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The Human Hippocampus and Spatial and Episodic Memory

Review

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Finding one's way around an environment and remembering the events that occur within it are crucial cognitive abilities that have been linked to the hippocampus and medial temporal lobes. Our review of neuropsychological, behavioral, and neuroimaging studies of human hippocampal involvement in spatial memory concentrates on three important concepts in this field: spatial frameworks, dimensionality, and orientation and self-motion. We also compare variation in hippocampal structure and function across and within species. We discuss how its spatial role relates to its accepted role in episodic memory. Five related studies use virtual reality to examine these two types of memory in ecologically valid situations. While processing of spatial scenes involves the parahippocampus, the right hippocampus appears particularly involved in memory for locations within an environment, with the left hippocampus more involved in context-dependent episodic or autobiographical memory.

Background

Impairments of spatial and episodic memory are often the first symptoms experienced by patients with damage to the medial temporal lobes due to progressive pathologies such as Alzheimer's disease (e.g. Kolb and Wishaw, 1996). The medial temporal lobes and the hippocampus in particular have long been implicated in the acquisition of new memories (Scoville and Milner, 1957), with visuo-spatial memory predominantly associated with the right (Smith and Milner, 1981) and verbal or narrative memory with the left (Frisk and Milner, 1990).

There is now a consensus that the human hippocampus is involved in episodic memory (Eichenbaum and Cohen, 2001; Kinsbourne and Wood, 1975; O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991; Vargha-Khadem et al., 1997), i.e. memory for personally experienced events set in a spatio-temporal context (Tulving, 1983). Equally, there is little dispute that the hippocampus in infrahumans is involved in spatial or topographical memory (Eichenbaum and Cohen, 2001; Morris et al., 1982; O'Keefe and Nadel, 1978), and this spatial role appears to remain in humans (Abrahams et al., 1999; Maguire et al.,1996a, 1998a, 1999; Spiers et al., 2001a; Vargha-Khadem et al., 1997). This latter observation is consistent with the cognitive map theory characterization of hippocampal function (O'Keefe and Nadel, 1978, 1979).

The cognitive map theory proposes that the hippocampus of rats and other animals represents their environments, locations within those environments, and their contents, thus providing the basis for spatial memory and flexible navigation. When it comes to humans, the theory suggests a broader function for the hippocampus, based at least in part on lateralization of function. The right hippocampus is still viewed as encoding spatial relationships, but the left has the altered function of storing relationships between linguistic entities in the form of narratives. In addition, one or both hippocampi incorporate temporal information derived from the frontal lobes, which serves to timestamp each individual visit to a location, thus providing the basis for a spatio-temporal contextual or episodic memory system.

The hippocampus has also been ascribed a much broader role in both animals and humans, encompassing episodic and spatial memory along with many other types of memory. Primary among these broader characterizations are "declarative" memory (Squire and Zola-Morgan, 1991), and "flexible relational" memory (Cohen and Eichenbaum, 1993). Declarative memory refers to all forms of conscious or explicit memory, including episodic, semantic, and familiarity-based recognition, with the additional suggestion that the hippocampus plays a time-limited role (i.e., being needed only for recently acquired information). Under the flexible-relational hypothesis, hippocampal function is closely related to declarative memory, including all explicit memory (Eichenbaum, 1999), but also favors flexible uses of memory and relational learning (e.g., performing transitive inference; Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997). See also Aggleton and Brown (1999) for a review.

Here, we focus on the involvement of the human hippocampus in spatial memory and review relevant neuropsychological, behavioral, and neuroimaging studies. In addition, we consider how results concerning its spatial role may relate to its accepted role in episodic memory. We also indicate some links to the pertinent nonhuman data, but do not consider this field in any detail (see Eichenbaum et al., 1999, and O'Keefe, 1999, for reviews). In the first instance, three concepts of particular importance to understanding spatial memory will be briefly reprised and key evidence reviewed: spatial frameworks, dimensionality, and orientation and self-motion. We will then discuss how the introduction of a novel methodology, namely the use of virtual reality to create large-scale, controlled environments, has provided new opportunities to explore these key concepts and the role of the hippocampus in space. In particular, a series of five recent virtual reality (VR) experiments that examined topographical and episodic memory within large-scale spatial contexts will be considered in detail (Burgess et al., 2001b; King et al., 2002; Maguire et al., 1998a; Spiers et al., 2001b, 2001a). We believe that experiments

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such as these are starting to provide convergent evidence from neuropsychology and neuroimaging about the role of the hippocampus in memory.

Spatial Frameworks

When investigating the processing of spatial information in the brain, it is natural to ask what type of spatial framework is being used to represent locations and what is the origin or center of that framework. Frameworks can be centered on different receptor surfaces, such as the retina, or they can be aligned with a body part, such as the midline of the head or the trunk, or with an effector, such as the arm or the hand. All of these frameworks, since they move with the body as it moves through the environment, are collectively labeled egocentric. In contrast, frameworks that are fixed to the environment itself or to individual objects in the environment are called allocentric. The locations of objects within allocentric frameworks do not change as the subject moves in the environment.

The cognitive map theory posits that the hippocampus specifically supports allocentric processing of space in contrast to other brain regions, such as the parietal neocortex, which support egocentric processing (O'Keefe and Nadel, 1978). This is consistent with hippocampal "place cells" encoding the rat's location within an open environment independently of its orientation (Muller et al., 1994; O'Keefe, 1976; Wilson and McNaughton, 1993) and the complementary encoding of the orientation, independently of location, by "head-direction cells" in the nearby presubiculum (see e.g., Taube et al., 1990). By contrast, neocortical representations of sensory and motor information tend to be egocentric, reflecting the fact that sensory receptors and motor effectors are attached to the body. Interestingly, as well as encoding information relative to various egocentric frames of reference (see e.g., Colby and Goldberg, 1999; Hyvarinen and Poranen, 1974; Mountcastle et al., 1975), neurons in the posterior parietal cortex also appear to support translations between different egocentric frames (Andersen et al., 1985) and between allocentric (room-centered) and egocentric (trunk-centered) frames (Snyder et al., 1998).

The different ways in which space is processed and represented impact upon neuropsychological testing in humans. In tests of memory for locations on a tabletop or computer screen relative to which the subject does not move, the use of egocentric or allocentric processing cannot be distinguished, as the two frames of reference coincide. Notions of ego- or allocentricity are naturally intimately linked to other factors. For example, the dynamic process of extracting spatial information from navigating through an environment will also differ from the process of extracting that information from a two-dimensional (2D) map or overhead view. Similarly, scene and landmark information stored as retinotopic snapshots (e.g., presented using pictures) will differ from that stored as a result of navigating through the environment. Several dissociations in performance across test types that speak further to the issue of the egocentric/allocentric distinction are discussed in the next sections.

Dimensionality

A fundamental distinction exists between simple iconic representations of single objects or 2D scenes and representations that include knowledge of the 3D locations of the elements of a scene. For example, either might suffice for recognition of a scene as familiar, but the latter would be needed to decide upon a novel shortcut or appreciate what the scene would look like from another point of view. The need to take care in distinguishing between different types of spatial information is illustrated by reports of patients with topographical memory deficits but preserved ability in tabletop tests of spatial or geographical knowledge (Habib and Sirigu, 1987; McCarthy et al., 1996) and conversely, a patient with preserved navigational ability but poor verbal and visual memory and poor geographical knowledge (Maguire and Cipolotti, 1998).

