

The hippocampus and memory: insights from spatial processing

Chris M. Bird and Neil Burgess

Abstract | The hippocampus appears to be crucial for long-term episodic memory, yet its precise role remains elusive. Electrophysiological studies in rodents offer a useful starting point for developing models of hippocampal processing in the spatial domain. Here we review one such model that points to an essential role for the hippocampus in the construction of mental images. We explain how this neural-level mechanistic account addresses some of the current controversies in the field, such as the role of the hippocampus in imagery and short-term memory, and discuss its broader implications for the neural bases of episodic memory.

Short-term memory

The conscious retention of information over a few seconds, often through active maintenance (rehearsal). When the information held in short-term memory is manipulated, this is often referred to as working memory.

Priming

A behavioural change that is manifested in the speed or accuracy with which a stimulus is processed following prior exposure to the same or a similar stimulus.

Procedural learning

The unconscious learning of a skill, such as a series of actions or perceptual processing functions (for example, learning to ride a bike), which typically results in increased speed or accuracy with repetition.

Lying deep in the medial temporal lobes, the hippocampal formation is one of the most studied neuronal systems in the brain¹ (FIG. 1). Researchers seeking to understand the function of the hippocampus have taken their inspiration from a wide range of sources. Some have started with the devastating effects on memory that follow bilateral medial temporal lobe damage and the similar, but milder, effects of selective damage to the hippocampus. In general, such patients are impaired in acquiring new, consciously accessible (that is, explicit) memories, whereas short-term memory, priming, procedural learning and some remote memories that were acquired well before the lesion are preserved^{2–6} (see FIG. 2; although see below for recent evidence that the hippocampus subserves some aspects of short-term memory). The pattern of spared and impaired cognitive processes in patients with hippocampal damage, combined with results from animal models of amnesia, has led to the Declarative Theory of hippocampal function^{7,8}. Others have sought more specific characterizations of hippocampal function, drawing on experimental data from animals and humans. This has led to, for example, the Multiple-Trace Theory^{9,10}, the Dual-Process Theory¹¹ and the Relational Theory^{12–14}. Lastly, some researchers have focused on building a neural-level understanding of hippocampal function in a specific cognitive domain; examples of this approach include the Cognitive-Map Theory¹⁵. These different theories are briefly described in BOX 1.

Of course, all of these approaches have their merits and drawbacks. The Declarative Theory is consistent with the bulk of human neuropsychological data, but it lacks the specificity that is necessary to make novel

predictions about the effects of hippocampal damage or to identify the computations that are performed in the hippocampus. More detailed theories do make predictions as to the effects of selective hippocampal damage, but the experimental data are equivocal, as summarized below. Theories that focus on a particular area of cognition can link neuronal firing to some limited aspects of behaviour but can be hard to generalize to other situations.

In parallel with the experiment-driven development of these theories, computational models of hippocampal function have also been proposed — on more theoretical grounds. This approach enables hypotheses regarding the operation of the hippocampus and related areas to be constrained by physiological data. Computational modelling of the hippocampus and its interaction with surrounding neocortical areas was started by Marr^{16,17}. In Marr's model, and in important work that extended or clarified it^{18–22}, a sparse hippocampal representation of an event is rapidly encoded through the modification of recurrent connections in area CA3 of the hippocampus. This representation affords subsequent retrieval by an incomplete cue through pattern completion, and thence reinstatement of the full representation of the event in disparate neocortical areas. Marr's model predicts that the hippocampus is required for the initial encoding of multi-modal information that is represented in cortical areas: it provides a 'convergence zone' to mediate these associations²³.

In this Review we briefly summarize the current state of the debate regarding the role of the human hippocampus in long-term memory. We then describe a model of hippocampal function that has similarities with Marr's model but specifically focuses on the spatial domain,

Institute of Cognitive Neuroscience and Department of Anatomy, University College London, London, WC1N 3AR, UK.
e-mails: chris.bird@ucl.ac.uk; n.burgess@ucl.ac.uk
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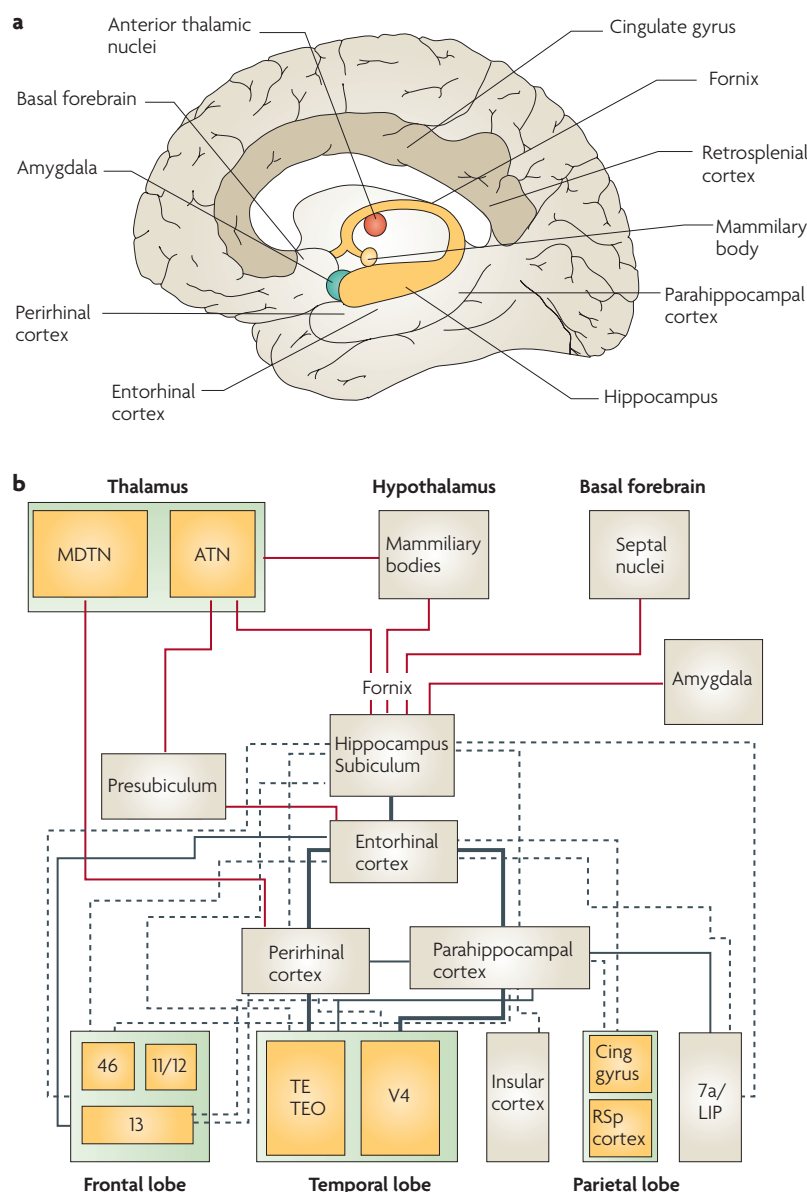


