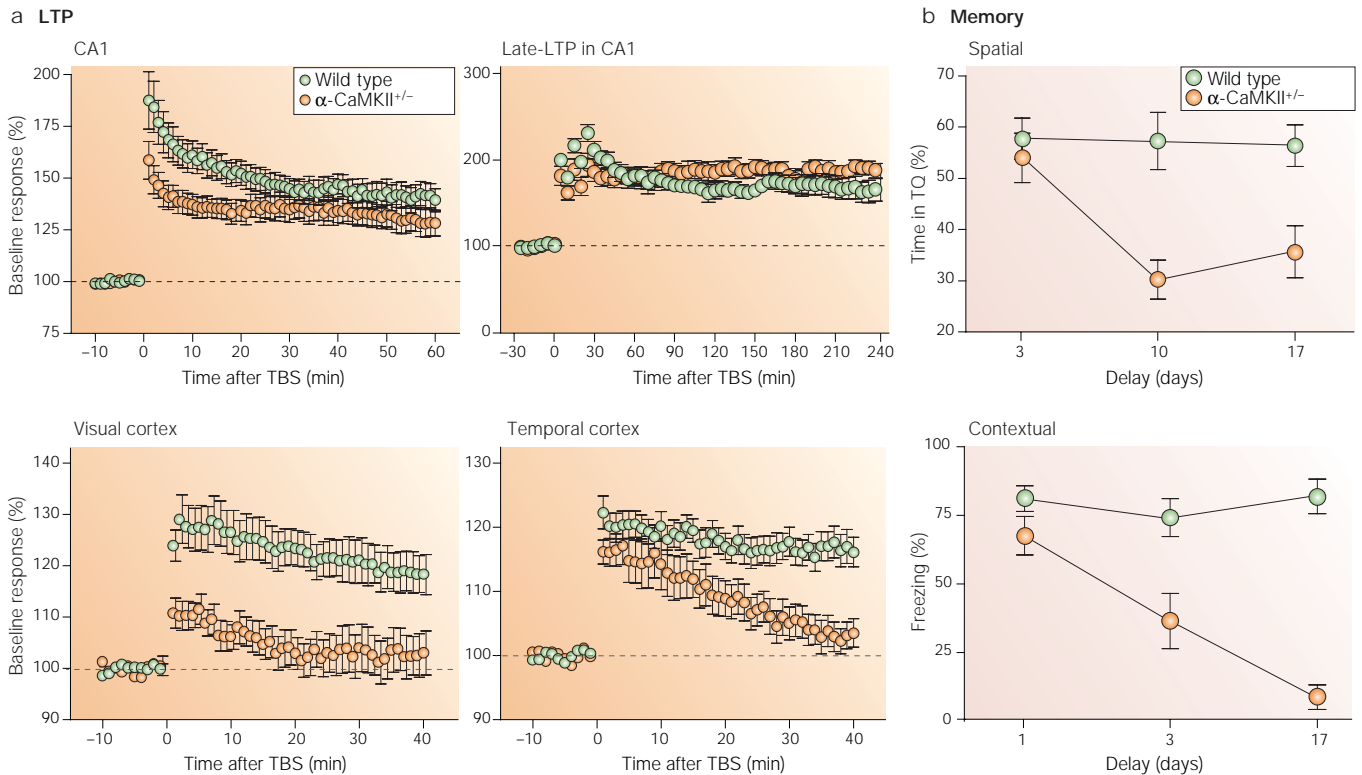


Figure 2 | Deficient cortical plasticity and memory consolidation in α -CaMKII^{+/-} mice. **a** | Physiology experiments indicate that a heterozygous null mutation for α -CaMKII has dissociable effects on hippocampal and cortical plasticity. Both early and late long-term potentiation (LTP) is normal 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) protocols¹¹³. **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 memories¹¹³.

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 Ca²⁺ 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 rats⁴², 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 plasticity¹¹² (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 cultures¹¹⁵, and altered spine structure and synaptic function are observed in mice that overexpress dominant-negative PAK¹¹⁶. 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 conditioning¹¹⁶.