There is some evidence that parahippocampal cortical areas are required for iconic representations of scenes, with hippocampus being required in addition when memory for locations in 3D space is required. Functional neuroimaging of recognition memory for object location within a 2D array (Johnsrude et al., 1999) and the perception of spatial scenes (Epstein and Kanwisher, 1998) and buildings (Aguirre et al., 1998) consistently activates posterior right parahippocampal gyrus, but not the hippocampus. Similarly, recognition-based tests of spatial memory, including the recognition of landmarks (Whiteley and Warrington, 1978) and topographical scenes (Warrington, 1996) have been associated with parahippocampal areas in neuropsychological studies (Bohbot et al., 1998; Habib and Sirigu, 1987). Recognition of spatial scenes has also been found to be impaired in right temporal lobectomy patients (Baxendale et al., 1998a; Pigott and Milner, 1993). Both recall and recognition of object locations is impaired in epilepsy patients after either right parahippocampal or hippocampal lesion (Bohbot et al., 1998). Testing of unilateral temporal lobectomy (Nunn et al., 1998, 1999; Smith and Milner, 1981, 1989) and amygdalohippocampectomy (Smith et al., 1995) patients has clearly implicated the right medial temporal lobe in recalling the locations of objects laid out in a two-dimensional array (i.e., they replace the objects on the table less accurately). Moreover, the severity of impairment correlates with the extent of right hippocampal damage. In the majority of these experiments, the impairment was only apparent after delays of several minutes or more between presentation and recall, showing that spatial perception was not impaired in these patients.

Orientation and the Role of Self-Motion

The mental representation of space must not only contain the relative locations of objects in the environment, but also has to be orientated appropriately with respect to that environment. Insight into how this is achieved comes from experiments in which the subject is shown objects in different locations in a symmetrical rectangular room, is then disoriented (using blindfolded rotation), and then asked to locate them. Young children (Hermer and Spelke, 1994) and adults performing verbal shadowing (Hermer-Vazquez et al., 1999) appear to reorient themselves solely according to the geometry of the room–ignoring a large, colored cue present on one wall that enables adults to orient correctly under normal circumstances. Interestingly, this effect is weakened when larger rooms are used (Learmonth et al., 2001). A similar disorientation procedure indicates that adults encode the locations of objects in a room individually, but en-

code the locations of geometric features (the corners of the room) within a single, unified representation (Wang and Spelke, 2000).

Experiments suggest that self-motion produces idiothetic signals that can be used to update the orientation of the spatial representation of an environment. Subjects were shown an array of objects on a circular table and, while a curtain was lowered over the table, either the subject moved around the table to a new viewpoint or else the table was rotated by an equivalent amount. Subjects were then better able to recognize object locations after self-motion than after rotation of the table (Simons and Wang, 1998; Wang and Simons, 1999). This result implies that self-motion causes an automatic updating of an internal representation of locations that is more accurate than our ability to deliberately perform the equivalent mental rotation. Note that this process probably corresponds to updating a viewpoint within a cognitive mental model but does not necessarily rely on vestibular or proprioceptive signals, as the experimental effect can also be shown using purely visual virtual reality (Christou and Bulthoff, 1999). While it is conceivable that one's knowledge of the location of objects or the layout of a simple environment is continuously updated to compensate for every movement, this ability is unlikely to be able to accommodate the complex movements, long time scales, rich and continuous stimuli, and multiple choices involved in navigation in the real world. The related process of maintaining a bearing to the start point of a trajectory on the basis of movement information alone (path integration) can be seen to be insufficient to accommodate complex movements in mammals (see e.g., Etienne et al., 1996).

The processes underlying spatial memory have been illuminated by several recent studies of performance and reaction times in healthy volunteers. Subjects being asked to indicate the locations of objects from a shifted point of view show a chronometric relationship between reaction times and the size of the shift in viewpoint. This relationship indicates that subjects perform an iterative mental manipulation to align the test viewpoint with the encoding viewpoint (Diwadkar and McNamara, 1997). The same type of chronometric relationship holds for imagined translations of viewpoint (Easton and Sholl, 1995). In a parallel result to that of Simons and Wang (1998), subject's memory for spatial locations is faster and more accurate following imagined movement of viewpoint around an array of locations than following an equivalent imagined rotation of the array (Wraga et al., 2000). See also Kosslyn (1994).

Performance or reaction time advantages have also been noted for novel viewpoints aligned with environmental axes or landmarks (Mou and McNamara, 2002; Shelton and McNamara, 2001). Several recent investigations of object-location memory in (pre- and postoperative) unilateral temporal lobectomy patients have used movement of the subject between presentation and retrieval of object locations displayed on a tabletop to encourage the use of allocentric processing (Abrahams et al., 1997, 1999). Related studies have looked at rotation of the array of locations, rotation of the subject's view using computer generated presentations (Feigenbaum et al., 1996), or rotation and translation of blindfolded subjects (Morris et al., 1999; Worsley et al., 2001). All of these studies, like the earlier ones, implicated the right medial temporal lobe. Correlation of performance with the extent of damage to the hippocampus and parahippocampal pointed to a crucial role for these two structures.

Further evidence for a hippocampal locus for spatial memory comes from a study of memory for the location of a spot of light in a patient with selective bilateral hippocampal pathology (Holdstock et al., 2000b). In this study, use of egocentric representations was encouraged by switching off the lights and testing from the same view, while allocentric representations were encouraged by leaving the light on and having the subject move between presentation and recall. A marginally greater impairment was found for the allocentric condition, although this also depended on the use of a filled delay and on increased variance in controls' performance in the egocentric (dark) condition. As noted above, while rotation of viewpoint around an array of objects does not guarantee the use of an allocentric representation, it does at least require some equivalent mechanism of generating a novel viewpoint on egocentrically encoded information. Equally, switching off the lights does not prevent the use of allocentric processes. Nonetheless, a hippocampal role in rotating or otherwise manipulating viewpoints in memory would be an interesting possibility, especially since hippocampal patients are not impaired at the related task of mental rotation of single objects from a fixed viewpoint (Holdstock et al., 2000b; Spiers et al., 2001a).

In summary, psychological studies indicate the presence of an automatic process that updates internal representations to accommodate the consequences of self-motion. Neuropsychological evidence indicates involvement of the medial temporal lobes (most particularly the hippocampus) in memory for locations after movement of the subject but does not conclusively identify the nature of its involvement, with issues such as frame of reference and generalizability from 2D to 3D real world situations still unclear.

Virtual Reality

Realization of the importance of self-motion in the construction and use of spatial representations, coupled with recent technological advances and the need for repeatability and control across subjects, has led to an increase in the experimental use of VR (see e.g., Burgess and King, 2001; Maguire et al., 1999). The extent of immersion or presence felt in a VR environment, i.e., the degree to which the user treats it as s/he does the real world and behaves in a similar manner, is obviously an important concern. In many of the experiments considered below, movements are simply generated using a joystick or keypad, which is not optimal for the perception of the amplitude of turning movements (Chance et al., 1998), which tend to be overestimated (Klatsky et al., 1998). Conversely, there is evidence that distances can be underestimated (Witmer and Klein, 1998). Despite these limitations, several studies have indicated good correspondence between the spatial knowledge of an environment acquired in the real world and a model of that environment in VR (Arthur et al., 1997; Regian and Yadrick, 1994; Ruddle et al., 1997; Witmer et al., 1996), and VR has been used to enable an amnesic patient to learn useful routes (Brooks et al., 2000) and

teach disabled children (Wilson et al., 1996). Care must be taken in designing realistic VR environments as, for example, realistic landmarks improve navigation while distinct colored patterns do not (Ruddle et al., 1997), and performance tends to correlate with the extent of presence felt by the subject (Witmer and Singer, 1994).

Viewpoint Dependence

Virtual reality provides an opportunity to investigate viewpoint dependence in human spatial memory with control over the exact views and transitions between views experienced by different subjects. A shifted-view object-location memory task was recently designed for this purpose (King et al., 2002). The subject is given a view from the rooftops surrounding a richly textured courtyard. During presentation, objects appear in different locations around the courtyard. During testing, several copies of each object are presented in different locations, and the subject is asked to indicate which objects were in the same location as at presentation. Between presentation and testing, the subject's viewpoint might remain the same or be changed to another location overlooking the courtyard. Salient features of this task, compared with previous tests noted above (e.g., Abrahams et al., 1997), include the sequential presentation of objects, instantaneous transfer between viewing locations, and use of perspective within large-scale space. These respectively ensure that any single representation of object locations would have to be cumulatively built up from the sequential visual input and that continuous spatial updating of the subject's location would be unlikely. Thus, although the same-viewpoint condition could be solved using either allocentric or egocentric strategies, solution of the shifted-viewpoint condition requires either an allocentric representation or a representation that includes the 3D locations of scene elements and a means of rotating and translating viewpoints within 3D space. We refer to both of these possibilities as allocentric processing.

