

The hippocampus, space, and viewpoints in episodic memory

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A computational model of how single neurons in and around the rat hippocampus support spatial navigation is reviewed. The extension of this model, to include the retrieval from human long-term memory of spatial scenes and the spatial context of events is discussed. The model explores the link between spatial and mnemonic functions by supposing that retrieval of spatial information from long-term storage requires the imposition of a particular viewpoint. It is consistent with data relating to representational hemispatial neglect and the involvement of the mammillary bodies, anterior thalamus, and hippocampal formation in supporting both episodic recall and the representation of head direction. Some recent behavioural, neuropsychological, and functional neuroimaging experiments are reviewed, in which virtual reality is used to allow controlled study of navigation and memory for events set within a rich large-scale spatial context. These studies provide convergent evidence that the human hippocampus is involved in both tasks, with some lateralization of function (navigation on the right and episodic memory on the left). A further experiment indicates hippocampal involvement in retrieval of spatial information from a shifted viewpoint. I speculate that the hippocampal role in episodic recollection relates to its ability to represent a viewpoint moving within a spatial framework.

I believe that the natural level for a mechanistic understanding of behaviour is the level of neurons. Accordingly, as someone interested in memory, I aim to gain an appreciation of how the actions of single neurons can result in this most important cognitive function. The possible complexity of the action of networks of neurons and their consequences for behaviour means that computational modelling has a central importance in helping to integrate information gained from experiments at the various levels of cells, systems, and behaviour. The term “memory” has been used to describe a wide range of phenomena; here I consider something

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closely related to its meaning in everyday usage: our enduring memory for personally experienced events, known to psychologists as “episodic” memory (Tulving, 1983).

The many and varied operational definitions of episodic memory tend to agree that it is crucial for tasks demanding the recollection of information tied to a particular spatio-temporal context (i.e., the details of an event). Where the stored information is divorced from a particular spatio-temporal context (semantic memory), or where context is not required (as in simple recognition), episodic memory need not be involved (see, e.g., Gardiner & Java, 1990; Knowlton & Squire, 1995). Note that all three processes (familiarity-based recognition, semantic memory, and episodic memory) are included in the definition of declarative or explicit memory (e.g., Squire & Zola-Morgan, 1991). Part of my reason for focusing on episodic memory is that it seems to be dissociable from the other two processes, in being particularly dependent on the integrity of the hippocampus, at least in some cases (see Vargha-Khadem et al., 1997, and later).

Studying the neural basis of episodic memory presents at least two obvious hurdles to overcome. First, personally experienced events and the contexts in which they occur are normally of a rich, varied, and subject-specific nature. Thus experimental control of the stimuli, valid inter-subject comparisons, and the ability to verify information from past events are all difficult to achieve (but see Kopelman, Wilson, & Baddeley, 1989). Second, little is known about the actions of single neurons during the storage or recall of episodic memories, although there is some evidence of consistent firing of neurons in the hippocampus in response to either presentation or imagery of various visual stimuli (Kreiman, Koch, & Fried, 2000).

Given these problems, where should one start? The use of spatial information can help us understand the action of more general processes such as episodic memory. The intrinsic constraints of 3-D space inform the likely computational demands of storing and retrieving spatial information, while the ability to examine similar spatial tasks in humans and animals enables a systems neuroscience perspective incorporating single-cell recording, neuropsychology, and functional neuroimaging. Accordingly, I start with the hippocampus for its role in both episodic memory and spatial behaviour, which I briefly introduce as follows.

Analysis of a large number of neuropsychological cases indicates that damage to the hippocampus in humans invariably leads to impaired performance in subsequent tests of recollection. Damage to the medial temporal lobes is often also associated with impaired memory for events occurring prior to the damage and impairments to semantic memory and familiarity-based recognition. However, the extent of impairment to these processes, and the critical medial temporal loci involved, remain controversial with apparent inconsistencies between different patients (see Spiers, Maguire, & Burgess, 2001, for a review). One suggested resolution of some of the conflicting patterns of memory impairment following various types of lesion was proposed by Aggleton and Brown (1999). In this view, to which I return later, a circuit comprising the mammillary bodies, anterior thalamic nuclei, and hippocampus supports episodic recollection, whereas an adjacent circuit comprising the medial thalamus and perirhinal cortex supports familiarity-based recognition. As well as providing an explanation of much of the literature by assuming damage to one or other of these circuits, this view also provides a clear functional interpretation of two anatomical circuits that are interesting in their own right.

The hippocampal system in the rat is one of the few brain systems in which single-unit recording has allowed the construction of models of cognitive behaviour (in this case spatial

navigation) in terms of the firing of neurons. So perhaps we can deduce functional constraints on the hippocampus from spatial data that can then be applied to memory. Single cells in the hippocampus encode the location of a freely moving rat within its environment, firing whenever it enters a restricted portion of the environment independently of local sensory cues (termed the “place field”, O’Keefe, 1976; O’Keefe & Dostrovsky, 1971). In open environments, the firing of these “place cells” is independent of the orientation of the rat (Muller, Bostock, Taube, & Kubie, 1994). Complementing these cells are “head direction cells” that encode the rat’s orientation within its environment independently of its location (e.g., Taube, 1998). Interestingly, head direction cells are found along the circuit from the mammillary bodies, anterior thalamus, and presubiculum, similar to that identified with supporting episodic recollection.

Location-specific responses have also been recorded in the entorhinal cortex, which forms the major cortical input to the hippocampus proper (Quirk, Muller, Kubie, & Ranck, Jr., 1992). A combined representation of the rat’s location and orientation has been found in the pre- and para-subiculum (Cacucci, Lever, Burgess, & O’Keefe, 2000; see also Sharp, 1996). These cells may form part of the interface between the location and orientation systems as they are found in a region also containing head direction cells that projects both to the entorhinal cells that input to the hippocampus (Caballero-Bleda & Witter, 1994) and to the subiculum, one of the major outputs of the hippocampal system. Note that both representations, of location and orientation, are relative to the external world, or “allocentric”. Consistent with the likely role of these cells in spatial behaviour, lesions of the hippocampus impair the rat’s ability to learn to navigate to a hidden goal (e.g., Morris, Garrud, Rawlins, & O’Keefe, 1982). Recordings in and around the hippocampus of freely moving monkeys have revealed both head direction cells and “spatial view cells” (Rolls, Robertson, & Georges-Francois, 1997), which fire whenever the monkey looks into a particular location (irrespective of the monkey’s location or orientation)—possibly the phylogenetic extension of place cells to creatures with moveable gaze and binocular vision.

To conclude the introduction I must mention the very-well-established involvement of the parietal cortex in spatial processing. Single cells in the posterior parietal cortex of monkeys encode the location of a stimulus in various “egocentric” reference frames: location relative to the eye or head or hand or trunk (e.g., Andersen, Essick, & Siegel, 1985). The responses of single neurons in and around Area 7a of the posterior parietal cortex show “gain field” responses—that is, the firing rate is modulated both by the location of the stimulus on the retina and by the location of the stimulus relative to one of the other reference frames. This type of coding enables information on stimulus location to be translated from one reference frame to another—for example, calculating the azimuthal angle of the stimulus from the head given the angle from the eye and the angle of the eye in the head (Pouget & Sejnowski, 1997; Zipser & Andersen, 1988). Recently, neurons in Area 7a have been found whose responses are modulated by the orientation of the monkey in the testing room, allowing translation of (egocentric) locations relative to the trunk into (allocentric) locations in the world (Snyder, Grieve, Brotchie, & Andersen, 1998). Interestingly, Area 7a is the part of parietal cortex best connected with the medial temporal lobe, projecting into the parahippocampus, presubiculum, and CA1 (Ding, Van Hoesen, & Rockland, 2000; Rockland & Van Hoesen, 1999; Suzuki & Amaral, 1994) and receiving connections from entorhinal cortex and CA1 (Clower, West, Lynch, & Strick, 2001). Consistent with a role in egocentric spatial processing, lesions most

often associated with the right inferior parietal cortex in humans often lead to hemispatial neglect (see, e.g., Vallar, 1993, but see also, Guariglia, Padovani, Pantano, & Pizzamiglio, 1993; Karnath, Ferber, & Himmelbach, 2001). In this condition, patients ignore stimuli as a function of how far to the left they are relative to the trunk or head or relative to other competing stimuli (see, e.g., Burgess, Jeffery, & O'Keefe, 1999; Thier & Karnath, 1997, for collected works). In one interesting form of this condition, neglect applies to the left of a given viewpoint in an imagined scene (Beschlin, Cocchini, Della Sala, & Logie, 1997; Bisiach & Luzzatti, 1978; Guariglia et al., 1993; Meador, Loring, Bowers, & Heilman, 1987; Ortigue et al., 2001).

