A CORTICAL–HIPPOCAMPAL SYSTEM FOR DECLARATIVE MEMORY

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Recent neurobiological studies have begun to reveal the cognitive and neural coding mechanisms that underlie declarative memory — our ability to recollect everyday events and factual knowledge. These studies indicate that the critical circuitry involves bidirectional connections between the neocortex, the parahippocampal region and the hippocampus. Each of these areas makes a unique contribution to memory processing. Widespread high-order neocortical areas provide dedicated processors for perceptual, motor or cognitive information that is influenced by other components of the system. The parahippocampal region mediates convergence of this information and extends the persistence of neocortical memory representations. The hippocampus encodes the sequences of places and events that compose episodic memories, and links them together through their common elements. Here I describe how these mechanisms work together to create and re-create fully networked representations of previous experiences and knowledge about the world.

EPISODIC REPRESENTATIONS
Neural firing patterns, which encode the sequence of events that compose a unique, personal experience.

SEMANTIC KNOWLEDGE
An organization of factual information independent of the specific episodes in which that information was acquired.

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Our everyday, conscious memories are not a passive or disconnected collection of images and associations. Rather, we create an intricate network of images and associations, constituting a record of our personal experiences that is continuously updated through an active organization of new information within the context of previous experience[1]. Recollection is similarly *re*-creative, and the course of remembering is therefore determined by the nature of our memory organization. This type of memory is called 'declarative memory', and is therefore a multifaceted process involving a synthesis of EPISODIC REPRESENTATIONS with our framework of general SEMANTIC KNOWLEDGE that mediates our capacity for recollection. In this review, I will summarize recent progress in characterizing a functional circuit diagram for the brain system that mediates declarative memory.

Hippocampal region and declarative memory

The hippocampal region has been identified as central to our capacity for declarative memory. Scoville and Milner's[2] initial report of memory loss in humans following removal of the hippocampal region showed that this area is dedicated to memory independent of other cognitive functions. In addition, even within memory, the role of the hippocampal region is selective both to a particular time window and a particular domain of memory processing.

Immediate memory, the ability to repeat or recognize items just brought into consciousness, is intact in patients with damage to the hippocampal region[3,4]. Also, remote childhood memories and general world knowledge acquired early in life are not affected. These findings indicate that the hippocampal region plays a critical role between the initial formation of memories and their final repository elsewhere in the brain. It has been suggested that the hippocampus is always critical for the expression of autobiographical and spatial memories[5]. However, it was recently shown that the role of the hippocampal region is time-limited even for memory of spatial environments learned in childhood[6]. The duration of critical hippocampal involvement may depend on mediation by cortical areas adjacent to the hippocampus, and damage outside the hippocampal region can result in temporally extensive memory loss[7,8].

In contrast to the observations of temporal specificity, the early evidence indicated that the domain of memory dependent on the hippocampal region was 'global'. However, it is now clear that there are several memory systems in the brain, of which the hippocampal system is only one[9]. As Cohen and Squire[10] first recognized, the hippocampal region functions selectively in declarative memory. Although the terminology used to characterize this kind of memory has varied, there is consensus that the phenomenology of declarative memory is composed of our capacity for episodic and semantic memory, and our ability for conscious recollection and 'flexible' memory expression[11]. By contrast, the hippocampal region is not required for the acquisition of many skills and biases that can be expressed unconsciously through alterations in performance on a broad variety of tasks (for example, REFS 12,13,17). Instead, systems that include the neostriatum and cerebellum mediate PROCEDURAL MEMORY, the acquisition of motor skills and habits[13–18]. A system that includes the amygdala mediates EMOTIONAL MEMORY[17] and modulates the strength and consolidation of memories in other memory systems[19]. Cortical regions are critical in short-term or WORKING MEMORY[20], and in the PRIMING of recently experienced stimuli[21], as well as in long-term declarative memory (see below).

We are beginning to characterize the neural circuitry and information processing mechanisms that mediate these aspects of memory through the use of animal models. Recent studies have shown that the general pattern of memory deficits and spared capacities, following damage to the hippocampal region in monkeys and rats, parallels the phenomenology of amnesia in humans[22,23]. Sensory, motor, motivational and cognitive processes are intact following hippocampal damage, confirming that this structure functions selectively in memory in animals as in humans. The role of the hippocampal region in animals is limited both to the transition from immediate to permanent memory, and to a particular domain of memory. So as in human amnesics, animals with damage to the hippocampal region can have an intact immediate memory and subsequent loss of memory after interpolated material or delay[24,25]. This pattern of intact immediate memory and abnormally rapid forgetting has also been observed after damage limited to the hippocampus itself in some cases of nonspatial memory[26] and spatial memory[27]. However, in other spatial tasks an impairment is observed at the briefest possible delays[28,29]. In addition, several studies on animals have shown that memories acquired shortly before hippocampal damage are lost