The above task was used to test a patient, Jon, with focal bilateral hippocampal pathology (Vargha-Khadem et al., 1997). He was found to be unimpaired at recognizing topographical scenes where targets at test were identical to those during learning (Spiers et al., 2001a). Although unimpaired on a spatial span task, the original report showed that he was impaired on a multitrial 2D object location task in which subjects learned from yes/no feedback (i.e., without representation of the correct stimulus) (Vargha-Khadem et al., 1997). On the VR same- or shifted-view task, Jon was mildly impaired on the same-view condition (tested using two foils) where performance exactly mirrored his 2D object location deficit. In contrast, he was massively impaired in the shifted viewpoint condition (King et al., 2002). His performance was above chance up to and including 13 item lists in the same-view condition, but at chance at all list lengths greater than 1 in the shifted-viewpoint condition. Healthy matched controls performed slightly better than Jon in the same-viewpoint condition and vastly better in the changed-viewpoint condition. Reducing the performance of controls by increasing the number of foils (to five) further confirmed Jon's deficit in the shifted-view condition over and above his deficit in the same-view condition. The response times of control subjects show a linear increase with the size of the shift in viewpoint, indicating some process of viewpoint manipulation. The same chronometric relationship held for each response in the list, indicating that the effect was not simply to do with the subject's initial reorientation to the novel viewpoint.

Thus, the use of an allocentric process capable of arbitrary manipulations of viewpoint within 3D space appears to be specifically dependent on the hippocampus. By contrast, demonstration of hippocampal deficits in traditional object location tasks usually requires a delay and is often no greater than the deficit caused by parahippocampal damage. This weaker, delay-dependent effect may be due to the fact that the control subjects can use an enduring hippocampal allocentric representation in addition to egocentric parietal representations or iconic parahippocampal representations that rapidly degrade with time or the number of stored objects, while hippocampal-damaged patients must rely entirely on the latter.

Spatial Navigation

There have been many different approaches to the study of spatial navigation. The need to control and manipulate stimulus presentation and to record behavior, as well as the desire to perform head-fixed functional neuroimaging, has seen a rapid increase in the use of VR. We now consider some recent behavioral, neuropsychological, and functional neuroimaging studies of active spatial navigation.

The success of the water maze (Morris, 1981) as a tool for studying spatial navigation in rats and for demonstrating the involvement of the hippocampus (Morris et al., 1982) has lead to its adaptation for humans. Some studies have used VR to present a circular pool of water (containing the hidden target location) within a simple room of plain walls and a few distinctive cues (Jacobs et al., 1997, 1998). As predicted by cognitive map theory (and similar to rats), they found that subjects could generalize to novel start locations, made preferential use of distal rather than proximal cues, and performed robustly despite the removal of subsets of distal cues, but not if the topological relationships between them were changed.

The simplicity of the water maze setup is both a strength and a concern when used to study human navigation. Its convex shape allows solution by visual pattern matching since the location of the goal and all of the landmarks are visible from all locations (see e.g. Cartwright and Collett, 1982). Similarly, simple corridor mazes allow solution by learning stimulus-response associations. In addition, environments without rich visual texture lack "immersion" (in the VR sense!). These reasons may explain the initial findings of parahippocampal, but not hippocampal, involvement in spatial memory within simple VR corridor mazes (Aguirre et al., 1996) or water maze-like tasks (Bohbot et al., 1998; Maguire et al., 1998b). In addition, recognition of the locations of scenes from a more complex virtual environment also activated the parahippocampus (Aguirre and D'Esposito, 1997), as did indicating the direction of a second location from the current location (although this latter task was more strongly associated with inferior parietal activation). By contrast, neuroimaging studies where a town layout was learned from watching film footage of travel through it (Maguire et al., 1996b), generating and

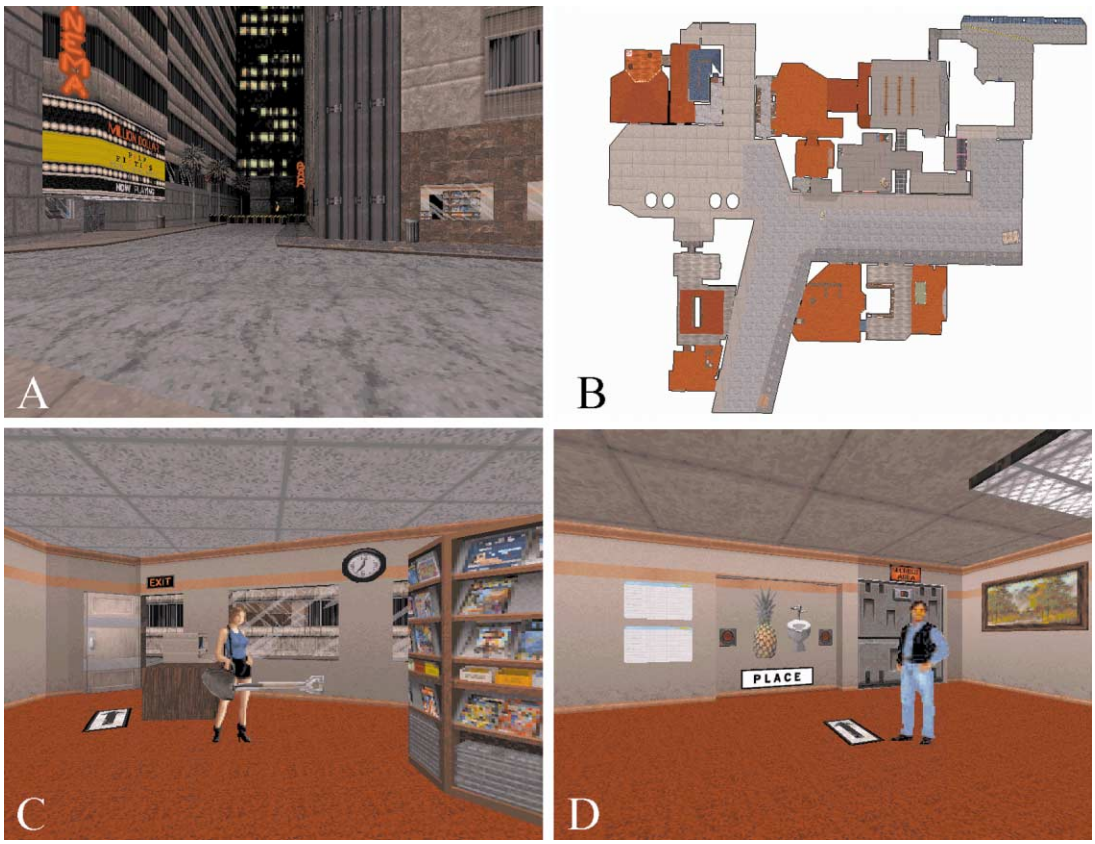

Figure 1. The Virtual Reality Town Used in Functional Neuroimaging and Neurophysiological Studies of Topographical and Episodic Memory
See Burgess et al. (2001b), Maguire et al. (1998a), and Spiers et al. (2001a, 2001b).
(A) A view from within the town, as seen by a subject.
(B) Aerial view of the area used for testing navigation in neuropsychological studies. This view was never seen by subjects; note that a slightly more extensive version of the town was used by Maguire et al. (1998a).
(C) Receiving an object in the episodic memory test.
(D) Answering a "place" question in the episodic memory test.

describing routes through a real city (Maguire et al., 1997) or recalling a route learned in the real world before scanning (Ghaem et al., 1997) have shown activation extending into the hippocampus proper.