Figure 1 | The hippocampus and its connections. **a** | The hippocampus lies in the medial temporal lobes, surrounded by the entorhinal, parahippocampal and perirhinal cortices. It is part of Papez's circuit, and so is connected to several subcortical and cortical structures, such as the anterior thalamic nuclei (ATN), the mammillary bodies, the septal nuclei of the basal forebrain, the retrosplenial cortex and the parahippocampal cortex. **b** | Cortical and subcortical connections of the hippocampus. Subcortical connections are indicated by red lines; cortical connections are indicated by black lines. The thickness of the black lines approximates to the strength of the connections. Most of the hippocampus's neocortical inputs come from the perirhinal and parahippocampal cortices, through the entorhinal cortex, and most of its neocortical output is through the subiculum, which also projects back to the entorhinal cortex. Both the perirhinal cortex and the parahippocampal cortex lie at the end of the ventral visual processing ('what') stream. The perirhinal cortex is crucial for the representation of complex objects, whereas the parahippocampal cortex, with its strong connections to the posterior parietal (7a/lateral intraparietal area (LIP)) and retrosplenial (RSp) cortices, has a greater role in the processing of visuospatial information (from the dorsal visual processing ('where') stream). Head-direction cells are found in the mammillary bodies, the ATN, the presubiculum and the entorhinal cortex. Some researchers have proposed that 'recollection' is dependent on the hippocampus and its links with the ATN, whereas 'familiarity' can be mediated by direct connections between the perirhinal cortex and the medial dorsal thalamic nuclei (MDTN)¹¹. Cing gyrus, cingulate gyrus, TE & TEO, inferior temporal areas TE and TEO.

in which the neuronal representations of memory have been well studied. Some of the controversies concerning the role of the hippocampus in long-term memory are then revisited in light of this model. We then discuss the model's implications for hippocampal processing outside the domain of long-term memory. Lastly, we highlight some of the aspects of cognitive processing that are not addressed by the model but that are nevertheless thought to be underpinned by the hippocampus.

Episodic and semantic memory

A striking feature of the memory problems that follow hippocampal damage is an inability to remember recent events. Nevertheless, patients with hippocampal damage typically have a normal vocabulary, and their general knowledge of facts remains intact. Interestingly, the opposite pattern of memory loss is associated with a specific form of neurodegenerative disease known as 'semantic dementia': here, recent events are retrieved accurately whereas knowledge of word meanings and facts is dramatically impaired²⁴. The type of memory that involves personally experienced events was termed 'episodic memory' by Tulving, who contrasted it with other aspects of declarative memory, such as knowledge of facts in the absence of memory for the context in which they were learned ('semantic memory') or context-independent recognition of stimuli based on a feeling of familiarity^{25,26}.

The Declarative Theory explains these dissociations in terms of the age of the memories. Based on clinical observations² and theoretical ideas¹⁷, it proposes that older memories become 'consolidated' to neocortical areas outside of the medial temporal lobe. According to this theory, recently acquired episodic memories are vulnerable to hippocampal damage, whereas facts that were learnt long ago are not. Similarly, the Declarative Theory predicts that hippocampal damage impairs the acquisition of new knowledge but leaves remote episodic memories intact. Nonetheless, a compelling alternative explanation for these data, as proposed by the Multiple-Trace Theory, is that both recent and remote episodic memories depend on the hippocampus. According to this theory, the hippocampus and adjacent regions (the perirhinal and parahippocampal cortices) connect and store memory traces of the information that represents an event and is stored in the neocortex. Each time the memory of an event is retrieved, a new hippocampally mediated trace is created, such that older memories are represented by more traces than new ones and are therefore less susceptible to disruption. In addition, as more traces of the same event are formed, the information belonging to that event, which is stored in the neocortex, becomes integrated with pre-existing knowledge in a process the authors refer to as 'semanticization' (REF. 10). Thus, the memories of remote events that survive following hippocampal damage tend to be semantic in nature rather than episodic (that is, they are memories of stereotyped oft-repeated scripts rather than of flexibly re-experienced events). Insofar as the remote memories are episodic, they continue to depend on the hippocampus²⁷.

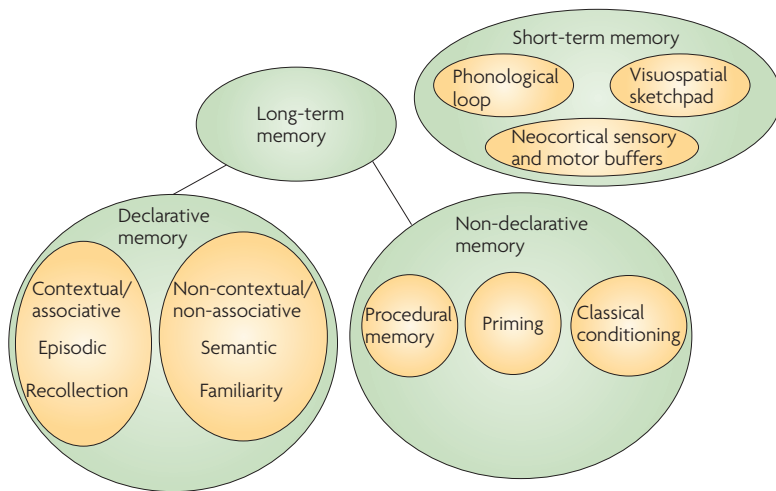


Figure 2 | The traditional taxonomy of memory systems. Inspired in part by experimental data from studies of medial temporal lobe amnesia, many researchers have divided long-term memory into a number of separate systems (for example, see REF. 7). Investigating the neural substrates of these systems and whether and how they interact, and gaining a mechanistic understanding of the processing that is associated with each, presents an exciting challenge for memory research.

The two theories are difficult to tease apart. Both acknowledge that some remote memories for personally experienced events will be resistant to hippocampal and medial temporal lobe damage, although the Multiple-Trace Theory (but not the Declarative Theory) predicts that the quality of these memories will be affected. Given the similarity between these predictions, it is not surprising that the experimental evidence is mixed: some patients have well-preserved semantic but impoverished remote episodic memories^{27–30}, whereas others have well preserved semantic and remote episodic memories^{31–33}. It should be noted that most functional-imaging studies in healthy adults suggest that the hippocampus has a role in episodic memory regardless of the age of the memory³⁴. Nevertheless, such studies do not provide evidence for exactly which aspect of the tasks activates the hippocampus, nor whether involvement of the hippocampus is strictly necessary.

Recognition memory

Semantic memory is a form of non-contextual memory in which the information was typically acquired in childhood or early adulthood. What about other non-contextual memories, such as recognizing someone's name or face without remembering how you know them? Dual-process theories of memory propose that recognition memory is supported by two processes: recollection, which corresponds to Tulving's definition of episodic memory, and familiarity, which is the ability to judge the prior occurrence of an item without retrieving the context in which the item was encountered^{35–37}. According to the Declarative Theory, both processes are underpinned by the hippocampus in concert with other medial temporal lobe regions. However, several researchers have linked these processes to distinct anatomical substrates^{11,38–40}, with the

hippocampus supporting recollection and the perirhinal cortex supporting familiarity. The main proponents of this version of the Dual-Process Theory drew their inspiration largely from electrophysiological and lesion studies in animals¹¹.