In the rest of this paper I review some computational and experimental studies relating to spatial and episodic memory and its neural bases. This reflects recent work with many collaborators, referred to as "we", and referenced as appropriate. One of the conceptual links that I will make between spatial representations and episodic recollection is simply that recalling the scene of an event or imagining a familiar place involves imposing a particular viewpoint on the stored information. Thus we might expect a link between systems representing the subject's location and orientation (such as the hippocampus and head direction system) and systems involved in recollection from memory.

Computational modelling

Single units and spatial memory

One of the most obvious questions raised by the observation of place cells is: How do the cells know when to fire—that is, what environmental features drive the representation of location? General types of mechanism had been suggested (e.g., Sharp, 1991; Zipse, 1985), which are consistent with the major aspects of place cell firing without specifying the detail of which environmental cues are used and how. To investigate this question more quantitatively, we recorded from the same place cells while the rat explored environments of different shape (O'Keefe & Burgess, 1996). In these experiments the rat's immediate environment is changed in size or shape in the presence of unchanged extra-maze orientation cues. The resulting pattern of shapes and sizes of place fields enabled us to approximate the functional input received by each place cell. The place fields of a given cell can often be modelled as a thresholded linear sum of a small number of postulated input cells with specific properties, referred to as "boundary vector cells" (BVCs: Burgess, Jackson, Hartley, & O'Keefe, 2000; Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000; see Figure 1). These BVCs are tuned to respond as a Gaussian function of the distance to the nearest boundary or barrier along a given allocentric direction (e.g., North). Note that the orientation of the overall pattern of place fields is determined by an allocentric directional reference system (i.e., which fields fire at which side of the environment or, equivalently, which environmental direction is taken to be "north"). We assume that this depends on orientational cues at or beyond the edge of the environment (see, e.g., Cressant, Muller, & Poucet, 1997) and is mediated by the head direction system. Evidence for this is that, in disoriented rats or situations in which stable orientation cues are not available, both the preferred directions of head direction cells and the orientation of the overall pattern of place fields drift over time but remain aligned with each other (e.g., Knierim, Kudrimoti, & McNaughton, 1995).

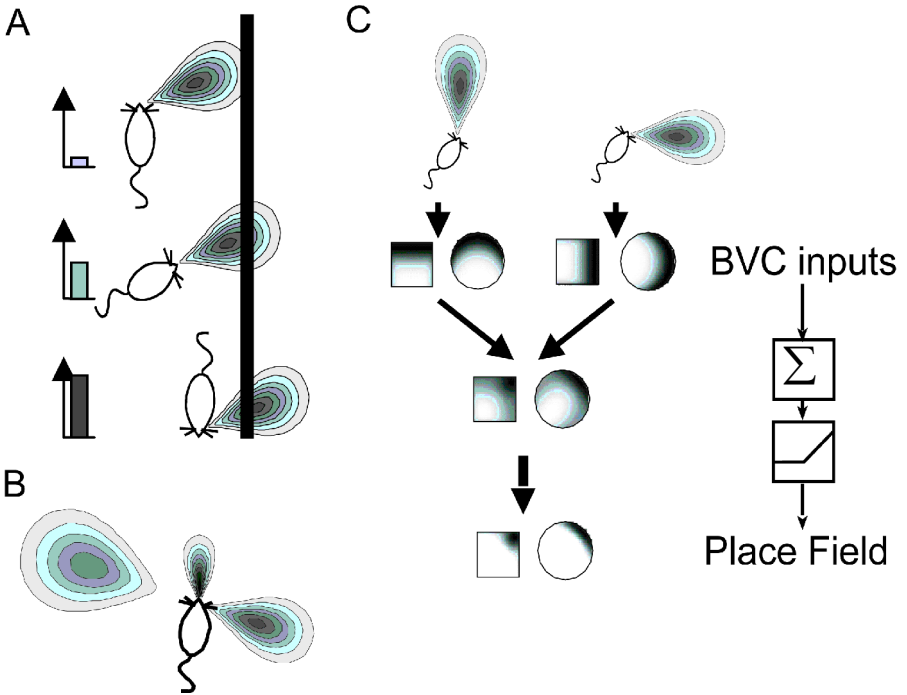


Figure 1. Geometric model of the spatial firing of place cells assuming a stable directional reference frame. Place cell firing rate reflects a thresholded linear sum of inputs referred to as “boundary vector cells” (BVCs). Each BVC has a Gaussian response tuned to the presence of an environmental boundary at a given distance and bearing from the rat. **A.** The firing rate of the BVC (illustrated as a bar chart) depends on the extent to which a boundary intersects with the BVC’s “receptive field” but is independent of the rat’s orientation. **B.** The sharpness of tuning of a BVC’s receptive field decreases with the distance from the boundary at which it is tuned to respond maximally. **C.** The BVC’s inputting to a place cell are summed together and passed through a threshold to produce the place field. This process is illustrated for two BVCs, showing their receptive fields relative to the rat (top), the firing-rate map of each BVC in a circular and a square environment (upper row), the firing-rate map of their sum before thresholding (middle row), and the firing-rate map after thresholding (lower row). Adapted from Hartley et al. (2000).

Specifically, for a BVC i tuned to a boundary at distance d_i and allocentric (compass) bearing ϕ_i from the rat, the response to a boundary segment at distance r and bearing θ subtending an angle $\delta\theta$ at the rat is given by:

$$\delta f_i = g_i(r, \theta) \delta\theta$$

where

$$g_i(r, \theta) = \frac{\exp[-(r - d_i)^2 / 2\sigma_r^2(d_i)]}{\sqrt{2\pi\sigma_r^2(d_i)}} \times \frac{\exp[-(\theta - \phi_i)^2 / 2\sigma_a^2]}{\sqrt{2\pi\sigma_a^2}}$$

The radial width $\sigma_r(d_i) = \sigma_o(1 + d_i / \beta)$ so that the width of tuning to distance increases with the distance to which the BVC is tuned (β sets the rate at which this happens, and σ_o sets the width at zero distance). The firing rate of BVC i , when the rat is at a location \underline{x} is found by integrating δf_i over θ .

This is done numerically as the distance r to the nearest boundary in direction θ is a function of \underline{x} and of the geometry of the environment. A place cell's firing rate $F(\underline{x})$ is then simply the thresholded linear sum of the firing rates of the n BVCs connected to it, that is:

$$F(\underline{x}) = AH \left(\sum_{i=1}^n \int_0^{2\pi} g_i(r, \theta) d\theta \right) - T$$

where $H(x)$ is the Heaviside function [$H(x) = x$ if $x > 0$; $H(x) = 0$ otherwise], and A determines the amplitude of firing. The way in which BVC inputs are added together and then thresholded to determine the firing of the place cell is illustrated in Figure 1.

A qualitative model for the firing of a given cell across a range of environments can be achieved using four BVC inputs, each tuned to respond to the presence of an environmental boundary at a given distance along one of four orthogonal directions. This model uses six free parameters: the four distances (d_i), the amplitude (A), and the overall orientation of the orthogonal inputs. The value of the threshold T is set for the entire population of cells to be considered (as are the values of β and σ_θ , earlier). The power of the model can be demonstrated by deducing the inputs to a cell from its firing fields in several different environments and by predicting its firing pattern in a new environment (see Figure 2 and Hartley et al., 2000). The model also fits data recorded from the same cells as the rat runs along a linear track of variable length (Gothard, Skaggs, & McNaughton, 1996).