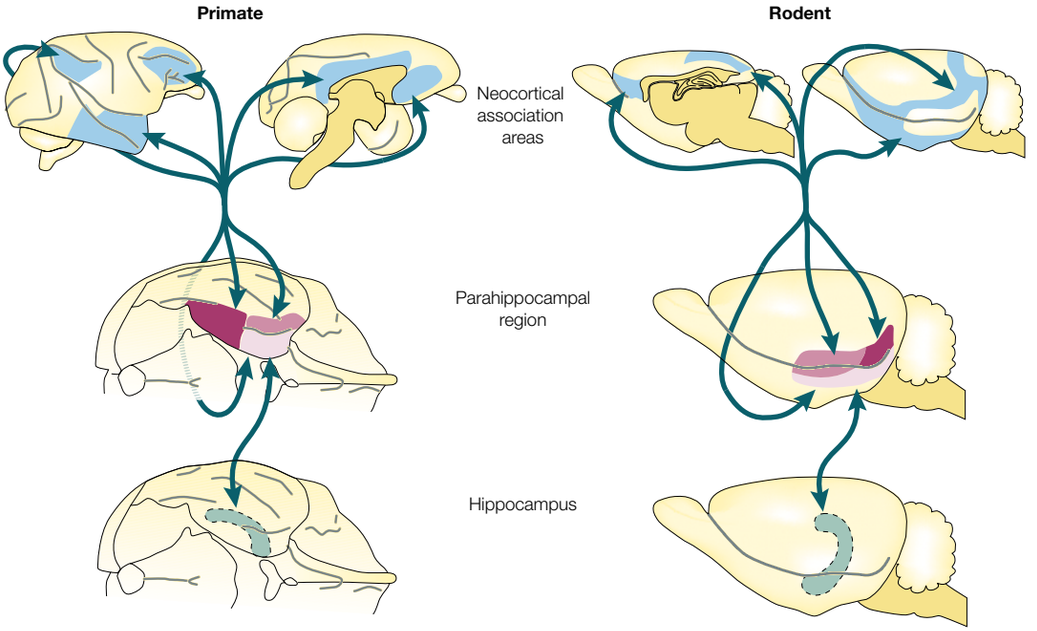

Figure 1 | **The anatomy of the hippocampal memory system.** In both monkeys and rats the origins of specific information for the hippocampus include virtually every neocortical association area[102,103]. Each of these neocortical areas (blue) project to one or more subdivisions of the parahippocampal region, which includes the perirhinal cortex (purple), the parahippocampal (or postrhinal) cortex (dark purple) and the entorhinal cortex (light purple)[42,43]. The subdivisions of the parahippocampal region are interconnected and send principal efferents to many subdivisions of the hippocampus itself (green), the dentate gyrus, the CA3 and CA1 areas, and the subiculum. So the parahippocampal region serves as a convergence site for cortical input and mediates the distribution of cortical afferents to the hippocampus. Within the hippocampus, there are broadly divergent and convergent connections that could mediate a large network of associations[104], and these connections support plasticity mechanisms that could participate in the rapid coding of new conjunctions of information[105]. The outcome of hippocampal processing is directed back to the parahippocampal region, and the output of that region is directed in turn back to the same areas of the cerebral cortex that were the source of input to this region[42,43]. Further structures have been included in this system, including the medial diencephalic structures that connect with the hippocampus along with other subcortical areas, through a major fibre bundle called the fornix[106].

PROCEDURAL MEMORY
The representation of a series of actions or perceptual processing functions that occur unconsciously, and typically result in increased speed or accuracy with repetitions.

EMOTIONAL MEMORY
The representation of a positive or negative affect associated with specific stimuli. Typically not subject to conscious recollection but reflected in attraction, avoidance or autonomic nervous system activation.

WORKING MEMORY
The representation of items held in consciousness during experiences or after retrieval of memories. Short-lasting and associated with active rehearsal or manipulation of information.

PRIMING
The facilitation of recognition, reproduction or biases in selection of stimuli that have recently been perceived.

Box 1 | **The 'delayed nonmatch to sample' task**

In this test subjects are initially presented with a single stimulus, called the sample, and must indicate that they have perceived it by an appropriate behavioural response. Subsequently the sample stimulus is removed and must be remembered across a variable delay. In the memory test phase, the subject is presented with the sample concurrently or sequentially along with an alternative stimulus. The subject is required to select against the sample in favour of the alternative, that is, to non-match to the sample. In a version of the task commonly used in monkey studies, the sample and alternative stimuli are three-dimensional 'junk' objects that are used on only one trial and then never presented again[95]. Typically the animals are initially trained with a minimal memory delay, and the delay is subsequently elongated to increase the memory demand. Several variants of the task are used in other behavioural and physiological studies. In physiological studies on monkeys, video-pictures are the stimuli, the test stimuli are presented sequentially, and a match-to-sample is required[63,64]. In a 'continuous nonmatch to sample' variant of the task, used in behavioural and physiological studies on rats, the stimuli are a continuous series of odours for which each stimulus acts as both the test of memory for the previous stimulus and as the sample to be remembered on the next trial[45].

whereas memories acquired much earlier are spared, similar to the temporally graded retrograde memory loss observed in human amnesic patients[30–35].

In addition, in animals as in humans, the domain of memory dependent on the hippocampal region is selective to a particular type of memory processing. It is impossible to assess in animals some aspects of declarative memory, such as conscious recollection. Nevertheless, several studies have succeeded in showing a selective role for the hippocampal region in mediating other central features of declarative memory. These include the linking of memories within a network of semantic knowledge and flexible, inferential expression of memories, as outlined below (see section on 'memory processing within the hippocampus')[36]. Conversely, there is abundant evidence that other brain systems in animals mediate procedural learning[37], emotional memory[38–40] and memory modulation[41]. These findings validate the application of animal models to the study of memory, and set the stage for a detailed neurobiological analysis aimed at identifying the relevant pathways and functional mechanisms of the declarative memory system.