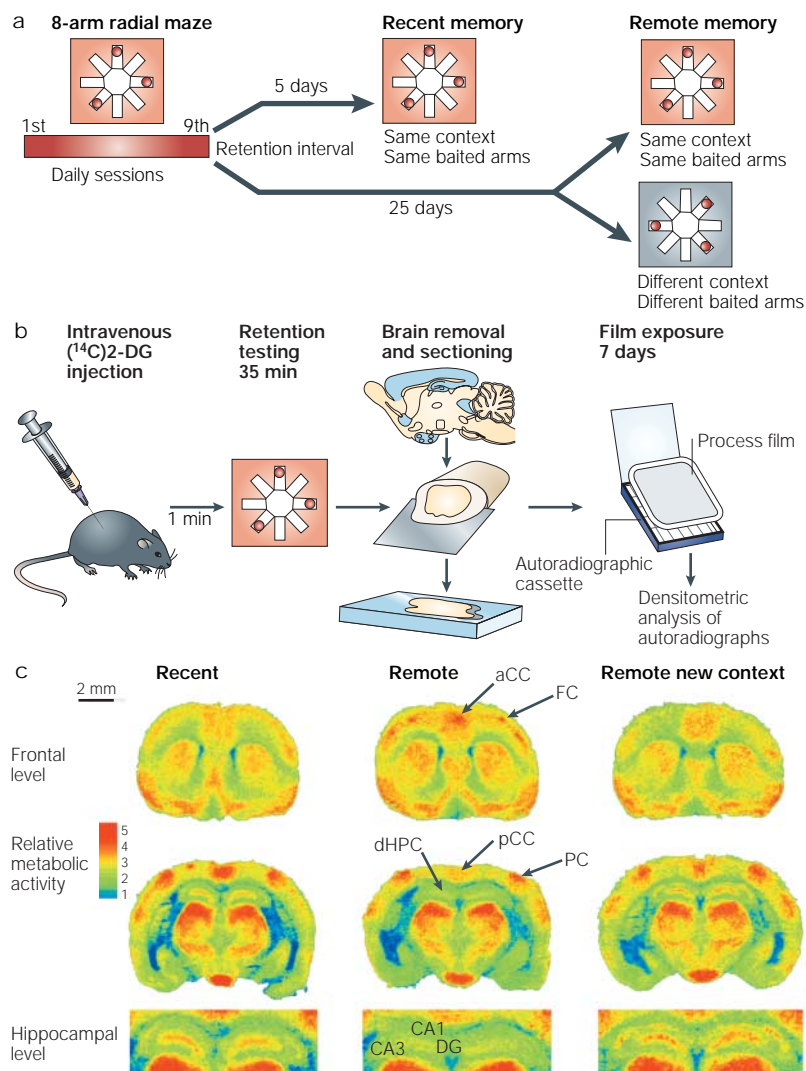


Figure 3 | Time-dependent reorganisation of brain circuitry that underlies spatial discrimination memories. **a** | Behavioural protocol. Mice were first trained to forage for food in an 8-arm radial maze. Training took place over 9 consecutive days, and the same 3 arms were baited on each day. Retention 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** | (¹⁴C)2-DEOXYGLUCOSE ((¹⁴C)2-DG) procedure. Testing-induced changes in neuronal activity were visualized using the (¹⁴C)2-deoxyglucose autoradiographic method¹⁴⁸, 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 hours⁹³. 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 time¹⁴, 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 (¹⁴C)2-deoxyglucose uptake to map changes in brain metabolic activity at the regional level¹¹⁸, or expression of activity-regulated genes such as *c-fos* and *Zif268* to visualize changes in neuronal activity at the cellular level⁴⁴. 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 memories¹¹⁴. 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 memories¹¹⁴, 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 knowledge¹⁴. 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 delays¹³. 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.