The reader will notice that the model of place cell firing described earlier does not require any "learning"—that is, no experience-dependent changes in connection strengths are required. For example, a model in which each place cell is driven by a randomly chosen selection of BVCs would account for the initial patterns of firing of place cells in new environments. However, the place cell representation of two different environments does show experience-dependent plasticity after extensive experience. Thus, although the model provides a good explanation of the data showing place cells firing in corresponding locations on initial

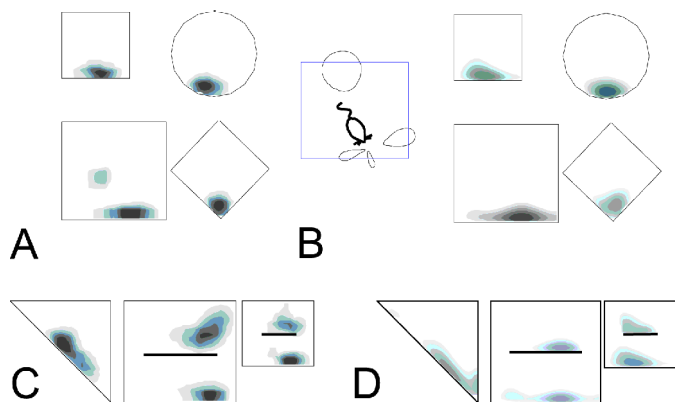


Figure 2. A. Place fields recorded from the same cell in four environments of different shape or orientation relative to the extra-maze cues in the room. B. Simulation of the place fields in (A) by choosing the best fitting set of four BVCs constrained to be in orthogonal directions (BVCs shown on the left, simulated firing fields on the right). C. Place fields from the same cell recorded in three novel environments. D. Predicted firing in these environments using the model in (B). Adapted from Hartley et al. (2000).

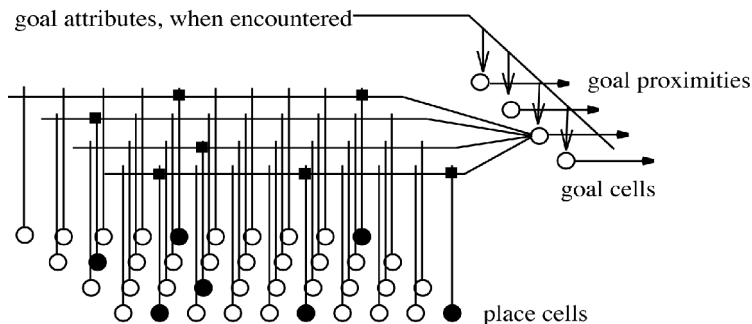


Figure 3. A simple model of using place cells to navigate. A “goal cell” is activated when the rat reaches the goal location. A Hebbian learning mechanism (e.g., long-term potentiation) establishes strong synaptic connections (shown as filled squares) from those place cells active at the goal location (shown as filled circles) to the goal cell. Subsequent movement of the rat to a hidden goal can be guided by the goal cell’s firing rate: Increasing rates indicate movement towards the goal. Adapted from Burgess and O’Keefe (1996).

exposure to environments of different shape, after a period of 1 to 3 weeks exploring environments of two different shapes (circular or square), place cells will have developed distinct representations of the different-shaped environments: either firing in only one of the shapes or firing in both shapes but in unrelated locations (Lever, Burgess, Cacucci, Hartley, & O’Keefe, 2002; Lever, Wills, Cacucci, Burgess, & O’Keefe, 2002). This learned differentiation then remains for at least several weeks, indicating that it might provide a neural correlate of long-term learning in the hippocampus.

A second obvious question raised by the observation of place cells is: How could their firing be used to drive behaviour; specifically, can we relate the firing of place cells to spatial memory? Place cells appear to encode the current location of the animal and possibly its immediately past and future locations when temporal coding is taken into account (Burgess, Recce, & O’Keefe, 1994), but not where the goal is (Speakman & O’Keefe, 1990), or how to get there. Perhaps the simplest model for this depends only on the existence of postulated “goal” cells downstream of the hippocampus (e.g., in subiculum) and Hebbian learning via synaptic modification when the rat is at the goal location (Burgess & O’Keefe, 1996; see Figure 3). If connections to the goal cell from place cells active at the goal location are switched on, then the subsequent firing of the goal cell will indicate the proximity of the goal simply because that is where the cells with strong connections to it fire the most. Thus the rat’s search for a goal location could be driven by attempting to maximize the firing rate of such a goal cell. This mechanism predicts that search will focus on the location for which the place cell representation is most similar to that previously occurring at the goal location and thus “stored” by synaptic change. Different goal cells would be required for each goal. Note that the use of “spatial view cells” instead of place cells would simply allow the model to work on the basis of movements of gaze rather than movements of the entire animal.

Retrieval of spatial scenes, imagery, and episodic memory

Detailed computational models have been proposed for spatial processing in the hippocampus and associated regions (see earlier) and in the posterior parietal cortex (e.g., Pouget & Sejnowski, 1997; Zipser & Andersen, 1988). These models are firmly grounded in the

extensive body of single-unit data recorded from rats and primates. It would be extremely advantageous to maintain contact with this low-level data, as any restricted data set regarding a cognitive process can usually be modelled by numerous different mechanisms, only one of which may correspond to what happens in the brain at the neural level. I attempt to link the constraints applying to the (spatial) processes considered earlier to those applying to a more general memory system, by considering memory for the spatial locations of the elements of the visual scene. One suggestion (see Milner, Dijkerman, & Carey, 1999) is that egocentric parietal representations are useful for short-term memory and the control of action, whereas allocentric hippocampal representations are useful for long-term storage as the subject will have moved between presentation and recall. Further, imagining a scene retrieved from (allocentric) long-term memory will require it to be translated into an egocentric (e.g., head-centred) representation for internal inspection.

This view of memory encoding and retrieval is consistent with the observation of hemispatial neglect in imagery following lesions to the right hemisphere, often involving the inferior parietal lobe, or prefrontal cortex (Guariglia et al., 1993; Karnath et al., 2001; Vallar, 1993). In their classic study, Bisiach and Luzzatti (1978) asked patients to describe the familiar Piazza del Duomo in Milan from two opposing viewpoints. Across both trials, the patients demonstrated knowledge of buildings on all sides of the Piazza, but showed an inability to report those on the left of a given viewpoint. These results, and subsequent studies (e.g., Meador et al., 1987) are consistent with an intact allocentric representation of the Piazza but an impaired ability in either generating or inspecting a viewpoint-dependent egocentric representation (see also Baddeley & Lieberman, 1980). In this section I describe an initial attempt to extend the previous model of spatial navigation to the retrieval and imagery of spatial scenes such as the Piazza del Duomo (Becker & Burgess, 2001; Burgess, Becker, King, & O'Keefe, 2001).

As a first step, the basic model of boundary vector cells inputting to hippocampal place cells (see earlier) was turned into an autoassociative memory for spatial layout. The basic model already produces a representation of the locations of large buildings around the Piazza (the BVC activation reflecting the presence of large buildings at particular distances along given compass directions) and of the location (but not orientation) of the subject in the place cell activations. We assume that the BVCs are located in the parahippocampal cortex. The BVCs perform a spatial analysis of the sensory scene that is consistent with the activation of the parahippocampal gyrus during visual processing of spatial scenes composed of walls and large buildings, as compared to viewing smaller objects or isolated walls that are not embedded in a space (Epstein & Kanwisher, 1998). This model was extended with the following additions:

1. The place cells are connected together via recurrent connections (assumed to be in region CA3) such that the strength of the connection between two place cells is proportional to the proximity of their place fields. This forms a continuous attractor in the representation of position (Zhang, 1996) such that the pattern of activation always returns to that corresponding to the representation of a single location.
2. A set of "texture" units encoding the distinct visual properties of the various landmarks are added and are assumed to be located in area TE, or perirhinal cortex, given its role in visual object recognition (see, e.g., Murray & Mishkin, 1998).