Several studies have shown that recognition memory, which can theoretically be subserved by familiarity alone, is impaired by selective hippocampal damage, consistent with the Declarative Theory^{41–43}. However, a number of detailed single-case studies and group studies have documented spared recognition memory in the context of hippocampal damage that resulted in marked episodic-memory deficits^{44–48}. Thus, the issue of whether dual-process theories offer a superior account of the patterns of impaired and spared memory processes following hippocampal damage remains controversial (compare REF. 49 with REF. 50).

Spatial processing

Spatial memory problems, such as getting lost or forgetting where objects have been placed, are a common consequence of hippocampal damage in humans. However, interest in spatial processing by the hippocampus was driven most strongly by the discovery of 'place cells' in rats⁵¹. In the 36 years since this discovery, place cells have also been documented in monkeys and humans^{52,53}, and a wealth of experimental data has accumulated that characterizes their properties⁵⁴ (BOX 2).

Place cells fire when an animal is at specific locations in an environment (the cell's 'place field') and, as the animal explores an open environment, the ensemble of cells provides a stable representation of the animal's location, independent of its orientation. Thus, place-cell firing does not simply reflect direct sensory input; if that were the case, the firing would change greatly as the rat changed the direction in which it was facing. Instead, place cells appear to be tuned to the conjunctions of bearings to extended boundaries in the environment, rather than local environmental features^{55,56}, although firing rates are nevertheless modulated by the latter. Place cells encode a 'sense of location', as corroborated by a consistency between search locations and place-cell firing^{57,58}.

Besides responding to incoming perceptual information, place cells are also driven by self-motion signals (proprioceptive, vestibular and reafferent signals from intended movements), which indicate the location of the animal on the basis of its own movements — a process referred to as 'path integration'. This process is probably supported by so-called 'grid cells', which have a strikingly regular spatial-firing pattern and are found in the entorhinal cortex⁵⁹ — the main neocortical input to the hippocampus. Consequently, the place fields are maintained even when all orienting cues are removed, demonstrating that they encode the 'memory' of a location.

Place fields in familiar environments remain stable for several weeks, which suggests that place cells encode a long-term memory for that environment⁶⁰. Place cells also perform pattern completion and pattern separation, which are indicative of an attractor network⁶¹. Thus, they generalize across minor changes to the dimensions

Recurrent connections

The extensive reciprocal connections between principal CA3 neurons. This unusual neural architecture might provide a substrate for the implementation of an attractor network that supports associative memory.

Pattern completion

A process by which a stored neural representation is reactivated by a cue that consists of a subset of that representation.

Path integration

The ability to keep track of the start position of a trajectory by integrating the movements made along the path.

Box 1 | Theories of hippocampal function

Several theories regarding the role of the hippocampus in memory have been proposed over the years. All regard the hippocampus as being critical for episodic memory, but there are key differences in whether they view the hippocampus as having a time-limited role in episodic memory and in whether they deem it to be necessary for the acquisition of non-contextual information.

Declarative Theory^{7,8}

The hippocampus, acting in concert with other medial temporal lobe regions, is crucial for all forms of consciously accessible memory processes (episodic and semantic, recollection and familiarity) for a time-limited period. Ultimately all memories are consolidated to neocortical sites and are thus unaffected by subsequent medial temporal lobe damage.

Multiple-Trace Theory⁹

The hippocampus, together with other medial temporal lobe regions, is crucial for the acquisition of episodic and semantic memories. The recollection of episodic memories remains dependent on the hippocampus for the duration of one's life and becomes more resistant to partial damage with repetition and/or rehearsal, whereas semantic memories become independent of the hippocampus and are stored in other brain regions over time.

Dual-Process Theory^{11,39,40,122}

The hippocampus is crucial for episodic recollection of the contextual details of an event. Familiarity-based recognition processes are subserved by other medial temporal lobe regions. Recollection is required for the associative recognition of non-unitized items (for example, voice-face pairs).

Relational Theory^{12–14}

The hippocampus allows the flexible association of information in neocortical modules that could not otherwise communicate. This enables the relations between elements of a scene or event to be retrieved or used for inference in novel situations, in addition to retrieval of the elements themselves. The Cognitive-Map Theory can be subsumed as a special case of spatial relational processing.

Cognitive-Map Theory¹⁵

A primary role of the mammalian hippocampus is to construct and store allocentric (world-centred) representations of locations in the environment to aid flexible navigation, for example, from a new starting position. In humans these predominantly spatial processes have evolved to support the spatio-temporal context of episodic memories.

and features of an environment, allowing the animal to remain orientated. However, if a familiar environment is dramatically changed or gradually altered to become more similar to a different familiar environment, the place-cell representation will abruptly change (referred to as 'remapping')⁶² to signal that the animal is now in a different environment.

Construction of mental images

The place-cell representation of spatial location, together with information encoded by head-direction cells (BOX 2) and parietal representations of the locations of stimuli relative to the eye, head or body, provides functional constraints for the processing of spatial information by the hippocampus and related structures. On this basis, Byrne, Becker and Burgess proposed a computational model of the neural mechanisms that underlie spatial memory and imagery^{63–65} (the BBB Model; see BOX 3 and see REF. 66 for a related model). Although the BBB Model involves a network of regions in the medial temporal, parietal and prefrontal lobes, we use it in this Review to explain the specific part that is played by the hippocampus.

When we think back to events that have occurred to us, we are often able to summon up a mental image of

the event and play through some of the details. The BBB Model proposes a crucial role for the hippocampus in this ability, with place cells reactivating representations of the spatial geometry of the environment and the locations of objects in it. The geometric information, distances and bearings to extended environmental boundaries (for example, walls of buildings) are probably represented in the parahippocampal cortex⁶⁷, whereas object information and featural information are probably represented in the perirhinal cortex⁶⁸. Following Marr's model^{16,17}, the BBB Model envisages reciprocal connectivity between place cells and these neocortical regions, so that activating place cells will reactivate the corresponding representations in the neocortex and allow events to be imagined in a spatially coherent manner. Thus, the full representation of a place, comprising the location of the observer as well as the location and appearance of the surrounding landmarks, can be retrieved following the presentation of a partial cue (for example, a single landmark) through the process of pattern completion. Place cells constrain the retrieval of information so that it is consistent with a particular environment and with perception from a single specific location in that environment. This constraint might be important considering the vast amount of information that is accessible to memory and the potentially exponential number of ways in which this information could be combined.

According to the BBB Model, the products of this reconstructive process can be examined in visual imagery: the allocentric parahippocampal representation (north, south, east, west) is translated into an egocentric medial parietal representation (left, right, ahead) by processing in the posterior parietal cortex and the retrosplenial cortex/parieto-occipital sulcus, and by using the representation of head-direction found along Papez's circuit⁶³. The model thus provides a functional explanation for the involvement of these extra-hippocampal areas in episodic retrieval^{11,69}. More generally, the brain areas that are required by the model correspond to the areas that are commonly activated during functional neuroimaging of memory tasks for spatial context and navigation⁶⁴, and also to areas that are involved in imagery^{70,71}.