Dissecting the hippocampal memory system

The hippocampal memory system is composed of three principal components: cerebral cortical areas, the parahippocampal region and the hippocampus itself[42,43]. The main pathways are similar in rodents and primates (FIG. 1). This anatomical organization complements the findings from studies of amnesia, leading to the working hypothesis that the parahippocampal region and hippocampus contribute to memory by altering the nature, persistence and organization of memory representations within the cerebral cortex.

Different roles of cortical areas

To fully understand the contribution of the hippocampus to memory, it is essential to characterize the nature of the information processing performed by the neocortical association areas and the parahippocampal region — areas that project to and are influenced by the hippocampus. The role of these areas has been studied in both rats and monkeys using a simple recognition memory task, called 'delayed nonmatch to sample' (DNMS), where subjects must remember a single stimulus across a variable memory delay (BOX 1)[23,44].

There is emerging evidence that neocortical association areas and the parahippocampal region have distinct and complementary functions in DNMS performance. In rats performing an odour-guided version of the DNMS task (BOX 1), damage to the orbitofrontal cortex resulted in a deficit in the acquisition of the task when the memory delay was minimal, suggesting that it is important in perceptual processing or in learning the nonmatching rule[45]. By contrast, rats with damage to the parahippocampal region acquired the DNMS task at the normal rate and did well at brief memory delays. However, their memories declined abnormally rapidly as the memory delay was extended beyond a few seconds, indicating a selective role in maintaining a persistent memory of the sample stimulus. Little if any deficit in nonspatial DNMS is observed following damage to the hippocampus or its connections through the fornix[28,45–47], indicating that the parahippocampal region itself mediates the persistence of memories for single items required to perform DNMS.

Parallel results have been obtained in monkeys performing visually guided versions of the DNMS task (BOX 1). Similar to rats, monkeys with damage to the parahippocampal region do well when the memory delay is brief. But when the memory demand is increased by extending the delay period, severe deficits in DNMS are observed[48,49], and these impairments are more severe than that following damage to the hippocampus[50] or its connections through the fornix[51]. Examination of performance on the DNMS task with brief delays has been difficult because the standard protocol used for monkeys is manual. However, using another recognition task that allowed testing at very brief delays, it has recently been shown that the inferotemporal area of the cortex is critical for visual recognition even for a one second delay, indicating a possible function in perceptual processing as opposed to memory. In contrast, the parahippocampal region was critical for memory in the same task only when recognition was delayed[52]. The parahippocampal region may also act at the intersection of perception and memory in situations where perceptual processes depend on learned associations among complex stimulus elements[53,54].

Parallel electrophysiological studies that involve recording from single cells in these same brain areas have provided a preliminary understanding of the neural coding mechanisms that underlie DNMS performance. In both monkeys and rats, three general responses have been observed (FIG. 2)[55,59]. First, many cells showed selective tuning to sample stimuli during the initial perception of the stimulus, indicating that these areas encode specific stimuli. Second, some cells continued firing in a stimulus-specific fashion during a memory period when the cue was no longer present, indicating the persistence of a representation of the sample. Lastly, many cells showed enhanced or suppressed responses to the familiar stimuli when they reappeared in the memory test

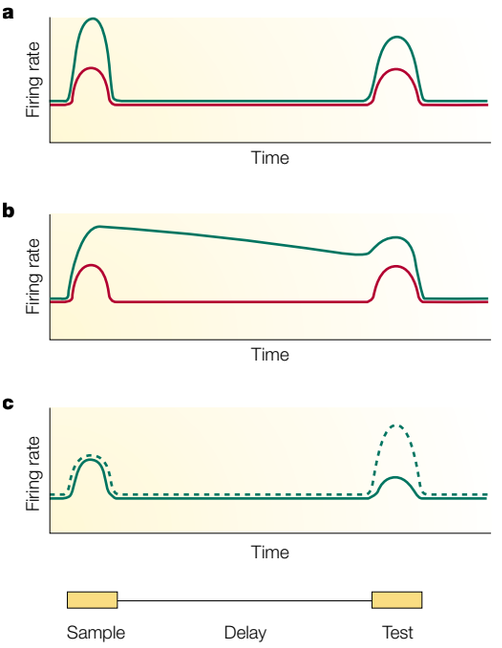

Figure 2 | **Firing patterns associated with memory performance in ideal cortical neurons.** Responses are shown for a sample period when a stimulus is presented, a delay period during which it must be remembered, and finally a match period when the memory of the sample must be matched to choice stimuli (BOX 1). **a** | Selective activation for some stimuli (green) compared with others (red), consistent with an encoding of stimulus properties. **b** | Stimulus-selective activation (green) during a delay period when the memory of a stimulus must be maintained, consistent with a role in maintaining a representation of the sample. **c** | Enhanced (dotted line) or suppressed (solid line) responses to stimulus repetition compared with initial presentations, consistent with processing comparisons between the sample and choice stimuli.

phase of the task, indicating involvement in the match/nonmatch judgment.

All three types of representations have been found in several neocortical areas and in the parahippocampal region, indicating that information about all aspects of the task may be shared among these areas. However, it is likely that each area makes a distinct contribution to the performance of the task. For example, in rats more cells in the parahippocampal region showed sustained stimulus-specific activity during the delay, whereas more cells in the orbitofrontal area showed stimulus-selective match enhancement or suppression[60]. In monkeys, a greater proportion of cells in the lateral prefrontal region showed sustained responses during the delay, and conveyed more information about the match–nonmatch status of the test stimuli compared with the perirhinal cortex in a task where the memory delay was filled with interpolated material[61]. By contrast, more neurons in the perirhinal cortex and inferotemporal cortex show greater stimulus selectivity. Furthermore, in a recognition task where the memory delay is not filled with interpolated material, a large fraction of temporal neurons show sustained stimulus-specific delay activity[62]. In addition, neurons in perirhinal and inferotemporal cortex areas show long-lasting decrements in responsiveness to highly familiar stimuli, which could provide signals about familiarity for extended periods[63,64].