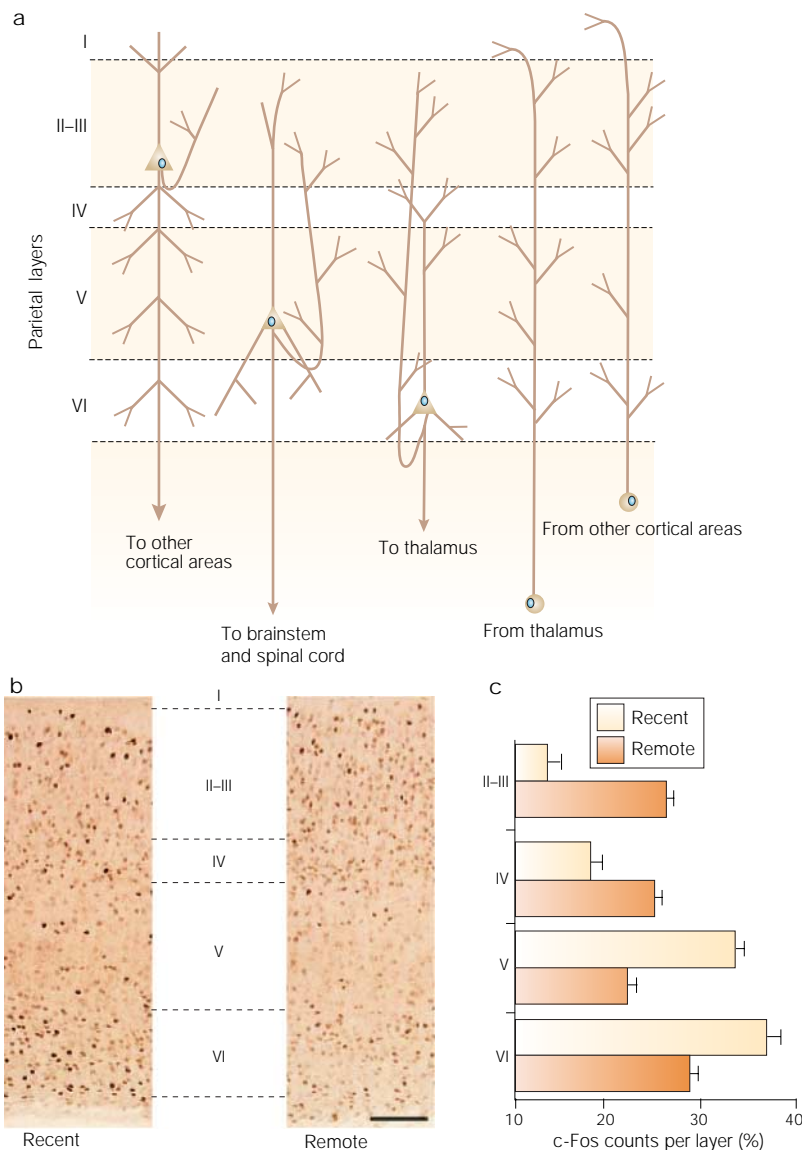


Figure 4 | Laminar reorganization in the parietal cortex. **a** | Schematic diagram of the parietal cortex showing local arborisation of dendrites and axons within layers, as well as more distant projections to and from the thalamus and other cortical areas. **b** | Mice were trained in a spatial discrimination procedure⁴⁴, 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 remodeling 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 synaptogenesis¹²⁰, 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 observed¹¹⁴. 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 memories⁴⁴. 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 connections¹²¹. 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 Hebb¹²² 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 organization¹²³.

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 study⁶⁵, 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

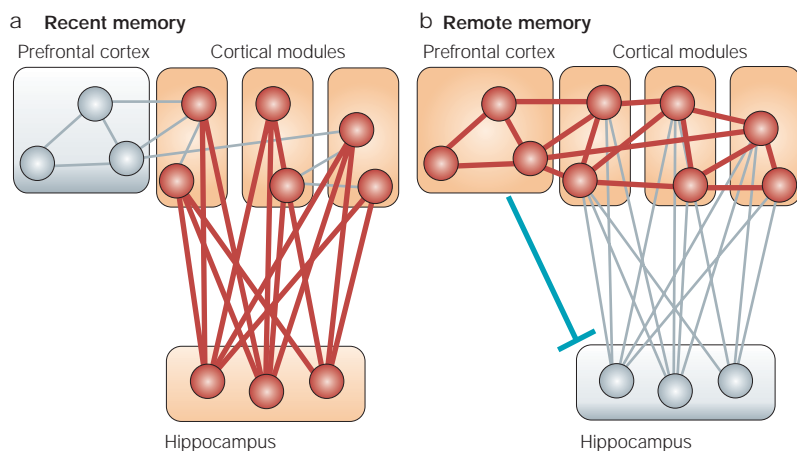


Figure 5 | Prefrontal cortex and remote memory. Results from imaging and inactivation studies using animal models indicate that the prefrontal cortex might have dual roles during remote memory recall. Initially, memories are encoded in hippocampal–cortical networks, as previously proposed^{13,14,26}. 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 direct¹⁴⁹ 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 information¹²⁴. 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 memories¹¹⁴. 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 lesions¹²⁵, 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 cortices¹²⁶, and are therefore ideally situated to integrate and synthesize information from a large number of different sources¹²¹. 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 regions¹²⁸. 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 recall¹²⁹) 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

¹⁴C-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, ¹⁴C-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 processing¹³⁰ and voluntary recall¹³¹ 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 cortex¹³². 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 mice¹⁴.

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 neurons¹¹⁹. This form of wiring plasticity is important in experience-dependent remodelling in primary sensory cortices¹³⁵. 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 hippocampus¹³⁶. 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 gradients¹⁴). 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 NMDARs¹³⁸ 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 traces¹³⁹. 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 neurogenesis¹³⁹. Interestingly, adult neurogenesis occurs at a much slower rate in the cortex, consistent with proposed slower rates of decay¹⁴.

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 nature³². 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}.

1. Squire, L. R. & Zola-Morgan, M. *Memory, Brain and Cognition* (Oxford University Press, Oxford, 1991).
2. Lechner, H. A., Squire, L. R. & Byrne, J. H. 100 years of consolidation — remembering Müller and Pilzecker. *Learn. Mem.* **6**, 77–87 (1999).
3. Müller, G. E. & Pilzecker, A. Experimentelle Beiträge zur Lehre vom Gedächtnis. *Z. Psychol. Ergänzungsband* **1**, 1–300 (1900).
4. Dudai, Y. The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* **55**, 51–86 (2004).

5. Ledoux, J. E. *Synaptic Self* (Viking, New York, 2001).
6. Ribot, T. *Diseases of Memory* (Appleton-Century-Crofts, New York, 1882).
7. Scoville, W. B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurochem.* **20**, 11–21 (1957).
8. Penfield, W. & Milner, B. Memory deficit produced by bilateral lesions in the hippocampal zone. *AMA Arch. Neurol. Psychiatry* **79**, 475–497 (1958).