What happens when you want to shift your viewpoint within a remembered scene? The BBB Model suggests that just as actual movement signals update the animal's sense of location in an environment, simulated movement signals that are generated in the prefrontal cortex might allow imagined shifts of view or position through processing in parietal or entorhinal cortices⁶³. The hippocampal place-cell representation would then constrain the imagined scene to ensure that it remains spatially coherent during motion and remains consistent with the imagined environment.

Episodic and semantic memory revisited

How do the insights gained from spatial processing bear on the role of the hippocampus in episodic and semantic memory? The BBB Model predicts that the hippocampus is necessary for the construction of a spatially coherent mental image of any remembered scene, including shifts in viewpoint that enable one to mentally play through

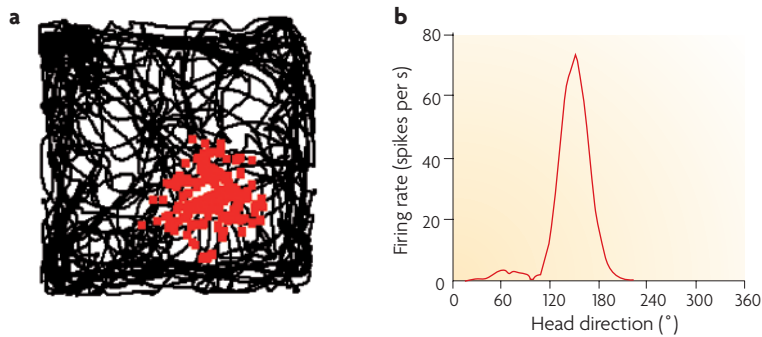
Pattern separation

A process by which small differences in patterns of input activity are amplified as they propagate through a network. This creates distinct representations.

Attractor network

Neural networks that have one or more stable 'states' (that is, patterns of firing across neurons). The stable states are determined by the strengths of the recurrent connections between the neurons in the network. Depending on the initial conditions, the network will end up in one of the stable states. This can allow pattern completion to occur.

Box 2 | **Neuronal representations of spatial location**



In this Review, we focus on insights provided by two types of neuron that are involved in the representation of a mammal's spatial location in its environment. Place cells are found in the hippocampus. Different place cells fire in different environmental locations (see part **a** of the figure; the rat's path is denoted by the black line and each red dot indicates the animal's location when an action potential was fired), and the firing of a population of place cells in an open field represents the animal's location in that field independently of the animal's orientation. The firing location of a place cell is controlled by self-motion and by perceptual information. Place cells have short-term and long-term memory properties and show pattern separation, firing differently in sufficiently distinct environments, and pattern completion, accommodating for smaller variations or missing cues. Head-direction cells are found throughout 'Papez's circuit'. Their firing represents the direction in which the animal is heading, independent of its current location (see part **b** of the figure, which shows the firing rate of a population of head-direction cells as an animal turns through 360° from a given direction), and the firing direction is controlled by self-motion and perceptual information. Head-direction cells show pattern completion and accommodation for missing cues, and probably set the environmental orientation of the responses of place cells. A third type of cell, grid cells, has recently been discovered⁵⁹, and these cells probably have an important role in providing self-motion information to place cells. Figure adapted, with permission, from REF. 143 © (2006) Elsevier Science.

events. This aspect of retrieval, we argue, is not only hippocampus-dependent, but might also typify the phenomenological experience of recollection. Crucially, this will not depend on the age of the memory itself. Thus, whenever a memory is tested by requiring this type of imagery, the performance will be hippocampus-dependent regardless of how long ago the memory was acquired (consistent with the Multiple-Trace Theory, experimental evidence from some amnesic patients^{27,29,30} and most neuroimaging studies³⁴). By contrast, abstract geometric information and object featural information will depend on the parahippocampal and perirhinal cortices, respectively, with even more widespread storage of other aspects of semantic knowledge.

One line of evidence that is apparently at odds with the predictions of the BBB Model is reports of patients with extensive hippocampal damage who show intact memory of complex spatial information that was acquired a long time prior to the occurrence of the damage^{72,73}. These patients were able to describe routes around their home towns, including when main routes were blocked, and were able to specify the directions and distances to particular landmarks from other locations. On the face of it, such evidence supports the Declarative Theory (which states that memories are consolidated to regions outside of the hippocampus) rather than the BBB Model described above, in which the hippocampus would be expected to aid performance.

Papez's circuit

A network of limbic brain structures that was originally thought to subserve emotional processing. These structures include the cingulate cortex, the hippocampus, the mammillary bodies, the anterior thalamus and the projections between these areas, such as the fornix.

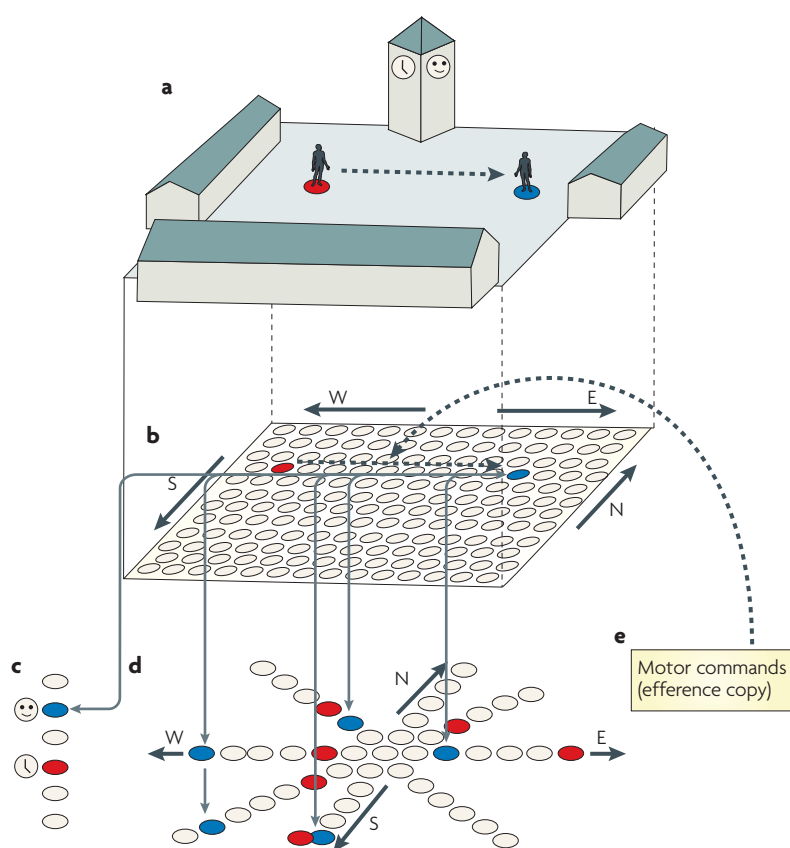
However, rather than a transfer of spatial representations out of the hippocampus and into neocortical regions, it is possible that alternative sophisticated spatial representations are established outside of the hippocampus in parallel with the hippocampal representation (as proposed by the Multiple-Trace Theory). We consider two such possible representations. First, people often have semantic knowledge of symbolic diagrams or maps of their region. These artefacts usually indicate the relative locations of landmarks, as well as direct and indirect routes between them. However, recollection of these artifacts does not require imagined travel along the route or the construction of a mental image of a scene, and so the artifacts can be retrieved and examined in working memory independent of the hippocampus. Second, the representation of routes between locations (which is thought to depend on the dorsal striatum rather than the hippocampus^{74–76}) might be more sophisticated than simple chains of stimulus–response associations or motor commands. Recent work suggests that the dorsal striatum can represent locations in terms of bearings from landmarks, and that these can be as effective for navigation as the representations that are mediated by the hippocampus^{77,78}.