It is difficult at this time to directly compare the data across species from studies that use different experimental strategies, focus on different components of the prefrontal and temporal cortex, and use different variants of recognition memory tests. However, the evidence is generally consistent with the idea that several neocortical and parahippocampal areas serve distinct functions in recognition memory. Neocortical areas have specific functions in the perceptual or cognitive processing required to complete the task, and are able to mediate some aspects of working or short-term memory. The parahippocampal region makes a different contribution. This region seems to be critical in extending the persistence of memory for single stimuli over brief periods in the absence of interference, and maintains information about stimulus familiarity for prolonged periods even with interference.

It seems that memory mediated by the hippocampus itself is not critical for performance in standard DNMS tasks, in that the deficits observed are, at most, modest compared with the effects of damage to the parahippocampal region. However, the hippocampus seems to be essential in other types of simple recognition memory tests[26,65] and in memory for configurations of items within scenes or places[66–69].

Memory processing within the hippocampus

The findings from studies using animal models point to a critical role for the hippocampus itself in central aspects of declarative memory. To understand this role it is important to reconsider the fundamental properties of declarative memory introduced earlier. We acquire our declarative memories through everyday personal experiences, and the ability to retain and recall these 'episodic' memories is highly dependent on the hippocampus in humans[70]. But the full scope of hippocampal involvement also extends to semantic memory[71]. For example, a typical episodic memory might involve recalling the specific events and places surrounding the meeting of a long-lost cousin. Your general knowledge about your family tree, and other facts about the history of your family, comes in great part from a synthesis of the representations of many meetings with relatives and other episodes in which family personalities or events are observed or discussed. Similarly, our episodic memory mediates the capacity to remember a sequence of events, places passed, and turns taken while walking across a city, and a synthesis of many such representations provides general knowledge about the spatial layout of the city.

In addition, declarative memory for both the episodic and semantic information is special in that the contents of these memories are accessible through various routes. Most commonly in humans, declarative memory is expressed through conscious, effortful recollection. This means that you can access and express declarative memories to solve new problems by making inferences

SPATIAL LEARNING
Acquisition of information about spatial relations among objects in the environment, typically reflected in the ability to navigate through the environment using new routes.