3. The place, BVC, and texture units are all reciprocally connected.

With these changes, provision of a partial cue such as the identifying texture and location (distance and allocentric direction from the subject) of a single landmark results in activation of the texture and location of the other landmarks, via activation of the place cell representation of the subject's location (see Figures 4 and 5). The reciprocal connections allow the entire system to settle to the most likely combined place BVC and texture representation given partial or noisy input (Deneve, Latham, & Pouget, 2001). In particular, the return projections from the hippocampus to parahippocampus enable recreation of the correct BVC representation of a spatial scene from a partial input.

The second step involves translating the parahippocampal representation of landmark locations, organized by distance and allocentric direction, into a representation organized by distance and egocentric direction—for example, organized by direction relative to the head or eye, for the purposes of mental imagery. This representation is assumed to be in a medial parietal area (the precuneus), following functional imaging studies of the imageability of retrieval products (e.g., Fletcher et al., 1995). It is modelled as a representation of landmark locations organized by distance and direction relative to the head. The mapping between allocentric and body-centred representations occurs in the posterior parietal area, making use of the subject's orientation in the world (encoded by a set of "head direction cells" and possibly carried by the projection that exists from the presubiculum to Area 7) (Insausti & Munoz, 2001). This translation occurs via layers of neurons, assumed to be in posterior parietal areas, bidirectionally connected to the parahippocampus, each layer repeating the parahippocampal representation but also modulated by head direction. Each layer has its own pattern of bidirectional connections to the egocentric representation. For example, cells representing landmarks to the north within a layer maximally modulated when the subject faces east are connected to cells representing 90° to the left in the egocentric representation (see Deneve et al., 2001; Pouget & Sejnowski, 1997; and Salinas & Abbott, 1995, for use of this type of model of parietal coordinate transforms). Given the current head direction, this network automatically translates allocentric representations into egocentric ones and vice versa.

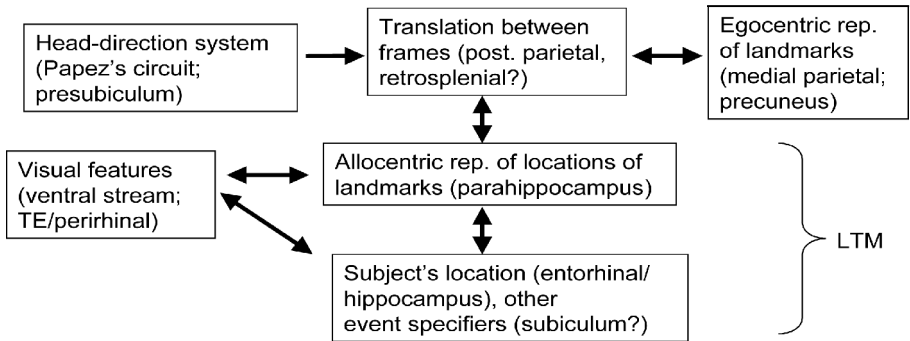


Figure 4. Schematic view of the functional architecture of the encoding and retrieval of the spatial context of an event. Long-term storage of the relative locations of landmarks (e.g., large buildings) are stored in the hippocampal and parahippocampal cortices. Long-term imagery for a spatial scene occurs in head-centred coordinates in the medial parietal cortices. The translation between coordinate reference frames occurs in posterior parietal cortices, making use of the head direction signal found along Papez's circuit. Adapted from Burgess, Becker et al. (2001).

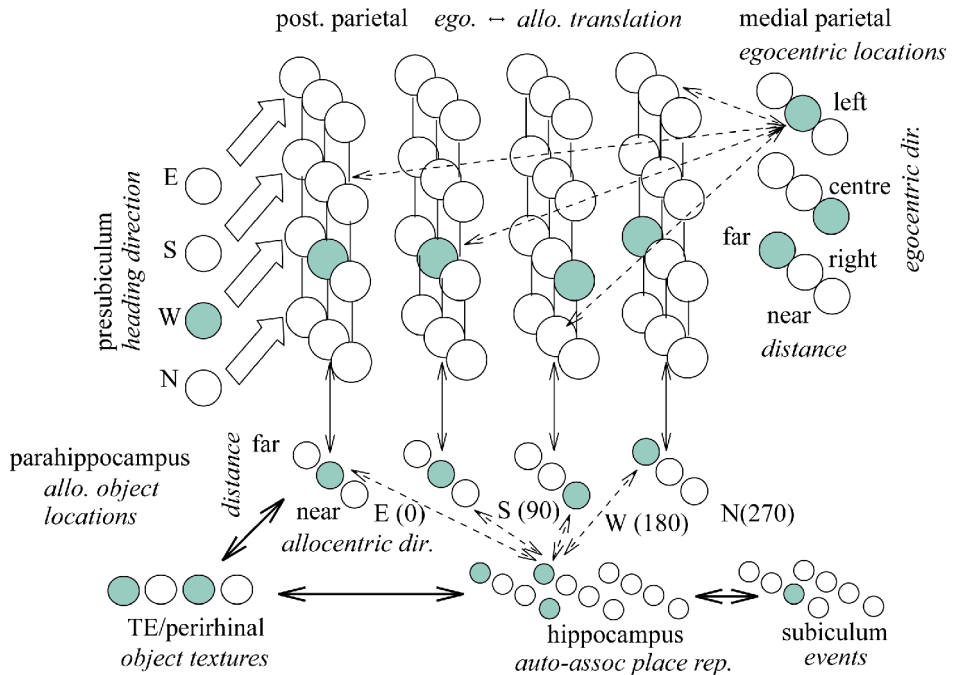


Figure 5. Detailed view of the functional architecture of encoding and retrieval of the spatial context of an event. The allocentric parahippocampal representation of landmarks resembles a set of boundary vector cells (see Figure 1) and is organized by distance and compass direction from the subject. The egocentric medial parietal representation is organized by distance and (left/right) direction from the subject. The posterior parietal cortex supports multiple-rotated representations of the parahippocampal representation. The active head direction effectively selects the rotation used in translating between these two representations—that is, it selects which of the posterior parietal representations to use. A possible set of activations across regions is shown as grey circles. Abbreviations: allo. (allocentric); ego. (egocentric); rep. (representation); post. (posterior); dir. (direction). Adapted from Burgess, Becker et al. (2001).

Finally, attending to one part of the imageable representation is modelled by boosting the activation of neurons in that part of the image. This extra activation flows back through the posterior parietal and parahippocampal representations to activate the perirhinal representation of the visual features at that part of the image. This allows simulation of the processing occurring in Bisiach and Luzzatti's (1978) task. The patients' lesions can be simulated by removing neurons on the left side of the egocentric representation, or the posterior parietal neurons that project to them (see Figure 6).