For these reasons, spatial-memory tasks that require the use of the hippocampus to recollect highly familiar environments are difficult to devise. One method is to use virtual-reality simulations of familiar real-world environments. A recent study that used this technique found that a patient with hippocampal damage was impaired on a navigational task, at least when they were virtually travelling on minor roads⁷⁹.

An interesting aspect of this conceptualization of hippocampal processing is that the imagined scene does not have to be a 'true' memory. Rather, the hippocampus is proposed to be necessary for dynamic mental imaging of any spatial scene. Thus, contrary to characterizations of hippocampal function in terms of 're-experience' or 'mental time travel' within episodic memory, the hippocampus should be just as necessary for imagining novel environments as it is for reconstructing images of previously experienced ones.

Direct evidence for hippocampal involvement in imagining novel events comes from a study⁸⁰ that, rather than specifically probing the ability of patients with hippocampal damage to imagine future personal events, required patients to imagine fictitious scenarios, such as standing in the hall of a museum or lying on a sandy beach. The study participants were specifically instructed neither to try to recall an actual memory nor to imagine something that they planned to do. Patients with hippocampal damage were significantly impaired on the task and produced less detailed descriptions of the imagined scenes than control participants. Further analyses suggested that the patients' descriptions were particularly lacking in spatial coherence, indicating a specific deficit in working memory for spatial scenes (see the section on short-term memory below). A functional-imaging study of this task in healthy adults showed that the hippocampus was activated during the period of imagination⁸¹, and the same authors concluded from

Box 3 | Modelling the firing properties of place cells (BBB Model)

**Place-cell firing when one is in an environment**

Part **a** of the figure represents a large arena surrounded by grey buildings. The building to the north has a clock face on one side and a face motif on the other. A man first occupies the red location (close to the west building and with the clock face in view) and then moves to the blue location (close to the east wall and with the face motif in view). Part **b** of the figure represents a set of place cells in the hippocampus. One is shown as being active when the man is in the red location and another is shown as being active when the man is in the blue location (in reality, multiple cells fire at any given location). Part **c** of the figure represents cells in the perirhinal cortex that are activated by visual objects. The blue cell is active when the face motif is visible and the red cell is active when the clock face is visible. Part **d** of the figure represents cells in the parahippocampal cortex that are active when an environmental boundary is present at a certain distance and bearing from the observer (boundary vector cells; BVCs). The BVC cells' distance from the centre indicates the boundary's actual distance from the man's current location (in the red position the west building is close and the east building is far; in the blue position the west building is far and the east building is near). Reciprocal connections between the three cell types (indicated for the blue cells only by grey arrows) and between place cells that represent similar locations bind the BVCs and the object and place representations together to allow subsequent pattern completion. The place cells are driven by a combination of perceptual inputs and self-motion information (path integration, represented by the dashed arrow in part **e** of the figure), either of which can individually update the place-cell representation.

Place-cell firing when one is imagining an environment.

When recollecting or imagining a scene, place cells are required to impose a location from which to view the scene. This ensures that the imagined scene is spatially coherent. Partial input cues (for example, two adjacent buildings) will instigate a process of pattern completion by which a specific place representation will become active and retrieve the surrounding environmental features that are bound to (that is, perceivable from) that location. The viewing direction is imposed by the head-direction cells that are found along Papez's circuit, allowing the generation of an egocentric image in medial parietal areas. Imagined movements in the (re)constructed scene are achieved through simulated self-motion information that is generated by prefrontal regions (part **e** of the figure).

a recent review of the imaging literature that the brain regions that are involved in memory tasks that involve rich mental imagery (such as episode recall and route planning/wayfinding), including the hippocampus, were the same as those involved in imagination⁷¹ (see also REFS 64,70,82).

Of course, any imagined scene is likely to be a recombination of elements from experienced events. Consequently, it is difficult to ascertain whether the hippocampal contribution to imagination is retrieving the elements of a scenario or combining them into a coherent scene. The BBB Model would strongly predict that it is the latter process — a prediction that appears to be borne out by reports of patients with amnesia. For example, amnesics are relatively good at generating exemplars of a particular semantic category and describing the appearance of objects^{83,84}.

Semantic memory is information that is divorced from the context in which it was acquired. Its retrieval does not require the construction of a mental scene, and is thus not likely to be hippocampus-dependent. However, can insights from spatial processing address the apparent role of the hippocampus in the acquisition of new semantic knowledge? Acquiring the simple motoric representation of a familiar route (that is, the sequence of movements to be taken) might provide an analogy for some types of semantic learning. Hippocampus-dependent spatial memory might be required to guide behaviour while the representation is being formed¹⁵, but once it has been formed the representation is independent of the hippocampus and can be expressed inflexibly — that is, independently of the current context (obstacles permitting). An extension of this interpretation is that the hippocampus might support the rehearsal of a learning event, which would enable the event to be incorporated into an extra-hippocampal semantic system. This would be consistent with Marr's model and the related complementary-learning-systems approach²¹, and also with the idea that the hippocampus can support imagery for the learning event. It also shares obvious conceptual similarities with the Multiple-Trace Theory (see above).

Recognition memory revisited

The debate concerning recognition memory and the hippocampus has recently revolved around the issue of whether or not the hippocampus is crucial for familiarity-based processes^{49,50}. Experimenters have traditionally not focused on the specific materials that have been used to test recognition memory. However, recent studies have suggested that the nature of the to-be-remembered materials has a profound effect on performance.

Clear-cut material-specific recognition-memory impairments have recently been described in the non-verbal domain, in which faces were compared with scenes. Carlesimo and colleagues described a patient with bilateral hippocampal damage who showed a selective sparing of face learning but had deficits in other non-verbal recall tasks and scene recognition⁸⁵. Another case report of a patient with selective hippocampal

Box 4 | A role for the hippocampus in spatial perception?

The question of whether the hippocampus has a role in perception is currently a subject of intense debate. Hartley *et al.*¹⁰⁶ investigated scene perception (matching locations from different views; FIG. 3a) in four patients with focal hippocampal lesions (one a unilateral lesion in the right hippocampus). Two of the patients with hippocampal damage performed normally, including the oldest and most densely amnesic patient, whereas two were mildly impaired and scored at the same level as the lowest-scoring healthy control participant. Imposing a 2-second delay between the presentation of the study and the test images caused the performance of all four patients to drop to almost chance levels.