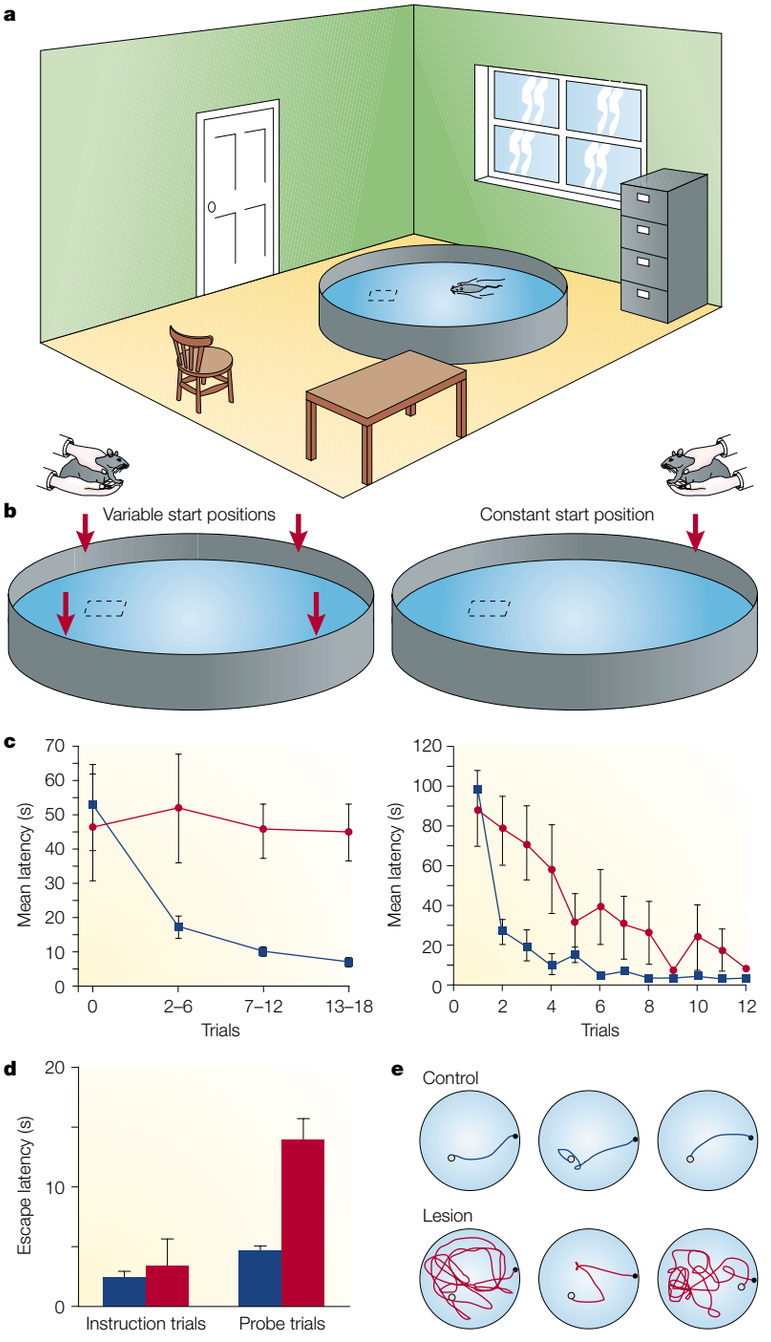

Figure 3 | **Performance of rats with hippocampal damage in the Morris water maze.** **a** | An illustration of the Morris water maze and typical environmental cues[74]. The escape platform, submerged just below the surface of the water, cannot be seen by the rat. **b** | In the conventional version of the task (left), the rat begins each trial from one of four starting locations, and the time required for it to locate the escape platform is measured. In the constant start position version of the task (right), one start location is used consistently. **c** | In the conventional version of the task (left), normal rats (blue) rapidly improve their swim latencies to find the platform across trials, whereas rats with hippocampal damage (red) do not. In the constant start position version of the task (right), rats with hippocampal damage are slightly impaired in acquisition rate, but successfully learn to locate the platform. **d** | During probe testing, normal rats (blue) rapidly locate the escape platform both on repetitions of the original instruction trials and on probe trials that begin at new start positions. Rats with hippocampal damage (red) also do well on repetitions of the instruction trials, but poorly on the probe trials. **e** | Example swim paths in new probe trials by normal rats (blue) and rats with hippocampal damage (red). Normal rats swim directly to the platform, but rats with hippocampal damage are severely impaired.

from memory. For example, even without ever explicitly studying your family tree, you can infer indirect relationships or the sequence of central events in the family history, from the set of episodic memories about your family. Similarly, without ever studying the map of a city, you can make navigational inferences from the synthesis of many episodic memories of previous routes taken. Large-scale networks for family trees and city layouts are but two examples of the kind of 'memory space' proposed to be mediated by the hippocampal system[72]. Within this view, a broad range of such networks can be created, with their central organizing principle the linkage of episodic memories through their common events and places, and a consequent capacity to move among related memories within the network.

These properties of declarative memory suggest an approach for the development of animal models. So a way to study the creation of a memory space from overlapping experiences, and to make inferences from the network knowledge, is to train subjects on several distinct experiences that share common elements and then test whether these experiences have been linked in memory to solve new problems. One can conceive of this approach as applied to various domains relevant to the lives of animals, from knowledge about spatial relations among stimuli in an environment, to categorizations of foods, learned organizations of odour or visual stimuli, or social relationships. Progress is being made in investigating these domains.

In some experimental protocols, the requirement to synthesize several overlapping experiences is enough to require hippocampal function. One case involves SPATIAL LEARNING, similar to the example of the learning of routes through a city given above, but involving rats and the Morris water maze task. In this test, rats or mice learn to escape from submersion in a pool by swimming towards a platform located just underneath the surface. Importantly, training in the conventional version of the task involves an intermixing of four kinds of trial episodes that differ in the starting point of the swim. Under this condition, animals with hippocampal damage typically fail to acquire the task[73]. However, if the demand for synthesizing a solution from four types of episodes is eliminated by allowing the animal to repeatedly start from the same start position, animals with hippocampal damage acquire the task almost as readily as normal rats and use the same distant spatial cues in identifying the escape site[74] (FIG. 3).

Other experiments indicate that the hippocampus may be required for new problem solving in familiar environments. So when rats with hippocampal damage that have successfully learned to locate the escape platform from a single start position are tested from new start positions, they fail to readily locate the platform. In contrast, normal animals swim directly to the escape locus on each new probe trial (FIG. 3)[74]. In another example, hippocampal damage results in failure to express memory for a single experience in social learning of food odours. Training in this task involves a social encounter during which the subject interacts

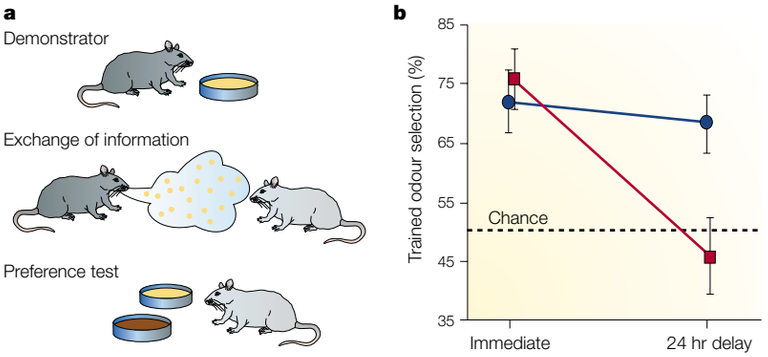

Figure 4 | **The social transmission of food preferences task. a** | Initially a 'demonstrator' rat eats food containing a new odour. Then, during a social encounter, the demonstrator exchanges information about the food odour with the subject rat[76]. Subsequently the subject is given a preference test for the new food odour versus another food odour. **b** | Preference test results. Normal rats (blue) show a strong preference for the demonstrated food odour both immediately and one day following the social encounter. Rats with hippocampal lesions (red) shown intact performance on the immediate test but forget within one day.

with a 'demonstrator' rat that has recently eaten a particular food (FIG. 4). During this exposure the subject sniffs the breath of the demonstrator and acquires an association between the odour of the recently eaten food and an odorous constituent of rat's breath, carbon disulphide[75]. The subsequent memory test involves presentation of a choice of foods, one of which is the same kind of food eaten by the demonstrator, in the absence of the social context. Memory for the learned association is reflected in an alteration of food selection choices by the subject. Rats with selective hippocampal damage show intact memory when tested immediately after the social encounter, but no memory when the test is delayed by 24 hours (FIG. 4)[33,76]. The observation of intact short-term memory is similar to the sparing of immediate memory in humans with amnesia, and indicates that the hippocampus is not required for the perceptual or motivational components of learning, for the critical social interactions, or for the ability to express a learned food selection. The loss of differential choice behaviour within a day indicates that the hippocampus is required for expressing the memory acquired during a single social encounter in a new situation involving food selection.