A more detailed model would simulate the allocentric to egocentric translation in separate stages: allocentric to body-centred, body-centred to head-centred, and, if necessary, head-centred to eye-centred. This would seem the natural way to take into account separate sources of information regarding bodily orientation, the angle of turn of the neck, and the angle of the eyes in their orbits, although the existence of a head direction signal indicates that allocentric to head-centred translation could also occur in a single step. In such a model, manipulating the signals indicating the direction of the head on the trunk would alter the translation process, effectively rotating the allocentric representation right (or left) onto the undamaged (or damaged) part of the egocentric image. This provides an explanation of the amelioration of

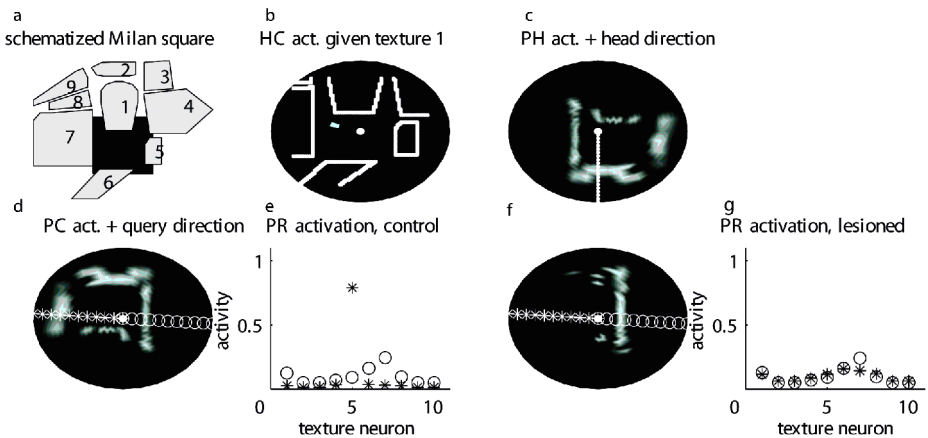


Figure 6. Simulation of the Milan square experiment of Bisiach and Luzzatti (1978). (a) Exploration of the square (shaded area, north is up) is simulated. Then the model is cued to imagine being near to the Cathedral (i.e., the perirhinal cell for the texture of Building 1 and parahippocampal cell for a building at a short distance north are activated), and the hippocampal–parahippocampal–perirhinal system settles to a stable state. (b) Hippocampal (HC) activation settles to a representation of a location in the north–west corner of the square (hippocampal cell activity shown as the brightness of the pixel corresponding to the location of each cell’s firing field). (c) Activation in the parahippocampus (PH) correctly retrieves the locations of the other buildings (parahippocampal cell activity shown as the brightness of the pixel for the location encoded by each cell, relative to the subject at the centre). The imagined head direction is set to south (indicated by a line). (d) Medial parietal cell (PC) activity reflects the egocentric image: showing the parahippocampal map, rotated given head direction south so that straight ahead is up. Stars indicate a direction of inspection to the left, circles to the right. (e) Perirhinal (PR) cell activations given inspection of the left of the internal egocentric image (stars) correctly show the texture of Building 5, and the texture of Building 7 when inspection is to the right (circles). (f) A right parietal lesion affects the medial parietal representation (near right: note lack of activation on the left) and thus the perirhinal representation (g); note decrease in activation of Building 5 when inspection is to the left. Adapted from Becker and Burgess (2001).

representational neglect when the head is turned to the left (Meador et al., 1987) or following somatosensory stimulation to the left side of the neck (Guariglia, Lippolis, & Pizzamiglio, 1998). One useful aspect of the model is that it provides an explanation for the two seemingly disparate functional associations of the mammillary bodies—anterior thalamic–hippocampal circuit—both in supporting episodic recollection (e.g., Aggleton & Brown, 1999) and in representing head direction (e.g., Taube, 1998).

This model of memory for spatial layouts can be extended to include memory for the spatial context of an event by including a representation of the location of the event. One way to do this is by adding “event cells” similar to the goal cells described earlier, possibly anatomically realized in the subicular complex. Thus the occurrence of an event causes an event cell to fire and enables modification of connections to it from concurrently active place cells and, presumably, from other cells encoding non-spatial attributes of the event. These event cells would not only allow navigation back to the location of the event, just like goal cells. In addition, if the place cell to event cell connections are bidirectional, as with the other connections in the model, then reactivation of the event cell via some non-spatial cue will allow reconstruction of the spatial context of the event. This occurs via reactivation of the place cell representation of the event’s location and thence, via parahippocampal and parietal layers,

reconstruction of the spatial scene corresponding to a given head direction (see Burgess, Becker et al., 2001).

Finally, it is important to note that some kinds of retrieval from long-term memory will not require the construction of a novel egocentric representation from a stored allocentric one. The most obvious example is familiarity-based recognition. Assuming that a record is kept of the stimulus as experienced at encoding, representation of the stimulus from the same point of view should allow recognition without requiring mechanisms for imposing arbitrary viewpoints on stored data. The retrieval of facts (i.e., knowledge abstracted from the, possibly very many, specific events during which they were learned) would not require egocentric imagery and so would also be independent of the system described earlier. Thus, in line with Aggleton and Brown's (1999) synthesis, we would expect familiarity-based recognition and semantic memory to show some independence from the system embodied by the hippocampus and Papez' circuit. To fully square the model with Aggleton and Brown's point of view, however, requires explanation of the link between the ability to manipulate viewpoints in memory and the ability to perform free recall. We return to this briefly in the discussion.

Experiments in humans

In this section I discuss some recent experiments testing some of the predictions following from the computational models described earlier and the more general conceptual models behind them. All of these experiments concern memory for either locations in large-scale space or events experienced within a rich on-going context. Virtual reality was used to provide experimental environments for these tasks, within which performance can be monitored and conditions controlled to be equivalent across subjects. With the aid of virtual reality, my group and I hoped to be able to create tasks that remained close to the everyday uses of topographical and episodic memory. This would also enable us to remain close to the actual symptoms with which patients with developmental amnesia (Vargha-Khadem et al., 1997) or Alzheimer's disease (Kolb & Wishaw, 1996) initially present. All of the virtual environments discussed here were simply presented visually in first-person perspective on a screen in front of the subject. Subjects moved through these environments by using either a joystick or cursor keys to indicate movement forwards or backwards or rotation left or right.

Spatial memory: A behavioural experiment

The simple navigation model predicts that the animal's search, guided by trying to maximize the activation of a goal cell, should concentrate in places that have a similar place cell representation to the representation of the goal location. To see this, imagine the following simple model. When the rat is at location \underline{x} , the activity of a goal cell $g(\underline{x})$ is simply the sum of the activities of the place cells $p_i(\underline{x})$ connecting to it, each weighted by the strength of its connection—that is, $g(\underline{x}) = \sum_i w_i p_i(\underline{x})$. Connection weights w_i are initially zero, and learning (when the goal location is encountered) corresponds to increasing each connection proportionally to the activity of the place cell—that is $w_i = p_i(\underline{x}_g)$, where \underline{x}_g is the goal location. Thus, the activity of a goal cell will be $g(\underline{x}) = \sum_i p_i(\underline{x}) p_i(\underline{x}_g)$, that is, the similarity (dot product) between the place cell representation at the current location with that at the goal location.

As we can model the firing of place cells in terms of their environmental inputs (BVCs), we can simulate the firing of a large population of place cells in an environment of a given shape

(Hartley et al., 2000) by choosing random sets of BVCs to drive each place cell. Thus we can predict the similarity of the representation of arbitrary locations to the representation of a goal location. The previous behavioural model implies that the density of search for such a goal location should be some monotonic function of the predicted similarity (see Figure 7 and Hartley et al., 2000). Interestingly, we can make this prediction even in situations in which the environment has changed size or shape between encountering the goal location and having to search for it.