Taking account of these issues, the brain regions involved in active navigation were directly investigated by making subjects find their way between locations within a complex, texture-rich VR town while in a positron emission tomography (PET) scanner (Maguire et al., 1998a). This town was created to appear as lifelike as possible and to include many different possible routes between any two locations (see Figures 1A and 1B). The right parahippocampus and hippocampus were activated by successful navigation between locations based on the subject's knowledge of the layout of the town compared to following a route of arrows through the town. The subject's accuracy of navigation was found to correlate significantly with activation in only two brain areas: the right hippocampus and the right inferior parietal cortex (see Figure 2A). Medial and right inferior parietal activation was associated with all conditions involving active movement through the town. Activation of the left hippocampus was associated with successful navigation, but did not correlate with accuracy of navigation. Speed of virtual movement through the town correlated with activation in the caudate nucleus, whereas performance of novel detours was associated with additional activations in left prefrontal areas beyond those seen in the navigation condition. These results are consistent with right hippocampal involvement in supporting a representation of location within the town that allows accurate navigation, left hippocampal involvement in more general mnemonic processes (see later discussion), posterior parietal involvement in guiding egocentric movement through space, orienting the body relative to doorways and avoiding obstacles, etc., and involvement of the caudate in movement-related aspects of navigation.

Essentially the same task was used to investigate navigation following either focal bilateral hippocampal damage (Spiers et al., 2001a) or unilateral anterior temporal lobectomy (Spiers et al., 2001b). Participants' topographical memory was tested by their ability to navigate accurately to ten locations in the town (shown to them as pictures), their ability to recognize scenes from the town compared to similar lures, and their ability to construct an accurate map of the town. The right temporal lobectomy patients were impaired on all three topo-

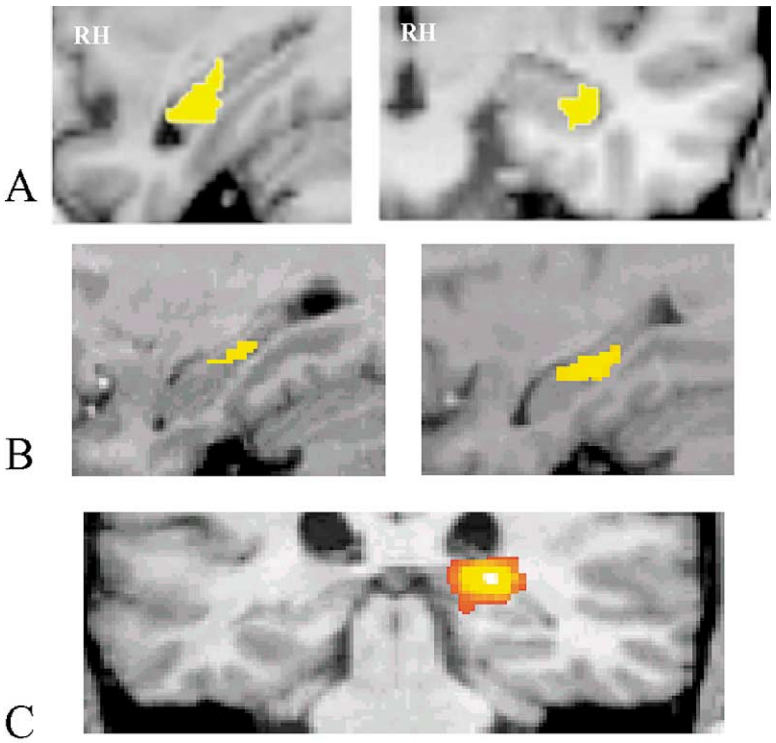

Figure 2. Topographical Memory and the Hippocampus

(A) Activation of the right hippocampus correlates with accuracy of navigation in the virtual reality (VR) town. The loci of significant correlation are shown superimposed on the structural template to which all scans were normalized ($r = 0.56$); significant correlation was also found in the right inferior parietal cortex (see Maguire et al., 1998a).

(B) Voxel based morphometry indicates increased posterior hippocampal volume bilaterally in licensed London taxi drivers compared with control subjects.

(C) Amount of time spent taxicab driving (corrected for age) was positively correlated with volume increase in the right posterior hippocampus (adapted from Maguire et al., 2000a).

graphical tasks compared to controls, taking longer routes, making worse maps, and recognizing fewer scenes. The left temporal lobectomy patients performed at a level intermediate to the controls and right temporal lobectomy patients on both overall topographical performance and on the navigation component (see Figures 3A and 3D).

The patient with focal bilateral hippocampal pathology, Jon (Vargha-Khadem et al., 1997), was also tested on the VR town task. He was impaired on all of the topographical tasks (Spiers et al., 2001a). (See Figure 3A and the section, Comparing Topographical and Episodic Memory). Together, these data provide evidence of right hippocampal involvement in human navigation. Note that neither Jon nor the temporal lobectomy patients had damage to the parahippocampal cortex, and yet, both Jon and the right temporal lobectomy patients were impaired at recognizing scenes from the environment they had actively explored. This scene recognition task differs from more standard tests, however, in that it requires the identification of scenes that have not been explicitly studied (i.e., scenes one would not necessarily have been able to store as a snapshot). Instead, successful discrimination of target views probably requires retrieval of abstracted environmental information, such as layout, that is dependent on the hippocampus.

What, then, are the hippocampal and parahippocampal roles in spatial processing? It seems likely that the parahippocampus supports processing of the spatial information present in visual scenes (Epstein and Kanwisher, 1998), e.g., extracting the distances to the nearest landmarks or boundaries (Burgess et al., 2001a; Hartley et al., 2000; O'Keefe and Burgess, 1996). In addition, the activation of the parahippocampus can be modulated by attention (O'Craven et al., 1999). These two findings provide an explanation for its activation in all of the above neuroimaging studies. The impairments of patients with parahippocampal damage, even in tasks whose spatial memory component appears very simple to humans (Bohbot et al., 1998), is further evidence for a more perceptual contribution of this medial temporal region. By contrast, the hippocampus appears only to be activated in more complex navigational situations (e.g., where the environment consists of several areas connected by many possible routes). Additionally, lesions to the hippocampus that exclude the parahippocampal cortex cause impairments in these tasks. These data are consistent with the idea that the hippocampus supports spatial behavior when a representation of the relative positions of the elements making up an environment is required (O'Keefe and Nadel, 1978). One way to test for knowledge of the relative locations of the elements in an environment, as opposed to the recognition of the scene itself, is to require recognition of the environment from a novel viewpoint. As mentioned above, hippocampal patient Jon is impaired at recognition of environments (Spiers et al., 2001a) and object locations (King et al., 2002) from a new viewpoint. Interestingly, however, patients with parahippocampal damage were unimpaired on a task requiring recognition of an environment made from Legos from a new viewpoint (Epstein et al., 2001).

We can summarize the main lessons to be drawn from the studies of medial temporal lobe involvement in spatial memory as follows: the right hippocampus appears to be involved in allocentric object location memory and in wayfinding through complex environments, a task that probably requires allocentric processing of environmental locations. Right hippocampus and bilateral posterior parahippocampal gyrus also ap-

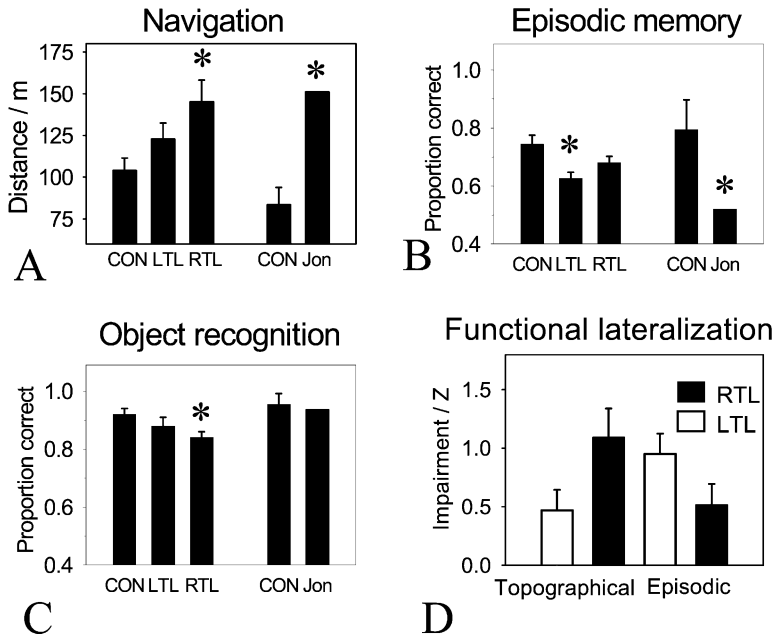

Figure 3. Attributing Function to the Left and Right Hippocampus and Surrounding Neocortex