In several other experimental protocols, animals with hippocampal damage successfully acquire a set of overlapping experiences, often at a rate not substantially different from that of normal subjects. But they fail to express their memories of the experience in new situations that require an inference on the basis of linking the distinct experiences in memory (BOX 2). In one of these studies, rats were trained on sets of odour 'paired associates' with shared elements and were then tested to see if they could infer an association between elements that were only indirectly related[77]. In another study, rats were trained on a series of four odour discriminations, with shared items such that the odour set could be construed as a hierarchy, and then were tested to see if they could infer transitive relations according to the hierarchical organization[78]. The results of these studies showed that some forms of stimulus–stimulus representations can be acquired independently of the hippocampus itself. However, these representations are 'hyperspecific', that is, they can only be expressed within the confined context of the reproduction of each of a set of distinct learning events[79]. Only a hippocampally mediated representation can support the inferential expression of associations that must be linked across separated experiences.

Box 2 | **Tests of transitive inference**

In one experiment rats learned overlapping sets of associations between odour stimuli[77]. On each trial one of two odours was initially presented, followed by a choice between two odours, one of which was baited as the assigned 'associate' for a particular initial odour (A goes with B, not Y; X goes with Y, not B). Following training on two sets of overlapping odour–odour associations (A–B and X–Y, then B–C and Y–Z), subsequent probe tests were used to characterize the extent to which learned representations could be linked to support inferential memory expression. Control rats learned paired associates rapidly and hippocampal damage did not affect acquisition rate on either of the two training sets. Intact rats also showed that they could link the information from overlapping experiences, and use this information to make inferential judgments in two ways. First, normal rats showed strong transitivity across odour pairings that contained a shared item. For example, having learned that odour A goes with odour B, and B goes with C, they could infer that A goes with C. Second, control rats could infer symmetry in paired associate learning. For example, having learned that B goes with C, they could infer that C goes with B. By contrast, rats with selective hippocampal lesions were severely impaired, showing no evidence of transitivity or symmetry. A subsequent study examined the ability of rats to solve the classic transitive inference task[78]. Animals initially learned a series of overlapping pairwise discrimination problems in which they were rewarded for selecting one odour over another (A > B, B > C, C > D and D > E, where the item before '>' is to be selected over the other item). In later probe tests, all the initial pairs were presented in random order, together with occasional probe trials with the pair B versus D as the critical test of transitive inference. Control rats acquired each of the premise pairs rapidly, and showed a robust capacity for transitive inference, indicating that rats are capable of linking information about the odours acquired across distinct experiences, and of making inferential judgments based on knowledge about the orderly series. Animals with different kinds of hippocampal damage acquired the premise pairs at the normal rate but showed no capacity for the transitive inference.

Linking episodic memories in the hippocampus

How are these memory capacities mediated within the circuitry of the hippocampus? Recent observations from extracellular recordings in behaving animals indicate that hippocampal neuronal networks may represent sequences of events and places that compose episodic memories. The content of information encoded by the firing patterns of these neurons includes both specific conjunctions of events and places unique to particular experiences and features that are common to overlapping experiences. Indeed, there is now evidence that the hippocampus creates separate and linked episodic-like representations even when the overt behaviours, and places where they occur, are the same but the events are parts of distinct experiences.

Hippocampal principal cells show firing patterns that are readily related to a broad range of events, which occur during sequences of behaviour in all tasks examined (BOX 3)[72]. For example, as rats complete spatial tasks where they are required to shuttle between a common starting location and one or more reward locations,

Box 3 | **Hippocampal 'place' cells, and more**

In 1971, O'Keefe and Dostrovsky[96] reported the observation of principal cells in the hippocampus that fired when a rat was in a particular location in its environment. Since then, there have been many characterizations of hippocampal 'place' cells. The spatial coding properties of these cells are most readily observed in rats moving randomly in an open field while foraging for food[97]. In this task, the animal's movements and behaviours are homogeneous throughout the environment, but many hippocampal cells are active only when the animal traverses a particular area within the environment[98]. These findings have been interpreted as evidence that the hippocampus is dedicated to mapping spatial layouts of the environment[99]. However, information about places reflects only part of the domain of hippocampal information coding. In many situations where rats move towards or away from important locations in the environment, the spatial firing patterns of these cells are strongly affected by the direction and speed of movement[81,82], by the targets of movement within the environment[80], and by demands of the behavioural test (FIG. 6)[83,100]. Furthermore, hippocampal cell firing is also associated with many nonspatial events, including conditioned behavioural responses[84], olfactory cues[85] and, in humans, categories of visual stimuli[101].

hippocampal PLACE CELLS fire during each moment as the animal traverses its path, with each neuron activated when the animal is in a particular place and moving toward the goal. A largely different set of cells fires similarly in sequence as the rat returns to the starting point, such that each cell can be characterized as an element of a network representing an outbound or inbound part of the episode[80–83]. One can imagine the network activity as similar to a videoclip of each trial episode, with each cell capturing the information about where the rat is and what it is doing in each sequential 'frame' of the clip.