Several interesting experiments have been performed on memory for the location of an object or reward hidden in one corner of a fixed rectangular enclosure. These experiments concern the determinants of the overall orientation of the spatial representation in memory. In these experiments, there are no distant orientational cues present beyond the walls of the enclosure, but one or more large coloured visual cues on the walls clearly polarize the environment, and subjects are disoriented (by rotation in the absence of visual input) before each trial. These experiments indicate that the geometrical shape of the enclosure determines the orientation of the search pattern, in rats (Cheng, 1986), young infants (Hermer & Spelke, 1994), and

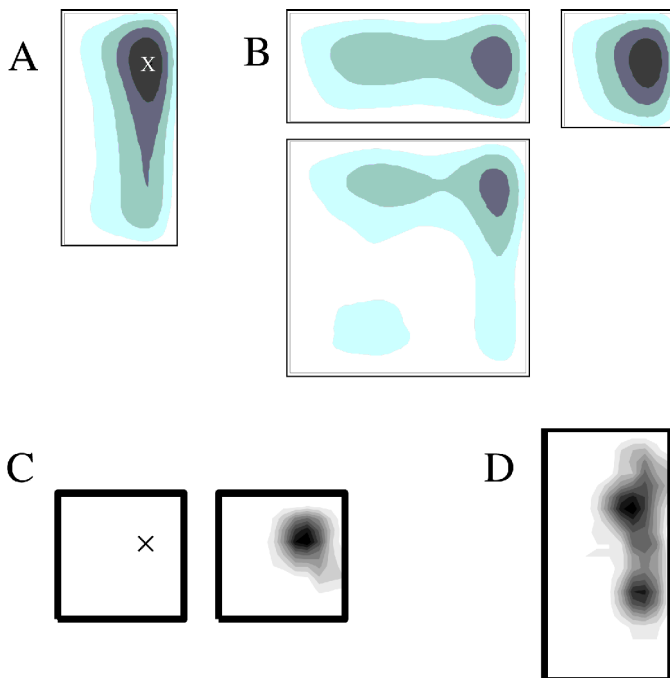


Figure 7. A. Similarity of the simulated place cell representation of locations within a rectangular enclosure to the representation at the position marked X. Similarity is quantified as the dot product of the vectors of place cell activations, shown as increasing darkness (white = 0; black = 1.0). Adapted from Hartley et al. (2000). B. Similarity of the simulated place cell representation of locations within enclosures of different shapes (but the same orientation relative to external cues) to the representation of the position marked X in the initial rectangular enclosure. Adapted from Hartley et al. (2000). C–D. Density of responses indicating where subjects thought they saw an object that was presented at the location marked X in the initial square-shaped enclosure, in that same enclosure (C), and after distortion of the shape of the enclosure into a rectangle (D). From Hartley, Trinklér, and Burgess (2002).

adults performing verbal shadowing (Hermer-Vazquez, Spelke, & Katsnelson, 1999), with equal search density at the correct corner and at the one opposite to it. In relation to the rat hippocampus, it is interesting to note that the visual cues in these experiments would normally control the orientation of the place cell and head direction cell representations. However, they do not do so if the rats are systematically disoriented between each trial (Knierim et al., 1995), as the subjects are in these experiments. Experiments have not so far examined environments with distant orientation cues, no disorientation of subjects, and manipulations of the shape of the environment (as in O'Keefe & Burgess, 1996).

To test the predictions of the model in situations like the O'Keefe and Burgess (1996) experiment, we designed a rectangular environment with a very salient distant cue to provide an orientational bearing (a large cliff). Subjects explored the environment, viewing an object presented at a particular location corresponding to "presentation"). When they indicated that they knew the object's location, the screen went blank for a short period after which they found themselves back in the environment, but without the object. Their task was to indicate where they thought the object had been located (corresponding to "recall"). Reasonably accurate responses in the conditions involving the same shape and size of environment at presentation and recall indicated that the task worked and that subjects could derive data regarding 3-D location from the 2-D displays. In other conditions, the environment was expanded or shrunk along one or both axes of the rectangle. In these conditions, responses showed reasonable agreement with the predicted behaviour where an expansion of the environment occurred (see Figure 7), but showed a more complex pattern when the environment had shrunk (Hartley, Trinkler, & Burgess, 2002).

Neuropsychology and functional neuroimaging of navigation and episodic memory

To examine the neural basis of spatial and episodic memory in naturalistic situations, I developed a small virtual-reality town (see Figure 8). (To view this figure in colour, please see the online version of the journal.) For the spatial test, after subjects had explored the town, their ability to navigate accurately could be tested by presenting them with a picture of a location within the town and asking them to get there as directly as possible. Once the target location was reached, a new location was shown and so on. The computer recorded the subject's path so that their accuracy could be assessed.

Subject's episodic memory could also be tested in the town. For this, subjects followed a route along which they repeatedly encountered one of two different characters in one of two different parts of the town. On each encounter, the subject approached the character and, on pressing a button, received an object from them. A different object was received during each event, and the characters and locations provided the spatial and non-spatial contexts of each event. Four types of question assessed memory for various aspects of the events. All questions involved a paired forced choice of one of two objects presented in a place and in the presence of a character, accompanied by a word indicating the question type. The question types were: "Place" (which object did you get in this place?); "Person" (which object did you get from this character?); "First" (which object did you get first?); "Object" (which object did you get?). For the first three (context-dependent) questions, the foil was one of the other objects, whereas for the "object" question the foil was a novel but similar-looking object.

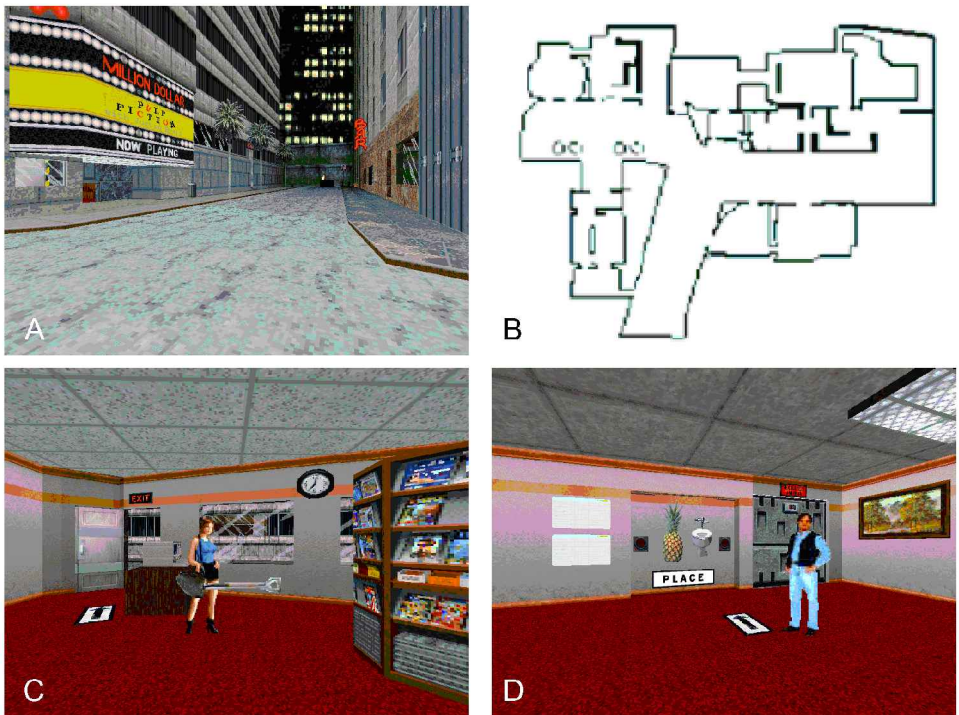


Figure 8. Tests of spatial and episodic memory using virtual reality. **A.** A view from within the virtual town showing the main crossroads. **B.** A plan view of the town. **C.** A view showing the occurrence of an “event” (encountering a person who gives you an object). **D.** A view showing a test situation (which object did you get in this place?). The town was viewed in colour. Adapted from Burgess, Maguire, and O’Keefe (2002). To view this figure in colour, please see the online version of the journal.

To attempt to identify the neural bases of topographical and episodic memory we used both tasks in conjunction with functional neuroimaging of healthy volunteers (Burgess, Maguire, Spiers, & O’Keefe, 2001; Maguire et al., 1998) and in neuropsychological studies (Spiers, Burgess, Hartley, Vargha-Khadem, & O’Keefe, 2001; Spiers, Burgess, Maguire et al., 2001). These latter studies involved Jon, a developmental amnesic with focal bilateral hippocampal pathology (Vargha-Khadem et al., 1997), a group of patients who had had left or right anterior temporal lobectomy (TL), and appropriately matched control groups. The background to this type of combined approach is that the majority of studies of early memory, using artificial memoranda such as lists of words, show little convergence between neuroimaging (predominantly activating parietal and prefrontal areas) and neuropsychology (predominantly implicating medial temporal areas). The neuropsychological studies additionally show some lateralization of function. The right medial temporal lobe has been predominantly associated with memory for visuo-spatial stimuli (Abrahams, Pickering, Polkey, & Morris, 1997; Baxendale, Thompson, & Van Paesschen, 1998; Bohbot et al., 1998; Nunn, Graydon, Polkey, & Morris, 1999; Pigott & Milner, 1993; Smith & Milner, 1981, 1989), whereas the left medial temporal lobe has been predominantly associated with memory for verbal stimuli such as narratives (Frisk & Milner, 1990) or pairs or lists of words (Baxendale, 1997; Dennis et al., 1988).