(A–C) Each graph shows the performance of 13 left (LTL) and 17 right (RTL) temporal lobectomy patients and their 16 controls (CON) on the left and the performance of a developmental case with focal bilateral hippocampal pathology (Jon; Vargha-Khadem et al., 1997) and his 13 controls (CON) on the right. Error bars indicate one standard error of the mean in all cases except for Jon's controls, which show one standard deviation. The asterisk indicates a significant difference compared to controls at $p < 0.05$ (1-tailed t test). In (A), performance at navigation is shown as the mean path length taken in finding ten target locations. The RTL group and Jon are both significantly impaired relative to controls, while the LTL group shows intermediate performance (see Spiers et al., 2001a, 2001b). In (B), performance in context-dependent episodic memory ("person," "first," and "place" questions, see text) is shown as the proportion of correct responses. The LTL group and Jon are both significantly impaired relative to controls, while the RTL group shows intermediate performance (see Spiers et al., 2001a, 2001b. In (C), performance in object recognition ("object" question, see text) is shown as the proportion of correct responses. The RTL group is significantly impaired relative to controls while the LTL group and Jon are not.

(D) Lateralization of function across temporal lobectomy cases. The mean standardized z scores of the LTL and RTL groups' overall performance relative to the control group mean and standard deviation on topographical (navigation, map construction, and environmental scene recognition) and episodic (person, first, and place questions) tasks are shown. These data show a significant group $\times$ task interaction ($p < 0.015$), with the differences between the groups in both topographical and episodic performance approaching significance ($p < 0.07$ and $p < 0.09$, respectively, 2-tailed t tests) (see Spiers et al., 2001b).

pear to be involved in more general object-location memory (i.e., in tasks not explicitly designed to require allocentric processing), but the right hippocampal involvement in these tasks is usually seen after delays. One possible interpretation of this delay dependence, consistent with involvement in allocentric tasks, is that allocentric representations are more enduring than egocentric ones and consequently become more necessary as a function of delay. The posterior parahippocampi are also more generally involved in tasks requiring the processing of spatial scenes. Wayfinding in very simple environments may be possible on the basis of perceptual matching in the parahippocampus alone or on the basis of learned stimulus-response associations, without requiring knowledge of relative locations within the environment and thus not requiring the hippocampus.

Cross- and within-Species Hippocampal Comparisons

How do the above findings on human spatial memory relate to studies in other animals? As observed above, a surprisingly close correspondence exists between the performance of humans and rats in the water maze, although there is not yet conclusive proof in humans that the hippocampus proper is required to solve the water maze as there is in rats (Morris et al., 1982). Another apparently close correspondence exists between some aspects of human spatial memory and the behavior of place cells recorded in the hippocampus of freely moving rats. These cells respond whenever the rat enters a specific portion of its environment (the place field) and do not depend simply on the presence of a sensory stimulus or, in open environments, on the orientation of the rat (see e.g. Muller, 1996; O'Keefe, 1976). We also note the various nonspatial correlates of firing that have been reported to be consistent with a more general memory function for the hippocampus (e.g., Eichenbaum et al., 1999; but see also O'Keefe, 1999).

The locations of place fields within an environment are largely determined by the geometry of the boundaries of the rat's enclosure (Hartley et al., 2000; O'Keefe and Burgess, 1996), as opposed to the locations of the objects within it (Cressant et al., 1997). This may relate to the tendency for the geometric features of a room (the corners) to be encoded in a single unified representation in human memory, while objects within the room are not (Wang and Spelke, 2000). It is also consistent with the finding that the parahippocampus (one of the major neocortical inputs to the hippocampal formation) shows activation in response to spatial scenes, including the bare walls of a room (Epstein and Kanwisher, 1998), relative to objects or nonspatial (i.e., scrambled) scenes. Experiments in rats also serve as a caution against the generality of results from disorientation paradigms (e.g., Hermer and Spelke, 1994; Wang and Spelke, 2000). The behavior (Cheng, 1986) of disoriented rats and the firing of their place and head direction cells (Knierim et al., 1995) are not controlled by visual orientation cues that do control both cells and behavior in normal circumstances (Muller and Kubie, 1987; O'Keefe and Speakman, 1987; Taube, 1998). See also (Wang et al., 1999).

Interesting parallels exist between findings in monkeys and those in humans and rats, although physiological experiments in freely moving primates are relatively

rare. As with research on humans (see Divisions of Hippocampal-Dependent Memory below), the hippocampal contribution to visual recognition memory in infrahumans is also controversial. While this process appears to be predominantly dependent on the perirhinal cortex (Zhu et al., 1996), controversy surrounds whether or not it also depends to some extent on the hippocampus. Some studies report a deficit following hippocampal lesions (Zola et al., 2000) and others do not (Murray and Mishkin, 1998). In the spatial domain, the spatial memory deficit due to hippocampal damage in freely moving rats (delayed alternation on a T maze) has been shown to occur in freely moving monkeys following lesions to the fornix (Murray et al., 1989). Analogues of place cells have also been reported in monkeys: cells that respond when the monkey visits a place (Matsumura et al., 1999) and spatial view cells that respond whenever the monkey looks at a given place in the environment (Rolls et al., 1997).

Further evidence linking the hippocampus to spatial memory in animals comes from comparative neuroanatomy. Hippocampal volume has been shown to be related to spatial ability in several species of birds and small mammals (Krebs et al., 1989; Lee et al., 1998; Sherry et al., 1992) in terms of their ability to keep track of large numbers of stored food items or large home ranges. Furthermore, variations in hippocampal volume in birds and small mammals have been found to track seasonal changes in the need for spatial memory (Lavenex et al., 2000; Smulders et al., 1995). Interestingly, neurogenesis in the dentate gyrus has now been associated with spatial memory and learning in birds and small mammals (Lavenex et al., 2000; Patel et al., 1997; Shors et al., 2001) and has been found in adult primates (Gould et al., 1999) and postmortem tissue in the adult human hippocampus (Eriksson et al., 1998).

In humans, the brain anatomy of London taxi drivers has been compared with that of age-matched nontaxi drivers (Maguire et al., 2000a), using voxel-based morphometry (VBM) analysis of structural MRI scans (Ashburner and Friston, 2000). Licensed London taxi drivers are required to undergo extensive training and pass stringent police examinations before being licensed to operate; this takes about 2 years. Significant differences in gray matter volume between the two groups were only found in the hippocampus, with the posterior hippocampus being larger on both sides in taxi drivers (see Figure 2B) and the anterior hippocampus being smaller. Moreover, the increase in right posterior hippocampus correlated positively with the time spent in the job (see Figure 2C). This study provides an intriguing hint of experience-dependent structural plasticity in the human brain, as compared to the well-known effects of functional reorganization in neocortex (Buonomano and Merzenich, 1998) and further suggests an intimate link with navigation and the hippocampus in humans, as well as other animals.

VBM has also been applied to the comparative neuroanatomy of men and women (Good et al., 2001), where increased gray matter volume in the medial temporal lobes was found in males compared with females (as well as several neocortical loci of reduced volume). The differential hippocampal volumes may relate to a number of performance and strategy differences found in behavioral and functional neuroimaging studies of navigational abilities. Better performance by men has been documented on a number of navigation tasks (Astur et al., 1998; Moffatt et al., 1998; see also Silverman and Eals, 1992). Interestingly, in the light of the studies linking hippocampal processing with geometric aspects of the local environment, men were shown to be able to make use of both geometric and landmark information in solving a VR water maze, while women predominantly used landmarks alone (Sandstrom et al., 1998). A functional magnetic resonance imaging (fMRI) study also found male-female differences. Both groups showed parietal, parahippocampal, and right hippocampal activation associated with navigation in a VR maze. In men, the left hippocampus was also activated, whereas right parietal and right prefrontal areas were activated in women (Gron et al., 2000). These differential activations are reasonably consistent with the strategy differences noted above, although differences in neuroanatomical structure (men having bigger hippocampi) or in experience with VR may also contribute (Moffatt et al., 1998).