In a task that required the matching of a test scene with the more similar of two sample scenes (FIG. 3c), Lee *et al.* documented an impairment in four patients with hippocampal damage, at least on the most difficult items¹⁰⁸. The same patients were additionally impaired at spotting the odd-one-out of four pictures of empty rooms shown from different viewpoints¹⁰⁷ (FIG. 3d). However, another study failed to replicate the first of these findings in six patients with hippocampal damage, two of whom had extensive additional medial temporal lobe atrophy¹¹⁰. Nevertheless, the scene-matching task requires assessment of the degree of overlap of features in the photographs, rather than matching of the location itself, so it is perhaps a less pure test of spatial perception than the empty-room, odd-one-out task.

Although the evidence for spatial-perception deficits resulting from hippocampal damage is mixed, it might be that terms such as 'memory' and 'perception' are poor labels for the processes that are being tapped by these tasks. Any perceptual test requires the maintenance of the information across saccades, and odd-one-out tests require more comparisons between stimuli than match-to-sample tests. The hippocampus seems to be involved in maintaining flexible representations of spatial stimuli (see main text), and so tasks that place greater demands on this capacity are more likely to be impaired by hippocampal damage. When alternative strategies to solve the task are available, such as point-to-point matching of visual features, impairment is less likely to be seen.

damage documented a general sparing of recognition memory, including in tasks that used faces, but performance in tasks that used scenes was consistently impaired⁸⁶. These findings were replicated in a recent study of three patients with hippocampal lesions. This study explicitly compared face recognition with scene recognition, and found that the patients' face recognition was intact but their scene recognition was impaired⁸⁷.

Are such impairments explained by dual-process theories? That is, is face recognition underpinned by familiarity whereas scene recognition is underpinned by recollection? This hypothesis was tested in a study of three patients with focal hippocampal damage^{84,88,89}. The study used receiver operating characteristic analyses to tease apart the putative contributions of recollection and familiarity to the recognition of faces and scenes following the presentation of long lists of these materials. In groups of healthy adults there was no difference in performance between the tasks, either in terms of overall difficulty or in the relative contributions of recollection and familiarity to task performance. The three patients showed the same pattern of spared face recognition but impaired scene recognition. Interestingly, both recollection and familiarity for faces was spared in all patients. Some residual scene recognition might have been supported by familiarity processes alone, but familiarity was clearly unable to support normal levels of scene-recognition performance in the patients.

According to the BBB Model, these findings reflect the ability of the hippocampus and surrounding areas to efficiently support scene recognition by capturing the

spatial geometry of a scene and the location of the objects in it. Limited numbers of scenes might be represented by areas outside of the hippocampus, so as to support recognition from the same point of view, but performance would become impaired in tasks that use large numbers of scenes. Conversely, it might be that the hippocampus simply does not have the machinery for representing unfamiliar faces presented in isolation. In that case, performance on face-recognition tasks would be similar in patients with hippocampal damage and healthy controls, at least over relatively short study-test intervals. Indeed, experimental evidence suggests that the fusiform gyrus, the perirhinal cortex and the temporal pole might be crucial for face-recognition memory^{87,90–92}.

Short-term memory

The traditional view of hippocampal amnesia is that short-term memory is preserved despite the severe impairment in long-term memory^{93–95} (FIG. 2). This is unquestionably the case when short strings of letters or digits⁹⁶, or short motoric sequences ('block tapping'), are to be remembered⁹⁷. However, these preserved abilities reflect the availability of dedicated neocortical systems that are capable of the short-term retention of specific types of stimulus (that is, the sensory buffers and verbal or visuo-spatial components of short-term memory⁹⁴). They do not imply that the hippocampal contribution to memory is necessarily constrained to long-term memory. Rather, there is now a large body of literature that documents impairments in retaining information over short intervals. The bulk of these studies have involved patients with medial temporal lobe lesions that were not necessarily restricted to the hippocampus. Deficits have been noted on tests that used materials such as faces^{98,99}, colours^{98,100}, locations^{98,100} and object-location or colour-location conjunctions^{98,100–102}. In this section we restrict our discussion to studies that have specifically investigated the role of the hippocampus in short-term memory. We also include studies that investigated spatial perception, because we wish to draw a distinction between long-term memory and the online representation of information (BOX 4).

We have suggested that the hippocampus is needed to mentally shift viewpoints in an imagined scene. Recognition memory for short lists of objects or locations is hippocampus-dependent if a shift in viewpoint is introduced between the study object and the test object (requiring a mental shift in view^{103,104}), but not if the environment is rotated in full view of the patient¹⁰⁵. In addition, the hippocampus-dependent impairment in same-view recognition becomes apparent with longer lists¹⁰⁴. What if the topographical information in a scene need only be retained for 1–2 seconds? This ability was tested by Hartley and colleagues¹⁰⁶ using a task that required retention of the topographical layout of computer-generated landscapes (FIG. 3a). Four patients with focal hippocampal damage showed dramatically impaired performance when they were asked to recognize a scene from a shifted viewpoint after a delay of approximately 2 seconds. The experiment also included

Saccade

Quick, simultaneous movements of both eyes in the same direction, allowing one to fixate rapidly on elements of a visual scene or a passage of text.

Receiver operating characteristics

(ROCs). An ROC describes the relationship between hits and false alarms across varying confidence levels. Yonelinas has argued that the shape of the ROC varies according to the independent contributions of recollection and familiarity to performance on a memory task.

Sensory buffers

Dedicated neocortical systems that (independently) support the short-term maintenance of sensory, motor, linguistic or other information.

a difficulty-matched non-spatial task, in which the time of day or year of the scene had to be matched using the conjunction of weather, lighting and vegetation (FIG. 3b). None of the patients was impaired on this task.

Scene-processing deficits were noted in the performance of four patients with bilateral hippocampal damage (two of whom had additional parahippocampal damage)^{107–109} in tasks that used two types of spatial