In our neuropsychological studies (Spiers, Burgess, Hartley et al., 2001; Spiers, Burgess, Maguire et al., 2001), the right TL group and Jon were significantly less accurate at spatial navigation than were their matched controls, whereas the left TL group showed intermediate performance. The left TL patients and Jon were significantly worse at the context-dependent episodic memory questions (“person”, “first”, and “place”), whereas the right TL group showed intermediate performance. The lateralization of function was reflected in a significant group (left vs. right TL) by task (context-dependent vs. topographical memory) interaction. Interestingly, the right TL group, but not Jon, was impaired on the “object” question. Taken together, these findings implicate the right hippocampus in spatial navigation, the left hippocampus in context-dependent episodic memory, and extra-hippocampal right anterior temporal regions in object recognition. The right lateralization of object recognition is probably due to the fact that foil objects varied in terms of their visual appearance but not their verbal categorization (see Figure 9).

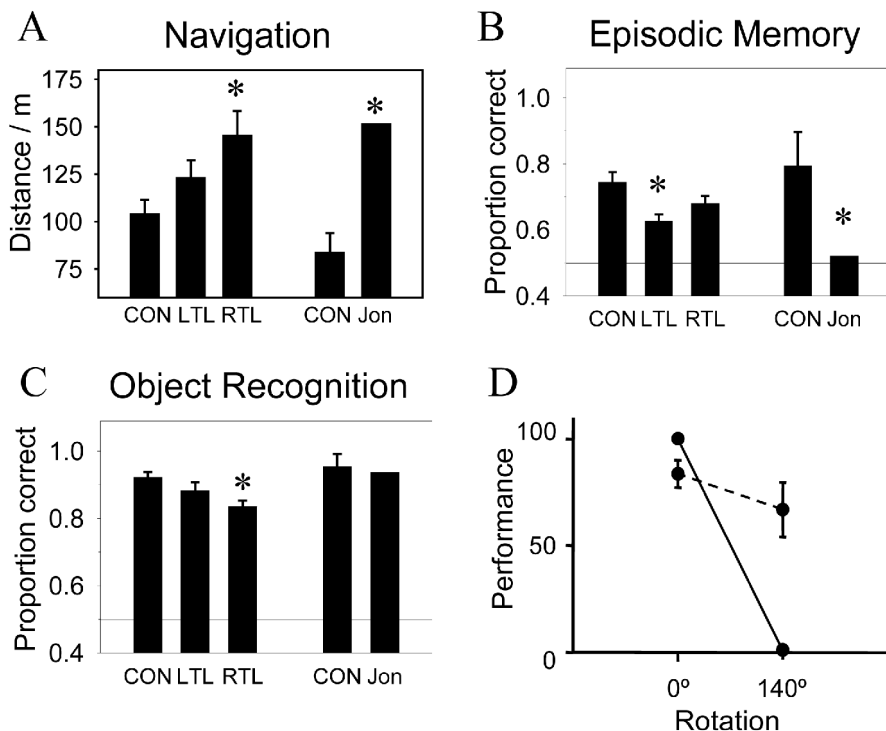


Figure 9. Neuropsychological studies. A–C. Performance of hippocampal case Jon; groups of left and right temporal lobectomy patients (LTL and RTL) and appropriate matched controls on spatial navigation (A), context-dependent episodic memory (combined score on “place”, “person”, and “first” questions, B), and object recognition (C). Error bars are one standard deviation for Jon’s controls and one standard error of the mean for the temporal lobectomy controls. Adapted from Burgess et al. (2002). See Spiers, Burgess, Hartley et al. (2001) and Spiers, Burgess, Maguire et al. (2001) for details. D. Jon’s performance in recognizing the locations of seven sequentially presented objects from the same viewpoint (0°) or a shifted viewpoint (140°), tested with two foils (full line). Also shown, the performance of matched controls on the same task, tested with five foils (dashed line). Adapted from King, Burgess, Hartley, Vargha-Khadem, and O’Keefe (in press). * Indicates a result that is statistically significant at the $p < .05$ level.

For functional neuroimaging studies we used additional conditions to control for sensory and motor aspects of the cognitive function in question: following a trail of arrows for spatial navigation, and answering a “width” question (“which object is wider?”) for memory questions. We studied the neural basis of spatial navigation in a positron emission tomography study (Maguire et al., 1998), finding activation of the right posterior parahippocampal gyrus, extending into the hippocampus, in a contrast of successful navigation compared to following arrows. Additionally, the correlation between estimated regional cerebral blood flow and navigational accuracy was found to be significant in two locations: right inferior parietal cortex and right hippocampus (see Maguire et al., 1998). Both left and right hippocampal activation was associated with successful vs. unsuccessful navigation (i.e., trials in which the target was never located). The parahippocampal activation is consistent with other studies using VR (Aguirre & D’Esposito, 1997; Aguirre, Detre, Alsup, & D’Esposito, 1996; Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000), spatial scenes (Epstein & Kanwisher, 1998), and filmed (Maguire, Frackowiak, & Frith, 1996) and imagined (Ghaem et al., 1997; Maguire, Frackowiak, & Frith, 1997) navigation. In the latter three studies, and in the study by Gron et al. (2000), activation was also reported in the hippocampus.

In the episodic memory study, using functional magnetic resonance imaging, the contrast of “place” and “width” questions produced an interesting pattern of activation: extending from the precuneus down through the parieto-occipital sulcus, retrosplenial cortex, and posterior parahippocampus, and into the hippocampus on the left (see Burgess, Maguire et al., 2001). Additional activation included the posterior parietal cortex, several prefrontal areas, and sub-threshold activation in the right hippocampus. A similar pattern was observed for the contrast of “person” with “width” but with significantly less parahippocampal activity, slightly less left hippocampal activity, and an absence of right hippocampal activity.

Where the imaging results concern the main area of interest in the neuropsychological study (i.e., the hippocampus), they are broadly consistent with it. They indicate predominantly right hippocampal involvement in accurate navigation, but also left hippocampal involvement in successful navigation. This is consistent with the impaired performance of Jon and of the right TL group, and the intermediate performance of the left TL group. In both imaging and neuropsychological studies, it is possible that the left hippocampal involvement reflects retrieval of general episodic or verbally mediated information from the exploration phase, whereas the right hippocampus is more specifically concerned with spatial processing.

The imaging of episodic memory also provided results broadly in line with the neuropsychological study, indicating greater left than right hippocampal involvement in context-dependent memory and no hippocampal involvement in object recognition. This is consistent with lesion studies showing that familiarity-dependent recognition memory may not depend on the hippocampus (e.g., Aggleton & Brown, 1999). Interestingly, primate lesion studies imply that perirhinal cortex is the critical locus for recognition memory (Murray & Mishkin, 1998; but see also Zola et al., 2000). This locus is consistent with the impairment shown by the right TL group, as their anterior TL operation would disrupt perirhinal cortex. The imaging results for object recognition did not show activation in this region (showing much more posterior lateral temporal activation instead). This may be due to technical problems in getting fMRI signals from the anterior medial temporal lobe.

Many brain areas beyond those implicated in the neuropsychological studies also showed activation in several of the comparisons made in the imaging studies. Here I concentrate on the remaining activations in the contrast of “place” and “width” and how they relate to the model of retrieval and imagery of the spatial context of an event described earlier. As is consistent with the model, see Figure 4, activation was found in the parahippocampus and posterior and medial parietal cortices. In addition, a continuous strip of activation from the parahippocampus, through the retrosplenial cortex, and into the precuneus appeared. This might correspond to the need to buffer information in many successive stages of translation from world-centred to body-centred to head-centred representations.