Comparing Topographical and Episodic Memory

Although spatial memory is the main focus of this review, an obvious question is: what is the relationship between the roles of the hippocampus in spatial processing and its acknowledged role in the broader aspects of memory?

Divisions of Hippocampal-Dependent Memory

As noted at the outset, episodic memory (Tulving, 1983) concerns our ability to consciously recollect personally experienced events. An event may be defined as a temporally localized change in the state of the world (e.g., "it started to rain," or "she called him"). Our memory of the event often includes both information corresponding to the content of the event itself (i.e., the change in the world), as well as information corresponding to the ongoing external context of the event, such as where and when it occurred, who was involved, etc. It is the recollection of an event's rich spatio-temporal context that distinguishes this class of memory from memory for facts (semantic memory) or the simple recognition of an object's familiarity (Gardiner and Java, 1991; Knowlton and Squire, 1995; Tulving, 1993). There is now a consensus that whatever else it may do, the human hippocampus supports this episodic type of memory (Cohen and Eichenbaum, 1993; Kinsbourne and Wood, 1975; O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991).

The attribution of different types of memory to different neural structures has a long and controversial history. There is general agreement that episodic memory is dependent on the hippocampus while priming and procedural memory are not (Aggleton and Brown, 1999; Kinsbourne and Wood, 1975; O'Keefe and Nadel, 1978; Squire and Zola-Morgan, 1991; Vargha-Khadem et al., 1997). The locus of visual recognition memory in humans is more controversial. Familiarity-dependent recognition is reported to be spared by focal hippocampal damage in developmental cases (Baddeley et al., 2001; Vargha-Khadem et al., 1997) and in some cases with adult onset (Holdstock et al., 2000a). In these cases, recognition of words, faces, and pairs of words and faces is unim-

paired. However, other adult cases with similarly restricted hippocampal damage do show impaired recognition (Rempel-Clower et al., 1996; Zola-Morgan et al., 1986; see also Manns and Squire, 1999). There is similarly little agreement concerning the key locus of semantic memory, although the comparative anatomical progression of semantic dementia (on the one hand) and Alzheimer's disease (on the other) implicates left anterior temporal lobe in semantic memory and bilateral medial temporal lobe in episodic memory (Chan et al., 2001; see also Holdstock et al., 2002). Supporting this distinction, the developmental amnesics have relatively spared semantic memory (Vargha-Khadem et al., 1997), although semantic learning is impaired in other (adult) cases (e.g., Holdstock et al., 2002; see Spiers et al., 2001c, for a review).

Resolution of these conflicting data is beyond the scope of this review and may involve unknown physiological factors relating to hidden damage in extrahippocampal tissue (see e.g., Bachevalier and Meunier, 1996; Mumby et al., 1996), developmental plasticity, and the possible functionality of residual hippocampal tissue (Bachevalier and Meunier, 1996; see also Maguire et al., 2001a). Here, we concentrate on the acknowledged roles of the hippocampus in topographical and episodic memory.

Theoretical Considerations

Navigation in a complex environment is not just an example of more general episodic memory. While navigation might include recalling a previously taken route, recognizing familiar scenes, or remembering the events that happened in a particular place, none of these processes alone will enable the generation of an accurate trajectory. Equally, while both the same and different view conditions in the VR shifted-view test (King et al., 2002) depend on memory for personally experienced events, the two are clearly dissociable. In addition, the gradual learning of spatial knowledge corresponds more to ideas of semantic than episodic memory. Finally, several neuroimaging studies of personal or autobiographical event memory have implicated the medial temporal lobes (Fink et al., 1996; Maguire et al., 2000b; Maguire and Mummery, 1999) and, particularly, the left hippocampus (Maguire et al., 2000b; Maguire and Mummery, 1999) for personal event compared with semantic memory (Maguire et al., 2001b). This compares to the predominantly right hippocampal involvement in spatial tasks. However, given that left hippocampal activations have been found in navigation neuroimaging studies (Gron et al., 2000; Maguire et al., 1998a) as well as left medial temporal lobe involvement in verbal or narrative memory, the precise division of labor between the left and right hippocampi is unclear.

A theoretical framework for considering the hippocampal roles in space and memory is provided by the cognitive map theory of hippocampal function (O'Keefe and Nadel, 1978). Based on the idea that the infrahuman hippocampal formation supports spatial navigation, the theory further suggested that in humans, the spatial role is extended to include episodic memory and that memory for spatial context may provide the basic scaffolding for this function. The cognitive map theory suggested that episodic memory was supported by the incorporation of a linear sense of time and (on the left) verbal/linguistic inputs into an allocentric spatial framework.

Other authors have suggested that the hippocampus provides a means of forming associations between information presented in different modalities or stored in different brain regions (Marr, 1971; Mayes et al., 2001; Squire and Zola-Morgan, 1991) and that this is required by episodic memory. Cross-modal associations are indeed one of the few aspects of recognition memory seemingly impaired after restricted hippocampal damage (Mayes et al., 2001); however, this theory does not account for our finding of impaired allocentric and relatively spared egocentric spatial memory, both within the visual modality. The hypothesis implicating storage of information represented in different neocortical areas suffers from our lack of knowledge of where memory traces are stored in the brain and the extent to which they are localized in the first place.

The declarative theory (Squire and Zola-Morgan, 1991) sees the hippocampi as involved in any form of explicit memory and so does not directly address the relationship between topographical and episodic memory or between different types of spatial representation. The relational theory (Cohen and Eichenbaum, 1993) attempts to unify the declarative and spatial functions of the hippocampus, suggesting a broader characterization including both functions: that the hippocampus encodes relational information that can be flexibly applied to new situations. There is an obvious link to be made here, since allocentric or viewpoint-independent processes might be considered more flexible than egocentric or viewpoint-dependent processes. In this respect, the relational and cognitive map theories cannot be distinguished. Overall, however, the declarative and relational terms seem too broad to capture the specific dissociations found in these spatial tasks and do not help in providing a mechanistic explanation of how they are solved. Egocentric spatial relations are also relational and declarable. Additionally, the declarative memory theory does not predict the sparing of object recognition seen in patient Jon. This patient also has well preserved semantic knowledge (Vargha-Khadem et al., 1997), information that is at least as declarable and capable of flexible expression as episodic information. A more specific version stresses associations between items that are discontinuous in time or space (Wallenstein et al., 1998) and explicitly relates the behavioral constraints to lower-level mechanisms, such as the properties of LTP.

Empirical Evidence

In order to examine how the roles of the hippocampi in topographical and episodic memory relate to each other, we performed neuropsychological and functional neuroimaging studies of context-dependent memory for personally experienced events in parallel to the studies of topographical memory outlined in the section on Spatial Navigation above. These tests used the same virtual reality town to allow both experimental control and the active participation in events set in a rich spatial context typical of autobiographical stimuli. The same patients (patient Jon, and left and right temporal lobectomy patients) were tested as in the topographical study (see Burgess et al., 2001b; Spiers et al., 2001b, 2001a).

Episodic memory was tested as follows: subjects fol-

lowed a prescribed route through the VR town and, along the way, repeatedly met two characters who gave them different objects in two different places. Each receipt of an object comprised an event, the memory for which was subsequently probed in a forced choice recognition test using two objects (see Figures 1C and 1D). Various aspects of the events were probed in different conditions: its spatial context ("place," i.e., which object was received in the current place), its temporal context ("first," i.e., which object had been received first), which person was involved ("person," i.e., which object was received from a given person), and recognition memory for the objects ("object," i.e., choosing the familiar object the subject had received versus a similar looking novel object).

In contrast to spatial navigation, the overall performance of the left temporal lobectomy patients on the context-dependent memory questions (place, person, and first) was significantly worse than controls, while the right temporal lobectomy patients showed an intermediate level of performance (see Spiers et al., 2001b, and Figure 3). There was a significant group (left, right) by task (topographical, episodic) interaction, with the difference between left and right temporal lobe patients in overall topographical and episodic scores both approaching significance (see Figure 3D). The dissociation between the right and left temporal lobectomy groups strongly suggests that the right temporal lobes are more involved in spatial memory and navigation and that the left temporal lobes are more involved in episodic memory.