9. Salmon, D. P., Lasker, B. R., Butters, N. & Beatty, W. W. Remote memory in a patient with circumscribed amnesia. *Brain Cogn.* **7**, 201–211 (1988).
10. Beatty, W. W., Salmon, D. P., Bernstein, N. & Butters, N. Remote memory in a patient with amnesia due to hypoxia. *Psychol. Med.* **17**, 657–665 (1987).
11. 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).

12. 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).
13. Squire, L. R. & Alvarez, P. Retrograde amnesia and memory consolidation: a neurobiological perspective. *Curr. Opin. Neurobiol.* **5**, 169–177 (1995).
This important paper provides a description of the standard view of system consolidation.
14. 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).
This landmark paper provides a thorough overview of connectionist models of learning and memory, focusing especially on the role of hippocampal-cortical interactions during the formation and consolidation of memories. The complementary concepts of the hippocampus as a fast learner and the cortex as a slow learner are developed.
15. Corkin, S. What's new with the amnesic patient H.M.? *Nature Rev. Neurosci.* **3**, 153–160 (2002).
16. Scoville, W. B. The limbic lobe in man. *J. Neurosurg.* **11**, 64–66 (1954).
17. Gabrieli, J. D., Corkin, S., Mickel, S. F. & Growdon, J. H. Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. *Behav. Neurosci.* **107**, 899–910 (1993).
18. Squire, L. R., Stark, C. E. & Clark, R. E. The Medial Temporal Lobe. *Annu. Rev. Neurosci.* **27**, 279–306 (2004).
19. Gaffan, D. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *J. Comp. Physiol. Psychol.* **86**, 1100–1109 (1974).
20. Hirsh, R. The hippocampus and contextual retrieval of information from memory: a theory. *Behav. Biol.* **12**, 421–444 (1974).
21. Nadel, L. & O'Keefe, J. In *Essays on the Nervous System* (eds Bellairs, R. & Gray, E. G.) 367–390 (Clarendon, Oxford, 1974).
22. Squire, L. R. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* **99**, 195–231 (1992).
23. O'Kane, G., Kensinger, E. A. & Corkin, S. Evidence for semantic learning in profound amnesia: an investigation with patient H.M. *Hippocampus* **14**, 417–425 (2004).
24. Bayley, P. J. & Squire, L. R. Failure to acquire new semantic knowledge in patients with large medial temporal lobe lesions. *Hippocampus* (in the press).
25. Sagar, H. J., Cohen, N. J., Corkin, S. & Growdon, J. H. Dissociations among processes in remote memory. *Ann. NY Acad. Sci.* **444**, 533–535 (1985).
26. Nadel, L. & Moscovitch, M. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr. Opin. Neurobiol.* **7**, 217–227 (1997).
This paper introduces the basic tenets of the multiple trace theory, challenges the standard model of system consolidation and provides original arguments to account for observations of flat retrograde amnesia gradients.
27. 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).
28. Manns, J. R., Hopkins, R. O. & Squire, L. R. Semantic memory and the human hippocampus. *Neuron* **38**, 127–133 (2003).
29. Rosenbaum, R. S., McKinnon, M. C., Levine, B. & Moscovitch, M. Visual imagery deficits, impaired strategic retrieval, or memory loss: disentangling the nature of an amnesic person's autobiographical memory deficit. *Neuropsychologia* **42**, 1619–1635 (2004).
30. Viskontas, I. V., McAndrews, M. P. & Moscovitch, M. Memory for famous people in patients with unilateral temporal lobe epilepsy and excisions. *Neuropsychology* **16**, 472–480 (2002).
31. Teng, E. & Squire, L. R. Memory for places learned long ago is intact after hippocampal damage. *Nature* **400**, 675–677 (1999).
32. Rosenbaum, R. S. *et al.* Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neurosci.* **3**, 1044–1048 (2000).
33. Nadel, L., Ryan, L., Hayes, S. M., Gilboa, A. & Moscovitch, M. in *Limbic and Association Cortical Systems — Basic, Clinical and Computational Aspects* (eds Ono, T. *et al.*) **1250**, 215–234 (Elsevier Science/Excerpta Medica International Congress Series, Amsterdam, 2003).
34. 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).
35. 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).
36. Cho, Y. H., Beracochea, D. & Jaffard, R. Extended temporal gradient for the retrograde and anterograde amnesia produced by ibotenate entorhinal cortex lesions in mice. *J. Neurosci.* **13**, 1759–1766 (1993).
37. Cho, Y. H. & Kesner, R. P. Involvement of entorhinal cortex or parietal cortex in long-term spatial discrimination memory in rats: retrograde amnesia. *Behav. Neurosci.* **110**, 436–442 (1996).
38. Clark, R. E., Broadbent, N. J., Zola, S. M. & Squire, L. R. Anterograde amnesia and temporally graded retrograde amnesia for a nonspatial memory task after lesions of hippocampus and subiculum. *J. Neurosci.* **22**, 4663–4669 (2002).
39. Debiec, J., LeDoux, J. E. & Nader, K. Cellular and systems reconsolidation in the hippocampus. *Neuron* **36**, 527–538 (2002).
40. Gaffan, D. Additive effects of forgetting and fornix transection in the temporal gradient of retrograde amnesia. *Neuropsychologia* **31**, 1055–1066 (1993).
41. Glenn, M. J., Nesbitt, C. & Mumby, D. G. Perirhinal cortex lesions produce variable patterns of retrograde amnesia in rats. *Behav. Brain Res.* **141**, 183–193 (2003).
42. Kim, J. J. & Fanselow, M. S. Modality-specific retrograde amnesia of fear. *Science* **256**, 675–677 (1992).
43. Kim, J. J., Clark, R. E. & Thompson, R. F. Hippocampotomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behav. Neurosci.* **109**, 195–203 (1995).
44. Maviel, T., Durkin, T. P., Menzaghi, F. & Bontempi, B. Sites of neocortical reorganization critical for remote spatial memory. *Science* **305**, 96–99 (2004).
45. Mumby, D. G. & Glenn, M. J. Anterograde and retrograde memory for object discriminations and places in rats with perirhinal cortex lesions. *Behav. Brain Res.* **114**, 119–134 (2000).
46. 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).
47. Ramos, J. M. Retrograde amnesia for spatial information: a dissociation between intra and extramaze cues following hippocampus lesions in rats. *Eur. J. Neurosci.* **10**, 3295–3301 (1998).