Similarly, in both simple and complex learning tasks, hippocampal cells fire at virtually every moment associated with specific relevant events[83,84]. For example, when rats complete an odour discrimination task, hippocampal cells fire during each sequential event, with different neurons firing during the approach to the odour stimuli, sampling of odours, execution of a behavioural response and reward consumption[83]. Again, it is as if each hippocampal cell encodes one of the sequential trial events with its activity reflecting both aspects of the continuing behaviour and the place where that behaviour occurred. In all of these situations, some cells fire during common events or places that occur on every trial, whereas the firing of other cells was associated with events that occurred only during a particular type of episode, such as sampling a particular configuration of two odours presented on that trial.

In an extension of these studies, we were recently able to distinguish hippocampal neurons that encoded specific combinations of both events and places, which were unique to particular experiences as well as particular features that were common across many related experiences[85]. In this experiment, rats performed a variant of the DNMS task at several locations in an open field. Again, different cells fired during each sequential trial event. Some cells were activated only in association with a specific event, for example, when the rat sniffed a particular odour at a particular place when it was a nonmatch with the odour presented on the previous trial. Other cells fired in association with features of the task that were common across many trials: cells fired as the rat approached the odour stimulus, or as it sniffed a particular odour, regardless of where the trial occurred, and cells fired as the rat performed the trial at a particular location, regardless of what odour was presented (FIG. 5).

Finally, there is emerging evidence of coding for information specific to particular types of episodes even in situations where the overt behavioural events and the locations in which they occur are identical between several types of experience. For example, in a spatial DNMS task, some hippocampal cells were activated when the rat was pressing one of two levers during the sample, or during the test phase of the task[86]. These cells can be characterized as elements encoding one temporally, spatially and behaviourally defined event in the network representation of a particular trial type. The firing of other cells was associated with common events (a particular lever position) regardless of trial phase, or during the sample or test phase regardless of location. These cells could be used to link the separate representations of different trial phases or episodes, and these codes were topographically segregated within the hippocampus. More direct evidence of episodic-like coding was found in a recent study where rats performed a spatial alternation task on a T-maze (FIG. 6). Each trial commenced when the rat traversed the stem of the 'T' and then selected either the left- or the right-choice arm[87]. To alternate successfully, the rats were required to distinguish between their left-turn and right-turn experiences and to use their memory of the most recent experience to guide the current choice. Different hippocampal cells fired as the rats passed through the sequence of locations within the maze during each trial. Most important, the firing patterns of many of the cells depended on whether the rat was in the midst of a left- or right-turn episode, even when the rat was on the stem of the T and running similarly on both types of trials — minor variations in the animal's speed, direction of movement or position within areas on the stem did not account for the different firing patterns on left-turn and right-turn trials. Other cells fired when the rat was at the same point in the stem on either trial type. Therefore, the hippocampus encoded both the left-turn and right-turn experiences using distinct representations, and included elements that could link them by their common features. In each of these experiments, the representations of event sequences, linked by codings of their common events and places, could constitute the substrate of a network of episodic memories.

Organization and consolidation

The studies described here indicate that each principal component of the memory system contributes differentially to declarative memory, although interactions between these areas are also essential. Initially, perceptual information as well as information about behaviour is processed in many dedicated neocortical areas. This processing includes complex cognitive rules and concepts, such as those likely to be processed in the prefrontal cortex or other association areas[58,88] (see Miller in this issue). However, the capacity of these components

PLACE CELLS
Hippocampal principal cells that fire selectively when an animal is in a particular location in its environment.