The above deficits might be due to the fact that extrahippocampal structures in either or both lobes are solely responsible for the deficits. To assess the hippocampal contribution to these deficits, we turn to the performance of patient Jon. As well as being impaired on the topographical tasks (see above), he was also impaired on all the context-dependent memory tests, but not impaired when asked to recognize objects (see Figure 3 and Baddeley et al., 2001). Again, this is consistent with preserved extrahippocampal iconic representations. Indeed, Jon is sufficiently good at using visual matching that during the context-dependent episodic memory questions he often tried to orient himself within the virtual world in such a way as to reestablish the exact visual arrangement of the objects, characters, and places pertaining to the presentation of that event. Note that this preserved object recognition memory is also observed in a nondevelopmental case with focal hippocampal damage (Mayes et al., 2001) but appears to be impaired in others (Manns and Squire, 1999; see Spiers et al., 2001c for a review).

Which areas are activated in the healthy brain during the retrieval of episodic memories? The neuropsychological results suggest that the right hippocampus should be more active than the left during navigation, with the reverse pattern during episodic memory retrieval. The first suggestion is supported by the PET data described earlier, with activation of the right hippocampus in particular associated with accuracy of navigation in the virtual reality town (Maguire et al., 1998a). The second suggestion was tested by using event-related fMRI scanning of healthy subjects during the retrieval phase of the episodic memory task (Burgess et al., 2001b). Memory was tested in the same way, using the place, person, and object conditions, while a perceptual control discrimination condition, width, was added (this required the subject to choose the wider of two familiar objects). The hippocampal response to memory for spatial context can be seen in the contrast of the place and width conditions. In agreement with the lateralization from the patient study, the left hippocampus was activated to a greater extent than the right (see Figure 4). Comparing the responses across all conditions, the bilateral parahippocampal areas (and its subthreshold extension into right hippocampus) are specifically activated by the place condition, while the left hippocampus is also activated by the person condition (Burgess et al., 2001b).

Overall, these studies implicate the left hippocampus in episodic memory in a primarily nonverbal task (Burgess et al., 2001b; Spiers et al., 2001b, 2001a). This confirms previous functional neuroimaging (Maguire and Mummery, 1999) and neuropsychological (Barr et al., 1990; Hokkanen et al., 1995; Kapur et al., 1997; Tanaka et al., 1999) findings of left hippocampal or medial temporal involvement in the retrieval of autobiographical event memories using verbal paradigms, but see also reports of right (Fink et al., 1996; Markowitsch, 1995) or bilateral (Viskontas et al., 2000) involvement.

How Do the Roles of the Left and Right Hippocampi Relate to Each Other?

Given the spatial role of the right hippocampus, what is the role of the left hippocampus in episodic memory? There are several speculative hypotheses relating to this question, which we discuss below. One hypothesis is that the episodic role of the left hippocampus derives directly from its spatial role in the rat. Under this hypothesis, one possibility is that it provides the spatial context for retrieval. However, we failed to find any evidence that the left temporal lobectomy patients (and Jon) had a greater impairment in the place as opposed to the person condition (Spiers et al., 2001b, 2001a). We also failed to find greater left hippocampal activation in the place condition than in the person condition (Burgess et al., 2001b) (see Figure 4C). A second possibility is that the necessity of supporting spatial behavior, such as returning to a goal from a new direction, has forced the hippocampus to specialize in allocentric memory (O'Keefe and Nadel, 1978), which is appropriate to long-term memory in general in being robust to changes in one's position between encoding and retrieval (Becker and Burgess, 2001; Burgess et al., 1999; Milner et al., 1999). The navigational requirements of representing a moving viewpoint within a 3D spatial representation of an environment may provide a mechanism capable of episodic recollection or reexperiencing of extended episodes (Burgess, 2002; King et al., 2002). This idea is consistent with the observation of hemispatial representational neglect in imagery in patients with right parietal damage (Bisiach and Luzzatti, 1978; Guariglia et al., 1993). These patients appear to have an intact viewpoint-independent, long-term representation of entire spatial layouts, but right neocortical damage has impaired their ability to construct a viewpoint-dependent representation in imagery (see also Baddeley and Lieberman, 1980; Burgess et al., 2001a).

An alternative hypothesis (O'Keefe and Nadel, 1978)

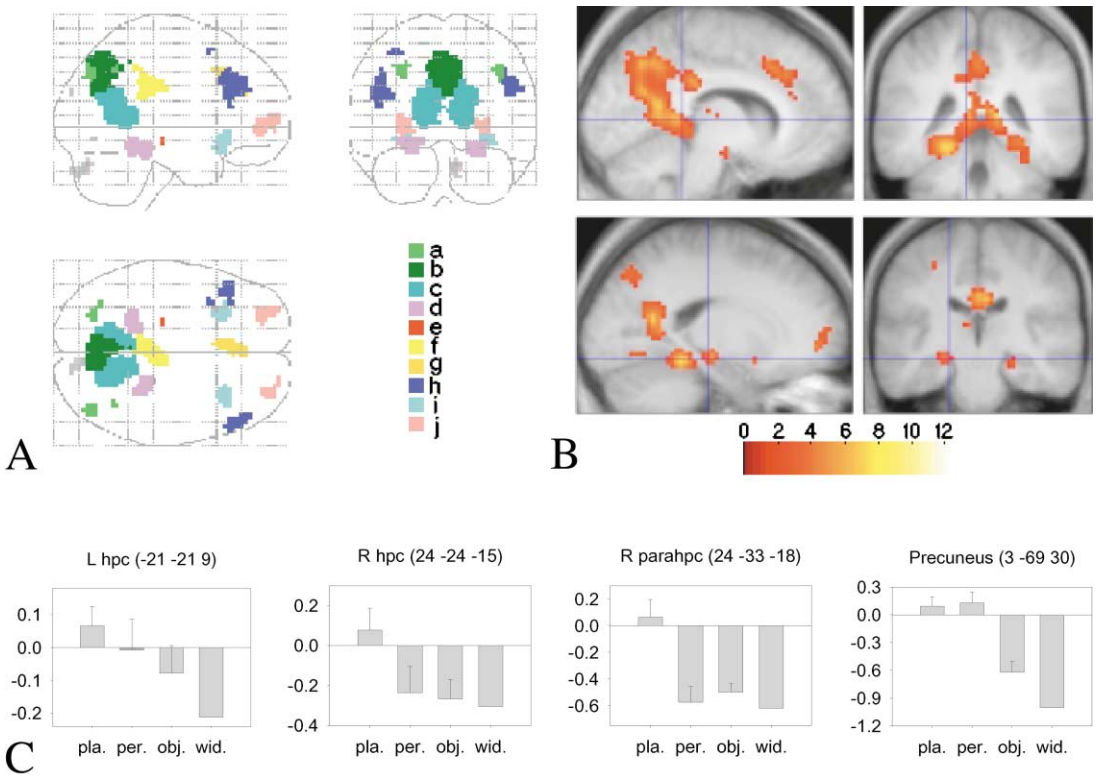

Figure 4. Functional Neuroimaging of the Retrieval of the Spatial Context of an Event

(A) Areas activated in the place condition relative to the perceptual control condition width are shown in color on a "glass brain" and include (a) posterior parietal, (b) precuneus, (c) parieto-occipital sulcus and retrosplenial cortex, (d) parahippocampal gyrus, (e) hippocampus, (f) midposterior cingulate, (g) anterior cingulate, (h) dorsolateral prefrontal cortex, (i) ventrolateral prefrontal cortex, and (j) anterior prefrontal cortex ($p < 0.001$ uncorrected for multiple comparisons).

(B) Activations in place-width shown on the averaged normalized structural MR images of the subjects, with threshold $p < 0.01$ uncorrected for multiple comparisons. Coronal and saggittal slices through the left retrosplenial cortex (above) and left hippocampus (below) are shown.