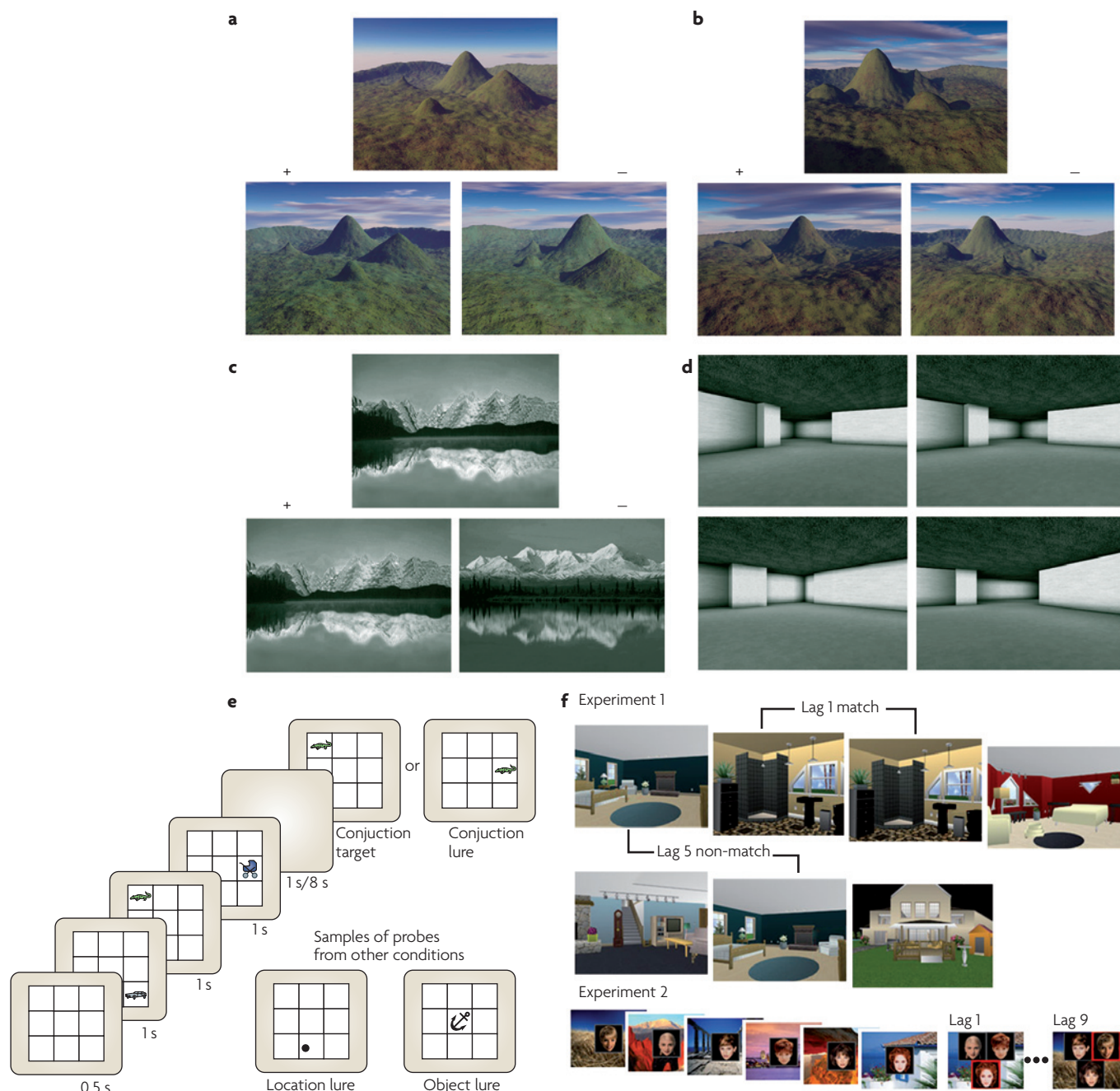


Figure 3 | Stimuli used to investigate the role of the hippocampus in perception and short-term memory. Correct matches are indicated by a +. **a** | Participants were asked to match the topography of the scene (the shape and layout of the mountains) with that of the same scene from a different view (3 foils were used in the actual task)¹⁰⁶. **b** | Participants were asked to match the time of year or time of day (using the weather, the lighting and the vegetation) of different locations (3 foils were used in the actual task). **c** | Participants were asked to match the most similar pictures. **d** | Participants were asked to select the odd-one-out: three of the pictures show the same room, whereas one shows a different room (the odd-one-out is the bottom left picture)¹⁰⁷. **e** | Participants were asked to remember the location of the object in the grid (conjunction trials), or just the location or the object (other trials)¹¹¹. **f** | Experiment 1: participants were asked to detect whether any of the objects in the scene had moved (non-match trials)¹¹⁵. Experiment 2: participants were asked to remember which face was paired with the scene. Part **c** reproduced, with permission, from REF. 108 © (2005) Wiley. Part **d** reproduced, with permission, from REF. 107 © (2005) Wiley. Part **e** reproduced, with permission, from REF. 111 © (2006) Society for Neuroscience. Part **f** reproduced, with permission, from REF. 115 © (2006) Society for Neuroscience.

stimuli: either paired pictures of outdoor scenes that had been digitally blended to reduce discriminability, or images of empty rooms that had to be matched across viewpoint changes (FIG. 3c,d). In tasks that used various test procedures (discrimination, oddity judgements, categorization and perceptual learning), the patients consistently showed impairments in the processing of scenes but not in the processing of faces or other complex objects. In fact, these deficits were noted even when the target and match stimuli were presented concurrently, suggesting an impairment in spatial-perception tasks. However, a separate study that used similar morphed images of scenes¹¹⁰ found no evidence for deficits in scene discrimination, either in patients with hippocampal damage or in patients with more extensive lesions of the medial temporal lobe (BOX 1).

The first clear evidence of a role for the hippocampus in the retention of information over short periods was reported by Olson and colleagues¹¹¹. The task involved watching a grid in which three objects were serially presented in different locations (FIG. 3e). Although patients with hippocampal damage were unimpaired at remembering the objects and the locations where the objects had been presented, they were impaired at remembering the object–location associations. The authors stressed that the key hippocampal impairment concerned processing the conjunctions of object identity and spatial location, rather than the retention interval — a finding that is consistent with impairments on ‘object-in-place’ tasks in animal lesion studies^{112–114}. According to the BBB Model, the place-cell representation is associated with both object information (in the perirhinal cortex) and environmental layout (in the parahippocampal cortex) (see also REF. 40). As each object is presented, it can be added to a single coherent representation of the spatial layout, from which ‘scenes’ from a specific viewpoint can be generated. This allows more efficient storage of multiple objects and their locations than alternative, egocentric representations of location in the parietal cortex, and also explains the role of the hippocampus in tasks that require the retrieval of information from a new viewpoint.

Another recent study that demonstrated object–location memory impairments over short intervals used three-dimensional pictures of computer-generated scenes¹¹⁵ (FIG. 3c). Again, hippocampal damage impaired the ability to detect changes in the positions of objects in the scene. Interestingly, the same patients were similarly impaired in a task that required memory for face–scene associations. The latter finding is not easily understood in a spatial-processing framework and illustrates the involvement of the hippocampus in processing non-spatial relationships between stimuli. We discuss this further in the next section.

To date, it is not clear whether some or all of the tasks discussed above involve the active maintenance of information in short-term memory, or whether the information must be stored and subsequently recollected after a brief delay. When one moves in an environment with one’s eyes closed (or when one imagines

moving in an environment), the impression one has is of a continuously updating representation of the relative locations of the environmental landmarks (which is consistent with place cells firing in the absence of visual input). However, further research is needed to clarify this issue.

Non-spatial processing

It is well established that hippocampal damage can impair performance on tasks that do not impose any overt spatial-processing demands. The BBB Model was not designed to address all of these non-spatial aspects of hippocampal processing, but other theories have been proposed to explain them. In this section we consider some of the clearest examples of non-spatial processing, and some of the models that might account for these findings.