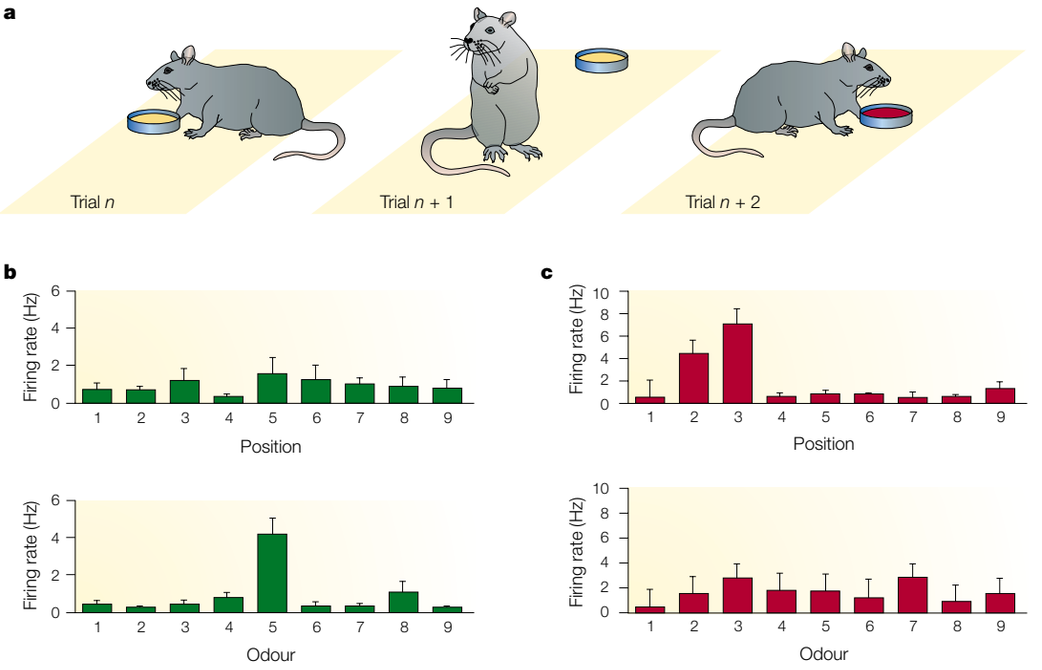

Figure 5 | **Hippocampal neuronal firing patterns in rats during an odour DNMS task. a** | On each trial the rat is presented with one of nine odours at any of nine randomly selected locations. To obtain a buried reward, the rat must identify whether the odour is the same as (matches, trial *n* + 1) or differs from (non-matches, trial *n* + 2) the odour presented on the previous trial[85]. Panels **b** and **c** show the average firing rates of two cells associated with all the places and all the odours. **b** | This cell fires selectively when the rat samples odour 5, but does not encode where the trial was performed. **c** | This cell fires selectively when the rat performs the trial at adjacent positions 2 and 3, but does not encode odour.

is limited in time, such that their representations may not outlast conscious processing by more than a few seconds[64]. The parahippocampal region, which receives convergent inputs from the neocortical association areas and sends return projections to all of these areas, seems to mediate the extended persistence of these cortical representations. Through interactions between these areas, processing within the cortex can take advantage of lasting parahippocampal representations, and so come to reflect complex associations between events that are processed separately in different cortical regions or occur sequentially in the same or different areas[53,54].

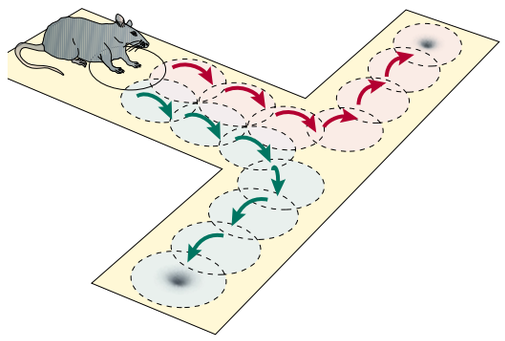

Figure 6 | **Place cell firing patterns associated with performance in a spatial memory task on a T-maze[87].** On left-turn trials, individual hippocampal cells fired as the animal passed through each of a series of locations (red circled areas and arrows) running up the stem of the T-maze and turning onto the left choice arm where it received a reward (black well). On right-turn trials, a different set of cells fired as the animal passed through the same set of locations on the stem as well as when it turned onto the right choice arm (green circles and arrows). These findings indicate that the hippocampus represents each type of trial separately.

However, these individual contributions and their interactions are not conceived as sufficient to link representations of events that are separated by long time periods or to form generalizations. Such an organization requires the capacity to rapidly encode a sequence of events that make up an episodic memory, to retrieve that memory by re-experiencing one facet of the event, and to link the continuing experience to stored episodic representations. It appears that the neuronal elements of the hippocampus contain the fundamental coding properties that can support this kind of organization. However, interactions among the components of the system are again undoubtedly critical. It is unlikely that the hippocampus has the storage capacity to contain all episodic memories. Indeed, sparing of remote memories obtained before hippocampal damage indicate that the hippocampus is not the final storage site[2]. Therefore, it seems likely that the hippocampal neurons are involved in mediating the re-establishment of detailed cortical representations, rather than storing the details themselves. Furthermore, one can imagine that repetitive interactions between the cortex and hippocampus (with the parahippocampal region as intermediary) serve to co-activate widespread cortical areas so that they eventually develop linkages between detailed mem-

ories without hippocampal mediation. In this way, the networking provided by the hippocampus may also underlie its temporary role in the consolidation of cortical memories[72,89,90].

Future directions

The model presented above combines many of the recent findings about hippocampal function in humans and animals. However, future studies are required to test and elaborate the model. In particular, we have only begun to conceptualize how information acquired in single learning episodes is encoded and preserved for long periods within this system[91,92]. The problem of creating behavioural protocols for testing episodic memory in animals is formidable. However, there is evidence that, for example, birds can remember a particular food cached at a particular time and in a particular place during a single episode[93]. Other recent studies have offered insights into hippocampal representation of single learning experiences in rodents and, in particular, about the role of NMDA-receptor-dependent plasticity in episodic-like memory[29,65].

These findings are consistent with the proposal that the hippocampus is critical for rapid encoding of events that compose episodic representations. Future studies must elaborate and extend these observations to show how rapid episodic coding in the hippocampus might mediate the protracted process of creating permanent links between representations within the cortex. This question may be pursued by relating the development of cortical representations to the development of episodic representations in the hippocampus, or by determining whether the development of such cortical representations depends on intact hippocampal function. A recent study on monkeys showed that the development of representations of visual paired associates in the inferotemporal cortex depends on an intact parahippocampal region[94]. This approach can be extended to an examination of the role of the hippocampus in both the acquistion and consolidation of cortical network representations.

Links

FURTHER INFORMATION Howard Eichenbaum lab page | John O'Keefe lab page | Richard Morris lab page

ENCYCLOPEDIA OF LIFE SCIENCES Learning and memory | Amnesia | Neural activity and the development of brain circuits | Neural networks and behaviour | Long-term potentiation | Protein phosphorylation and long-term synaptic plasticity

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