(C) Level of activation in four regions across all conditions place (pla), person (per), object (obj), and width (wid), shown as estimated percent signal change relative to background activation (i.e., when the subject is moving between questions). The name of region and x, y, and z coordinate of location (the voxel of peak response) is given above each graph. Note the strongly spatial response of right (R) hippocampal (hpc), and parahippocampal (parahpc) areas. The left parahippocampus (not shown) shows a similarly spatial pattern, whereas the responses in left (L) hippocampus and the precuneus do not. Error bars show the standard error of the mean of the difference between the parameter estimate for that condition and the parameter estimate for the width condition.

Figure adapted from Burgess et al., 2001b.

is that the left hippocampal involvement in episodic memory derives from its undoubted role in the storage of verbal material; for example, memory for paired associates, free recall of word lists, and narratives (Baxendale et al., 1998b; Frisk and Milner, 1990; Milner 1971; Seidenberg et al., 1993). The roots of this verbal role may also have a spatial derivative, i.e., the mechanism of abstracting an allocentric representation from the egocentric detail of sensory perception may have been co-opted on the left to store the gist of the narrative (O'Keefe, 1996). Note, however, that in common with Barr et al. (1990), we found no evidence of direct verbal mediation in our episodic task. In addition, there is evidence of episodic-like memory in other (nonlinguistic) species (Clayton and Dickinson, 1998; Emery and Clayton, 2001; but see also Tulving, 2001).

Functional Interpretation of the Memory Network

To fully appreciate the hippocampal involvement in topographical and episodic memory discussed above, we must attempt to set it in the context of the functional roles of other brain regions involved in these two behaviors. Firstly, topographical memory: in our PET navigation study (Maguire et al., 1998a), the correlation of right hippocampal activation with the accuracy of navigation and its activation during wayfinding compared to following a trail of arrows is consistent with allocentric processing of locations in the town. The activation of medial and right inferior parietal areas in all movement conditions and (lesser) correlation of right inferior parietal activation with accuracy of navigation is consistent with a more general involvement in moving through an environment, processing optic flow (de Jong et al., 1994), and maneuvering around obstacles. More specifically, the inferior parietal activation is consistent with translation of an allocentric (hippocampal) specification of the destination (e.g., North) into an egocentric representation (e.g., left) (Burgess and O'Keefe, 1996). The right parahippocampal activation in wayfinding compared to following a trail of arrows, but not correlated with accuracy, is consistent with processing of the spatial layout

of the current scene (Epstein and Kanwisher, 1998). The left hippocampal activation associated with successful navigation, but not correlated with accuracy, is consistent with a role in retrieving more general (nongeometric) information. Finally, the activation of left prefrontal areas in the presence of novel barriers compared to straightforward navigation is consistent with a prefrontal role in planning a new route, but not in the basic processes of navigation in a familiar environment.

In terms of episodic memory (Burgess et al., 2001b), we propose that information about the events in our VR episodic memory task is retrieved in the form of an index-like code in the hippocampus, based in part on the location of the subject (see Burgess et al., 2001a). This is used to generate an allocentric representation of the locations of the elements of the scene of the event in the parahippocampal gyrus, analogous to that suggested by Hartley et al. (2000). This representation is successively translated from allocentric to body-centered to head-centered representations with the aid of right posterior parietal cortex and BA7 into a viewpoint-dependent representation for visual imagery. Note that this translation requires knowledge of the subject's current heading, which suggests an explanation for the intriguing similarity between the head-direction system in the rat (mammillary bodies, anterior thalamus, and presubiculum) and the circuit associated with episodic recollection (Aggleton and Brown, 1999). In addition, we assume that the precuneus supports inspection of the mental image, having been associated with the imageability of the products of retrieval (Fletcher et al., 1995), while the continuous strip of activation seen between the parahippocampus and precuneus (including retrosplenial cortex) reflects the buffering of successively translated representations of the scene of the event. This model is consistent with the anatomical connections of both retrosplenial cortex (Morris et al., 2000) and posterior parietal areas (BA7; Andersen, 1997; Burgess et al., 1999) with the parahippocampus, and with recent a single unit study implicating BA7 in allocentric-egocentric translation (Snyder et al., 1998). For further details and a computational model, see Burgess et al. (2001a; 1999), Becker and Burgess (2001), and Maguire et al. (2000b; 2001b) for neuroimaging data on the effective connectivity between these regions.

No discussion of the neural bases of memory (spatial or episodic) would be complete without mention of prefrontal cortex. In the study of navigation, only the detour condition produced significant prefrontal activation, consistent with a general role in planning. Extensive prefrontal activation was seen in the retrieval of context-dependent memory for virtual events and also in experiments using conventional laboratory stimuli. However, the puzzle here is that autobiographical memory studies (e.g., Maguire et al., 2000b; Maguire and Mummery, 1999) typically activate only a single area of medial prefrontal cortex. One difference concerns the similarity of the events used in the VR study (and in conventional experiments on memory), both to each other and of their contexts (all 16 event involving one of two people and one of two places within a short space of time). This contrasts with the rich diversity and temporal separation of autobiographical events (e.g., being at a wedding, going to the dentist, etc.). Thus, much of the prefrontal involvement in the VR episodic memory task might reflect processes required to overcome the interference caused by the similarity of the events and their context. This would be consistent with comparisons of frontal and temporal lesions, implicating the medial temporal lobes in the storage of episodic memory and the frontal lobes in the use of organizational strategies in encoding and retrieval (Frisk and Milner, 1990; Gershberg and Shimamura, 1995; Incisa della Rocchetta and Milner, 1993; Kopelman and Stanhope, 1998; Owen et al., 1996; Smith et al., 1995), including those relating to interference (Incisa della Rocchetta and Milner, 1993; Smith et al., 1995).

Summary and Conclusions

Although it may be premature to attempt to provide a comprehensive view of the brain structures involved in spatial and episodic memory, the data reviewed here are consistent with the following tentative mapping of structure to function. The right hippocampus appears to be involved in standard object-location memory tests, but no more so than the parahippocampus, and usually requires a delay to bring out a significant deficit. The parahippocampus also appears to be specifically involved in representing the geometry of spatial scenes, whether or not this is used in memory. However, the right hippocampus appears to be specifically involved in memory tasks requiring allocentric processing of spatial locations. The need for allocentric processes to guide accurate navigation probably accounts for the right hippocampus involvement in accurate large-scale navigation. By contrast, the left hippocampus appears to be involved in episodic/autobiographical memory, although not necessarily through verbal mediation.

Outside of the medial temporal lobe, we have outlined the possible nature of the interaction with egocentric representations found in the parietal lobe. In both navigation and episodic retrieval, this might consist of translation of stored (hippocampal) allocentric information into the (parietal) egocentric representations required to guide movement or to support imagery of the retrieval products. We further suggested that prefrontal involvement corresponded to planning of detours in navigation and strategic organization of retrieval in cases where the similarity of events or their contexts create substantial interference. Within this analysis, spatial behavior and its neural bases also show both interesting differences within humans (as a function of gender and occupation) and instructive similarities between humans and infrahumans (not least allowing contact to be made with much useful single unit data).

Important questions remain regarding the relationship between the hippocampal roles in spatial and episodic memory. Can this relationship be understood in terms of the use of viewpoint-independent mechanisms in long-term memory (Burgess, 2002; Burgess et al., 1999; O'Keefe and Nadel, 1978) or in terms of both requiring specific types of relationships (Cohen and Eichenbaum, 1993) or associations (Marr, 1971; Mayes et al., 2001; Squire and Zola-Morgan, 1991)? At a more detailed level, what is the relationship between the specific deficit in shifted-viewpoint spatial memory (Holdstock et al., 2000b; King et al., 2002) and the otherwise generally

spared recognition memory but impaired recollection seen in some patients with focal hippocampal damage (Gadian et al., 2000; Mayes et al., 2001; Vargha-Khadem et al., 1997)? Based on convergent evidence from recent behavioral, neuropsychological, and neuroimaging studies, we have suggested a unified framework for considering the functional roles of the human hippocampi and their relationship to the hippocampal involvement in spatial navigation in infrahumans. The VR methodology presented here allows controlled investigation of the everyday tasks of wayfinding and remembering personally experienced events. More generally, it enables controlled future investigation of the neural bases of memory and cognition in ecologically valid situations.

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