48. Riedel, G. *et al.* Reversible neural inactivation reveals hippocampal participation in several memory processes. *Nature Neurosci.* **2**, 898–905 (1999).
49. Shimizu, E., Tang, Y. P., Rampon, C. & Tsien, J. Z. NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. *Science* **290**, 1170–1174 (2000).
Genetic disruption of NMDAR function in the CA1 region of the hippocampus immediately following training blocks memory consolidation. This study is consistent with the idea that hippocampal replay drives memory consolidation, and shows that NMDAR-mediated mechanisms have a central role.
50. Sutherland, R. J. *et al.* Retrograde amnesia after hippocampal damage: recent vs. remote memories in two tasks. *Hippocampus* **11**, 27–42 (2001).
51. Takehara, K., Kawahara, S., Takatsuki, K. & Kirino, Y. Time-limited role of the hippocampus in the memory for trace eyeblink conditioning in mice. *Brain Res.* **951**, 183–190 (2002).
52. Takehara, K., Kawahara, S. & Kirino, Y. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. *J. Neurosci.* **23**, 9897–9905 (2003).
Using a trace eyeblink conditioning protocol, this study is the first to identify an important role for the prefrontal cortex in processing remote memory.
53. Thornton, J. A., Rothblat, L. A. & Murray, E. A. Rhinal cortex removal produces amnesia for preoperatively learned discrimination problems but fails to disrupt postoperative acquisition and retention in rhesus monkeys. *J. Neurosci.* **17**, 8536–8549 (1997).
54. Wang, H. *et al.* Inducible protein knockout reveals temporal requirement of CaMKII reactivation for memory consolidation in the brain. *Proc. Natl Acad. Sci. USA* **100**, 4287–4292 (2003).
55. Wig, K. A., Cooper, L. N. & Bear, M. F. Temporally graded retrograde amnesia following separate and combined lesions of the perirhinal cortex and fornix in the rat. *Learn. Mem.* **3**, 313–325 (1996).
56. Winocur, G. Anterograde and retrograde amnesia in rats with dorsal hippocampal or dorsomedial thalamic lesions. *Behav. Brain Res.* **38**, 145–154 (1990).
57. Winocur, G., McDonald, R. M. & Moscovitch, M. Anterograde and retrograde amnesia in rats with large hippocampal lesions. *Hippocampus* **11**, 18–26 (2001).
58. Zola-Morgan, S. M. & Squire, L. R. The primate hippocampal formation: evidence for a time-limited role in memory storage. *Science* **250**, 288–290 (1990).
Using circumscribed lesions of the hippocampal formation, this is the first study to provide evidence for graded retrograde amnesia in non-human primates.
59. Quilfield, J. A. *et al.* Different brain areas are involved in memory expression at different times from training. *Neurobiol. Learn. Mem.* **66**, 97–101 (1996).
60. Izquierdo, I. *et al.* Sequential role of hippocampus and amygdala, entorhinal cortex and parietal cortex in formation and retrieval of memory for inhibitory avoidance in rats. *Eur. J. Neurosci.* **9**, 786–793 (1997).
61. Clark, R. E., Broadbent, N. J. & Squire, L. R. The hippocampus and remote spatial memory in rats. *Hippocampus* (in the press).
62. 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* (in the press).
References 61 and 62 show that hippocampal lesions produce a flat retrograde amnesia for spatial (water maze) memories, which indicates that the expression of detailed spatial memories in rats always depends on hippocampal function.
63. 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).
64. Salmon, D. P., Zola-Morgan, S. M. & Squire, L. R. Retrograde amnesia following combined hippocampus-amygdala lesions in monkeys. *Psychobiology* **15**, 37–47 (1987).
65. Remondes, M. & Schuman, E. M. Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory. *Nature* **431**, 699–703 (2004).
This paper shows that lesioning the temporomammic input from the entorhinal cortex to the CA1 region of the hippocampus allows hippocampal memories to form normally, but prevents them from becoming consolidated in cortical networks.
66. Laurent-Demir, C. & Jaffard, R. Temporally graded retrograde amnesia for spatial information resulting from afterdischarges induced by electrical stimulation of the dorsal hippocampus in mice. *Psychobiology* **25**, 133–140 (1997).
67. Gaskin, S., Tremblay, A. & Mumby, D. G. Retrograde and anterograde object recognition in rats with hippocampal lesions. *Hippocampus* **13**, 962–969 (2003).
68. Fanselow, M. S. Contextual fear, gestalt memories, and the hippocampus. *Behav. Brain Res.* **110**, 73–81 (2000).
69. Galef, B. G. Jr. Food selection: problems in understanding how we choose foods to eat. *Neurosci. Biobehav. Rev.* **20**, 67–73 (1996).
70. Eichenbaum, H. Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron* **44**, 109–120 (2004).
71. Anagnostaras, S. G., Gale, G. D. & Fanselow, M. S. The hippocampus and Pavlovian fear conditioning: reply to Bast *et al.* *Hippocampus* **12**, 561–565 (2002).
72. Winocur, G., Moscovitch, M., Fogel, S., Rosenbaum, R. S. & Sekeres, M. Preserved spatial memory following hippocampal lesions: effects of extensive experience in a complex environment. *Memory Disorders Research Society*, New York, Oct 10 2004.
73. Whishaw, I. Q. & Maaswinkel, H. Rats with fimbria-fornix lesions are impaired in path integration: a role for the hippocampus in 'sense of direction'. *J. Neurosci.* **18**, 3050–3058 (1998).
74. Marr, D. A theory for cerebral neocortex. *Proc. R. Soc. Lond. B* **176**, 161–234 (1970).
75. Marr, D. Simple memory: a theory for archicortex. *Philos. Trans. R. Soc. Lond. B* **262**, 23–81 (1971).
76. Cipolletti, L. *et al.* Long-term retrograde amnesia... the crucial role of the hippocampus. *Neuropsychologia* **39**, 151–172 (2001).
77. 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).
78. 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).
79. 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).
80. Maguire, E. A. & Frith, C. D. Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. *J. Neurosci.* **23**, 5302–5307 (2003).
81. Mednick, S. C. *et al.* The restorative effect of naps on perceptual deterioration. *Nature Neurosci.* **5**, 677–681 (2002).

82. Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A. & Stickgold, R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron* **35**, 205–211 (2002).

83. Stickgold, R., James, L. & Hobson, J. A. Visual discrimination learning requires sleep after training. *Nature Neurosci.* **3**, 1237–1238 (2000).

84. Gais, S. & Born, J. Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proc. Natl Acad. Sci. USA* **101**, 2140–2144 (2004).

85. Fenn, K. M., Nusbaum, H. C. & Margoliash, D. Consolidation during sleep of perceptual learning of spoken language. *Nature* **425**, 614–616 (2003).

86. Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. Sleep inspires insight. *Nature* **427**, 352–355 (2004).

87. Walker, M. P. & Stickgold, R. Sleep-dependent learning and memory consolidation. *Neuron* **44**, 121–133 (2004).

88. Vertes, R. P. Memory consolidation in sleep: dream or reality. *Neuron* **44**, 135–148 (2004).

89. Maquet, P. *et al.* Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neurosci.* **3**, 831–836 (2000).

90. Huber, R., Ghilardi, M. F., Massimini, M. & Tononi, G. Local sleep and learning. *Nature* **430**, 78–81 (2004).

91. Peigneux, P. *et al.* Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* **44**, 535–545 (2004).

92. Hoffman, K. L. & McNaughton, B. L. Coordinated reactivation of distributed memory traces in primate neocortex. *Science* **297**, 2070–2073 (2002).
This study provides the first evidence that coordinated replay occurs in multiple cortical regions and supports the idea that offline reactivation of distributed cortical traces is crucial for cortical consolidation.

93. Ribeiro, S. *et al.* Long-lasting novelty-induced neuronal reverberation during slow-wave sleep in multiple forebrain areas. *PLoS Biol* **2**, E24 (2004).

94. Slapas, A. G. & Wilson, M. A. Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* **21**, 1123–1128 (1998).

95. Lee, A. K. & Wilson, M. A. Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* **36**, 1183–1194 (2002).

96. Louie, K. & Wilson, M. A. Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* **29**, 145–156 (2001).

97. Wilson, M. A. & McNaughton, B. L. Reactivation of hippocampal ensemble memories during sleep. *Science* **265**, 676–679 (1994).

98. Skaggs, W. E. & McNaughton, B. L. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* **271**, 1870–1873 (1996).

99. 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).

100. Dave, A. S. & Margoliash, D. Song replay during sleep and computational rules for sensorimotor vocal learning. *Science* **290**, 812–816 (2000).