The extensive prefrontal activation seen in our context-dependent memory conditions does not relate to the model. In terms of a purely speculative explanation, it is interesting to note that retrieving artificial memoranda tends to produce very reliable prefrontal activation of the same areas (e.g., Lepage, Ghaffar, Nyberg, & Tulving, 2000), whereas retrieving autobiographical memories often does not (Maguire, Mummery, & Buchel, 2000). Thus it is possible that the prefrontal cortex becomes involved in order to organize retrieval in the face of contextual interference (see also, Incisa della Rocchetta & Milner, 1993). In our study, all 16 events occurred in just two places and involved just two characters. Studies using artificial memoranda often involve entire lists of items presented on a blank screen. Thus in both types of study, events must be remembered against very similar contexts. By contrast, autobiographical events are usually extremely varied in both nature and their spatial and temporal contexts.

The hippocampus and viewpoint dependence in memory for locations

The subject's viewpoint plays an important role in spatial memory. When exposed to a scene of objects in different locations from one viewpoint and given a recognition memory test from a second viewpoint, subject's reaction time varies linearly with the angular difference between the views (Diwadkar & McNamara, 1997). Thus some type of mental rotation analogous to that found in object recognition (Shepherd & Metzler, 1971) may be at work. There are hints that this type of shifted-viewpoint recognition memory paradigm involves an automatic mechanism related to self-motion within an allocentric framework. First, subject's recognition of a scene of objects in different locations on a circular table top is better when the subject moves to a new viewpoint before testing than when the subject returns to same viewpoint for testing but the table is rotated equivalently to the shifted-viewpoint case (Simons & Wang, 1998; Wang & Simons, 1999). Interestingly, the effect is still observed in darkness (using phosphorescent objects) and when the subjects themselves rotate the table. This was interpreted as evidence for an automatic updating process driven by the active motion of the subject. A slightly different interpretation is indicated by a recent study replicating the Wang and Simons result using visual virtual reality (Christou & Bulthoff, 1999). In this experiment stimuli were entirely visual, so the difference does not depend on muscular or vestibular signals, but simply on the movement of viewpoint relative to the subject's mental model of the world (derived from whatever source) compared to rotation of the table alone. Indeed, a similar effect is seen in imagery: Subjects are quicker and more accurate in indicating the locations of objects

within an array following imagined movement of themselves than following an equivalent imagined movement of the array (Wraga, Creem, & Proffitt, 2000).

One of the basic assumptions behind the model of memory for spatial context was that the hippocampus supports memory for spatial locations defined relative to the environment (allocentric memory), whereas a variety of egocentric representations are supported by other parts of the brain, most notably the posterior parietal cortex. In addition, we reasoned that allocentric memory was appropriate for long-term storage of spatial information because the subject would have moved between encoding and retrieval. To test these assumptions we designed a shifted-viewpoint recognition task to compare memory for locations within a large-scale virtual space in which subjects either did or did not change their viewpoint between presentation and retrieval (see King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, *in press*).

We reasoned that recognizing the location of an object from the same point of view as encoding could be solved by reference to either egocentric or allocentric representations of the presented scene, whereas recognizing the location of an object from a different point of view would not be possible simply by reference to an egocentric representation. Instead this task requires either an allocentric representation or an egocentric representation and a three-dimensional world model within which to perform the rotations and translations of the viewpoint needed to support an equivalent function. Evidence that the hippocampus was involved in either of these functions would provide an interesting link between space and memory. A study with a similar aim used the exclusion of external visual cues by darkness to reduce the influence of allocentric mechanisms and movement of the subject to reduce the influence of egocentric mechanisms (Holdstock et al., 2000). In this study, a patient with hippocampal damage was found to have a greater impairment in indicating the location of a spot of light relative to controls in the movement condition, although this was partly due to increased variance in the control's responding in the other (dark) condition.

In our task, subjects first explored a courtyard and the tops of surrounding buildings. At the start of each trial, they moved to one of three standard viewing locations looking down into the courtyard from roof-top level and watched as a sequence of items appeared on one of 21 small plinths in the courtyard. The screen then briefly went blank, and testing began. In same-viewpoint trials the screen came on to display the scene from the same viewpoint as before, whereas in the shifted-viewpoint trials it displayed the scene from another viewpoint. Memory was tested for each object's location by presenting several copies of the object in different locations and asking which copy was in the same location as at presentation. Task difficulty could be varied parametrically by varying list length or the number of choices. Patient Jon and 12 controls matched for age and performance IQ were tested.

Relative to control subjects, Jon showed a mild impairment in the same-viewpoint condition, but still performed above chance at a list length of 13. By contrast, he showed a striking impairment in the shifted-viewpoint condition, performing at chance on all list lengths greater than 1. To demonstrate an additional impairment specific to the shifted-viewpoint condition over and above his same-viewpoint impairment, we tested control subjects with five foils and Jon with two foils so as to match same-viewpoint performance (see Figure 9D). Interestingly, Jon's relatively mild same-viewpoint impairment is of almost exactly the same size as his known impairment in 2-D object location tasks (Vargha-Khadem et al., 1997).

These results are consistent with our position regarding hippocampal involvement in spatial processing (and also with less specific theories stressing the "flexibility" of

hippocampal representations, Cohen & Eichenbaum, 1993). That is, although egocentric memory is sufficient for the same-viewpoint task, allocentric processing also makes an important additional contribution when long lists (or possibly delays) are used—for example, for large numbers of object locations, incorporating all of them into a single abstracted framework may have intrinsic benefits compared to separate storage of independent egocentric snapshots for each item (such as allowing the additional information of relative locations of the different objects to be used). However, when the viewpoint is shifted within a rich 3-D environment, hippocampal-dependent allocentric mechanisms are crucial as soon as there is more than one location to remember. We are currently planning reaction time experiments to see whether the hippocampus and associated head direction system support a Wang and Simon's type mechanism of viewpoint rotation and translation.

The proposal that the hippocampus supports manipulation of viewpoints in memory is broadly consistent with conclusions drawn from single-unit (Robertson, Rolls, & Georges-Francois, 1998) and lesion (Gaffan, 1998) studies in primates. Robertson et al. note that the firing of spatial view cells is probably updated by ideothetic information relating to eye or body movements. Gaffan suggests that the role of the hippocampus is to provide ideothetic spatial information relating to the environmental locations of body parts to extra-hippocampal memory systems (see also, O'Keefe & Nadel, 1978).

Conclusions

Starting from the results of single-unit recordings in rats and monkeys, my collaborators and I are attempting to build a computational model of episodic memory that makes sense at the level of single neurons as well as of behaviour. So far, we have started to model some aspects of memory for spatial context, making use of some of the computational constraints inherent in spatial data. We have also tried to clarify the role of the hippocampus and related structures in spatial navigation and episodic memory, two of the most common everyday behaviours associated with these regions in developmental (e.g., Vargha-Khadem et al., 1997) or neurodegenerative (e.g., Alzheimer's disease, Kolb & Wishaw, 1996) pathology. In our model, the imposition of a particular viewpoint on long-term allocentric (hippocampal) information in order to retrieve imageable visuo-spatial information provides a link between spatial and mnemonic considerations.

By making use of the emerging technology of virtual reality we have sought to design controlled but realistic experimental paradigms capable of providing a rich spatial context to test these ideas. We found a surprisingly good convergence between neuropsychological and functional neuroimaging results using these methods. This allowed us to demonstrate the involvement of the hippocampus in spatial navigation (predominantly right lateralized) and context-dependent episodic memory (predominantly left lateralized). We also demonstrated hippocampal involvement in tasks requiring a change of viewpoint between presentation and recognition. It is possible that the role of the hippocampus in enabling recognition of information from new viewpoints will generalize. Thus there may be a link between the ability of the hippocampus to represent motion along a spatial trajectory and its ability to guide the recollection of events set in a continuous spatio-temporal context (see also O'Keefe & Nadel, 1978).

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