Hippocampal damage often impairs the learning of arbitrary associations between items, such as word–word pairings or face–voice associations, even if recognition of the items in isolation is intact^{40,49,116}. In addition, the learning of sequences of digits and the ability to make judgments about the order in which items were presented in a test is hippocampus-dependent^{97,117,118}. In rodents, simple stimulus–reward association learning is resistant to hippocampal damage, but the information that is learnt is relatively inflexible¹¹⁹. The Relational Theory of hippocampal function¹² was advanced to account for these findings, as well as the spatial findings considered by O’Keefe and Nadel¹⁵. It proposes that the hippocampus is required for associating perceptually and conceptually distinct items. By forming such associations, information that is learnt in one context can be flexibly expressed in another, and generalizations and inferences about conjunctions of individual stimuli can be made. According to this theory, ‘space’ merely describes one way of organizing multiple stimuli, and spatial processing is only one example of relational processing. As well as capturing aspects of the experimental data that are not addressed by purely spatial theories, the Relational Theory also explains deficits that are not restricted to long-term explicit memory. For example, deficits have been found in implicit memory^{120,121} and in memory over short delays using relational materials¹¹⁵. The precise nature of the relational processing that is supported by the hippocampus, and its relationship to episodic or declarative memory, remains a topic of current research.

There are also many computational models of hippocampal function that are based at a level of abstraction above the specific characteristics of the information to be processed, be it spatial or non-spatial. For example, Norman and O’Reilly implemented a dual-process model of memory that models recollection- and familiarity-based recognition judgements¹²². According to this model, the hippocampal system can retrieve the entire sample stimulus for comparison with the target (approximating recollection), much as Marr suggested. By contrast, the neocortex can only support a familiarity signal by comparing the target with the sample’s synaptic trace (see also REF. 123). This allows quantification

of the increasing dependence of recognition memory on the hippocampus as targets and foils increase in similarity. This dependence was observed in a patient with selective hippocampal damage¹²⁴ (although see REF. 125, which failed to replicate these findings). We note that increasing the difference between the test cue and the presented item also increases the reliance on hippocampus-dependent recollection and/or pattern-completion, rather than familiarity. This corresponds to the increased dependence on the hippocampus when testing spatial memory from a new point of view compared with an old one. However, it is not so clear how the notions of recollection and familiarity apply more generally to the continuous updating of spatial representations with real or imagined self-motion.

Relational theories^{12–14} and dual-process theories^{11,39,40,122} offer domain-general explanations of hippocampal function. However, there is no consensus for defining exactly what constitutes the ‘items’ that do not require hippocampal processing in order to be stored and retrieved. Such items are often referred to as being ‘unitized’. It has been variously argued that these include: single items but not inter-item associations¹²⁶; single items and also within-domain (such as face–face) associations¹¹⁶; or that they are the output of domain-specific modular processing systems¹³. Nonetheless, the predictive power of these theories is weakened by the difficulty in applying these ideas to specific stimuli. For example, it is unclear why the topographical layout of a scene (that is, its surface geometry) should be less unitized than the arrangement of eyes, nose, mouth, *et cetera* that defines a face.

Other models of hippocampal function focus on the ability to store sequential information, either through associations from one pattern to the next through recurrent connections in CA3 (for example, see REFS 127–129) or through temporal coding in each theta frequency-range cycle¹³⁰. An extension of this approach sees the hippocampus as providing a slowly varying temporal-context signal that is suitable for encoding sequences of stimuli or actions, as these can be associated to successive states of the context signal^{131–135}. These models also suggest that the hippocampus mediates associations between spatially or temporally discontinuous events¹³⁶. They also provide a common explanation for the way in which, in humans, recollection of one word from a list tends to lead to the retrieval of the next few words, and for the way in which, in rats, the firing of some entorhinal cortical neurons reflects the recent pattern of the rat’s movement¹³². Moreover, these models capture the sequential nature of some aspects of episodic memory and link this to the neural mechanisms of spatial memory, retrieving sequences in the same way that a previously travelled route could be retrieved as a sequence of locations.

Future directions

We have discussed a new model of hippocampal processing that is based on the spatial firing properties of hippocampal neurons. In remaining close to the neurophysiological data, we can specify the nature of

the information that hippocampal neurons represent and the computations that they perform on it. These data provide powerful constraints on the way in which information can be recalled — that is, they specify how retrieved information must be consistent with being at a single location. They also provide constraints on the mechanisms by which the products of retrieval could be imagined — that is, they specify how a specific viewpoint or series of viewpoints could be imposed onto the retrieved information. This view of hippocampal function is consistent with the proposal that the hippocampus provides the ability to ‘re-experience’ episodic events²⁶, as long as the subjective feeling of ‘re-experience’ equates to the ability to generate detailed visuo–spatial imagery from a dynamic viewpoint.

However, both the identification of hippocampal processing with subjective re-experience and our identification of this with detailed dynamic imagery require further work, and it seems likely that the hippocampus does support aspects of memory that do not overtly rely on visuo–spatial imagery. For example, memory for an event will include actions and knowledge specific to that event, which can be recollected without needing to imagine the entire scene. Can our approach be extended to such non-spatial aspects of episodic memory? One starting point might be the non-spatial factors that modulate the firing of hippocampal place cells, including aspects of the rats’ behaviour, as well as objects, odours^{137–141} and the passage of time¹³⁵. At the very least, these findings suggest a combined encoding of locations with the content and temporal context of the events occurring there.

In a more general sense, place-cell firing might offer insights into the organization of conceptual space in the human hippocampus. For example, a recent study investigated memory for knowledge that is associated with a specific person. In this study, neurons in the hippocampus of epilepsy patients responded to the faces of particular famous people¹⁴². As with place cells, these neurons did not respond to specific sensory details, but rather to the concept of the person’s identity, irrespective of the specific photo and even of the person’s name. These ‘face cells’ might exist in a conceptual space with a structure that resembles that of the place-cell representation of physical space. This possibility could be investigated by systematically morphing faces to provide a metric for assessing neural-response curves.

In conclusion, we hope that highlighting the mechanistic constraints on memory and imagery that are provided by neural-level physiological data has provided some insight into competing theories of hippocampal function. Even though these data come predominantly from the spatial domain, they allow a consideration of computationally specific mechanisms that complement the traditionally erudite but often intangible theorizing in this field. It is our hope that integrating neuronal data into the consideration of the mechanisms that underlie human memory will advance the field beyond the current apparent impasse of conflicting descriptions.

Unitized stimuli

Uni-modal elements of an event that, according to dual-process and relational theories, can be represented and subsequently recognized by brain regions outside of the hippocampus.

Theta frequency range

Rhythmic activity (4–12 Hz) detected in the local field potential or by electroencephalogram. This rhythm is particularly prominent in the hippocampus of rats during locomotion and has recently been related to mnemonic processing in both rats and humans.

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This book is an excellent source for anyone interested in hippocampal function: it reviews molecular, synaptic, physiological and cognitive data.
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This book lays out the Cognitive-Map Theory, summarizing the properties of hippocampal place cells, the effects of hippocampal lesions in rats and implications for the role of the hippocampus, including one of the first suggestions of a specific role in context-dependent memory.
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FURTHER INFORMATION

Neil Burgess's homepage: <http://www.icn.ucl.ac.uk/research-groups/Space-and-Memory-Group/index.php>

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