101. Wilson, M. A. Hippocampal memory formation, plasticity, and the role of sleep. *Neurobiol. Learn. Mem.* **78**, 565–569 (2002).

102. Sutherland, G. R. & McNaughton, B. Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Curr. Opin. Neurobiol.* **10**, 180–186 (2000).

103. Qin, Y. L., McNaughton, B. L., Skaggs, W. E. & Barnes, C. A. Memory reprocessing in corticocortical and hippocampocortical neuronal ensembles. *Philos. Trans. R. Soc. Lond. B* **352**, 1525–1533 (1997).

104. Cirelli, C., Gutierrez, C. M. & Tononi, G. Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron* **41**, 35–43 (2004).

105. Jones, M. W. *et al.* A requirement for the immediate early gene *Zif268* in the expression of late LTP and long-term memories. *Nature Neurosci.* **4**, 289–296 (2001).

106. Lee, J. L., Everitt, B. J. & Thomas, K. L. Independent cellular processes for hippocampal memory consolidation and reconsolidation. *Science* **304**, 839–843 (2004).

107. Ribeiro, S., Goyal, V., Mello, C. V. & Pavlides, C. Brain gene expression during REM sleep depends on prior waking experience. *Learn. Mem.* **6**, 500–508 (1999).

108. Ribeiro, S. *et al.* Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal *zif-268* expression during ensuing rapid-eye-movement sleep. *J. Neurosci.* **22**, 10914–10923 (2002).
This elegant series of studies (references 107 and 108) shows that the plasticity-related gene Zif268 is induced in cortical regions during sleep following either behavioural exploration or induction of LTP in the dentate gyrus.

109. Wittenberg, G. M. & Tsien, J. Z. An emerging molecular and cellular framework for memory processing by the hippocampus. *Trends Neurosci.* **25**, 501–505 (2002).

110. Cui, Z. *et al.* Inducible and reversible NR1 knockout reveals crucial role of the NMDA receptor in preserving remote memories in the brain. *Neuron* **41**, 781–793 (2004).

111. Lisman, J., Schulman, H. & Cline, H. The molecular basis of CaMKII function in synaptic and behavioural memory. *Nature Rev. Neurosci.* **3**, 175–190 (2002).

112. Elgersma, Y., Sweatt, J. D. & Giese, K. P. Mouse genetic approaches to investigating calcium/calmodulin-dependent protein kinase II function in plasticity and cognition. *J. Neurosci.* **24**, 8410–8415 (2004).

113. Frankland, P. W., O'Brien, C., Ohno, M., Kirkwood, A. & Silva, A. J. α -CaMKII-dependent plasticity in the cortex is required for permanent memory. *Nature* **411**, 309–313 (2001).

114. 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).
This paper combines cellular imaging, mouse genetic and pharmacological inactivation approaches to establish a crucial role for the anterior cingulate cortex in processing remote contextual fear memories.

115. Penzes, P. *et al.* Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF Kallirin. *Neuron* **37**, 263–274 (2003).

116. Hayashi, M. L. *et al.* Altered cortical synaptic morphology and impaired memory consolidation in forebrain-specific dominant-negative PAK transgenic mice. *Neuron* **42**, 773–787 (2004).
Together with reference 113, this study shows that mice with abnormal cortical plasticity are unable to form enduring, hippocampus-independent memories.

117. Hall, J., Thomas, K. L. & Everitt, B. J. Cellular imaging of *zif268* expression in the hippocampus and amygdala during contextual and cued fear memory retrieval: selective activation of hippocampal CA1 neurons during the recall of contextual memories. *J. Neurosci.* **21**, 2186–2193 (2001).

118. Bontempi, B., Laurent-Demir, C., Destrade, C. & Jaffard, R. Time-dependent reorganization of brain circuitry underlying long-term memory storage. *Nature* **400**, 671–675 (1999).
Using regional brain imaging approaches in mice, the results of this paper show that the hippocampus has a transitory role in memory storage. In addition, this study was the first to identify possible sites of permanent storage in the cortex.

119. Chklovskii, D. B., Mel, B. W. & Svoboda, K. Cortical rewiring and information storage. *Nature* **431**, 782–788 (2004).
This excellent review contrasts mechanisms underlying weight and wiring plasticity, and proposes that the latter may play a crucial role in cortical memory consolidation.

120. Benowitz, L. I. & Routtenberg, A. GAP-43: an intrinsic determinant of neuronal development and plasticity. *Trends Neurosci.* **20**, 84–91 (1997).

121. Miller, R. Neural assemblies and laminar interactions in the cerebral cortex. *Biol. Cybern.* **75**, 253–261 (1996).

122. Hebb, D. O. *The Organization of Behavior* (Wiley, New York, 1949).

123. Haist, F., Bowden, J. & Mao, H. Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nature Neurosci.* **4**, 1139–1145 (2001).

124. Ridderinkhof, K. R., Ullsperger, M., Crone, E. A. & Nieuwenhuis, S. The role of the medial frontal cortex in cognitive control. *Science* **306**, 443–447 (2004).

125. Lashley, K. S. In search of the engram. *Symp. Soc. Exp. Biol.* **4**, 454–482 (1950).

126. Uylings, H. B., Groenewegen, H. J. & Kolb, B. Do rats have a prefrontal cortex? *Behav. Brain Res.* **146**, 3–17 (2003).

127. Morris, R. G. *et al.* Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos. Trans. R. Soc. Lond. B* **358**, 773–786 (2003).

128. Miyashita, Y. Cognitive memory: cellular and network machineries and their top-down control. *Science* **306**, 435–440 (2004).

129. Ungerleider, L. G. Functional brain imaging studies of cortical mechanisms for memory. *Science* **270**, 769–775 (1995).

130. Miller, E. K. & Cohen, J. D. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* **24**, 167–202 (2001).

131. Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I. & Miyashita, Y. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* **401**, 699–703 (1999).

132. Moody, S. L., Wise, S. P., di Pellegrino, G. & Zipser, D. A model that accounts for activity in primate frontal cortex during a delayed matching-to-sample task. *J. Neurosci.* **18**, 399–410 (1998).

133. O'Reilly, R. C. & Rudy, J. W. Computational principles of learning in the neocortex and hippocampus. *Hippocampus* **10**, 389–397 (2000).

134. Lisman, J. & Morris, R. G. Memory: why is the cortex a slow learner? *Nature* **411**, 248–249 (2001).

135. Trachtenberg, J. T. *et al.* Long-term *in vivo* imaging of experience-dependent synaptic plasticity in adult cortex. *Nature* **420**, 788–794 (2002).

136. Willshaw, D. J. & Buckingham, J. T. An assessment of Marr's theory of the hippocampus as a temporary memory store. *Philos. Trans. R. Soc. Lond. B* **329**, 205–215 (1990).

137. Genoux, D. *et al.* Protein phosphatase 1 is a molecular constraint on learning and memory. *Nature* **418**, 970–975 (2002).

138. Villarreal, D. M., Do, V., Haddad, E. & Derrick, B. E. NMDA receptor antagonists sustain LTP and spatial memory: active processes mediate LTP decay. *Nature Neurosci.* **5**, 48–52 (2002).

139. Feng, R. *et al.* Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. *Neuron* **32**, 911–926 (2001).

140. Fortin, N. J., Wright, S. P. & Eichenbaum, H. Recollection-like memory retrieval in rats is dependent on the hippocampus. *Nature* **431**, 188–191 (2004).

141. Day, M., Langston, R. & Morris, R. G. Glutamate-receptor-mediated encoding and retrieval of paired-associate learning. *Nature* **424**, 205–209 (2003).

142. Bourchouladze, R. *et al.* Different training procedures recruit either one or two critical periods for contextual memory consolidation, each of which requires protein synthesis and PKA. *Learn. Mem.* **5**, 365–374 (1998).

143. Kida, S. *et al.* CREB required for the stability of new and reactivated fear memories. *Nature Neurosci.* **5**, 348–355 (2002).

144. Shadmehr, R. & Holcomb, H. H. Neural correlates of motor memory consolidation. *Science* **277**, 821–825 (1997).

145. McBride, S. M. *et al.* Mushroom body ablation impairs short-term memory and long-term memory of courtship conditioning in *Drosophila melanogaster*. *Neuron* **24**, 967–977 (1999).

146. Menzel, R. Searching for the memory trace in a mini-brain, the honeybee. *Learn. Mem.* **8**, 53–62 (2001).

147. Gale, G. D. *et al.* Role of the basolateral amygdala in the storage of fear memories across the adult lifetime of rats. *J. Neurosci.* **24**, 3810–3815 (2004).

148. Sokoloff, L. *et al.* The [¹⁴C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *J. Neurochem.* **28**, 897–916 (1977).

149. Laroche, S., Davis, S. & Jay, T. M. Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. *Hippocampus* **10**, 438–446 (2000).

150. Dutar, P., Bassant, M. H., Senut, M. C. & Lamour, Y. The septohippocampal pathway: structure and function of a central cholinergic system. *Physiol. Rev.* **75**, 393–427 (1995).

Acknowledgements
We thank R. Costa, T. Durkin, S. Josselyn and M. Moscovitch for discussions and comments on earlier drafts. This work was supported by a Canadian Institutes of Health Research Canada Research Chair (P.W.F.) and the Centre National de la Recherche Scientifique (B.B.).

Competing interests statement
The authors declare no competing financial interests.

 **Online links**

DATABASES
The following terms in this article are linked online to: **Entrez Gene:** <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene> α -CaMKII | *c-fos* | *Zif268*

FURTHER INFORMATION
Encyclopedia of Life Sciences: <http://www.els.net/>
Learning and memory
Frankland's homepage: <http://individual.utoronto.ca/franklandlab/>
Bontempi's homepage: <http://www.neurocog.u-bordeaux1.fr/bontempl.htm>
Access to this interactive links box is free online.